

European Journal of Breast Health

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Aims and Scope

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

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

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

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

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

European Journal of Breast Health indexed in PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Embase, EBSCO, CINAHL.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.eurjbreasthealth.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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- Grant information and detailed information on the other sources of support,
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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (<https://www.nlm.nih.gov/mesh/MBrowser.html>).

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Materials, Results, Discussion and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

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

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

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

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Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
Current Opinion	300	No abstract	5	No tables	No media
BI-RADS: Breast imaging, report and data systems					

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

Tables

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

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. References published in PubMed should have a PMID: xxxxxx at the end of it, which should be stated in parenthesis. The reference styles for different types of publications are presented in the following examples.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Bartlett JG, Blacklow NR, editors. *Infectious Diseases*. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. *Martindale the Complete Drug Reference*. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. *Functional reconstructive nasal surgery*. Stuttgart-New York: Thieme; 2003.

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

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

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki İlişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. *Scand J Dent Res*. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. *Diagn Interv Radiol*. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: [http:// www.cdc.gov/ncidod/EID/cid.htm](http://www.cdc.gov/ncidod/EID/cid.htm).

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A New Technical Mode in Mammography: Self-Compression Improves Satisfaction

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ABSTRACT

Objective: We aimed to evaluate the mammography experience of patients using a manually controlled self-compression tool compared to their previous experience based on technician performed breast compression by a questionnaire survey study.

Materials and Methods: The survey studies of 365 patients who underwent screening or diagnostic mammography between April 2017 and July 2017 at our center were reviewed retrospectively. Each patient had completed a 12-item questionnaire following mammography examinations. Women who never had a mammography before or who had a previous mammography examination more than 2 years ago or who did not want to use the self-compression device were excluded from the study. 106 women were included in the study.

Results: Patient satisfaction was high. Regarding the comparison of the experience of the exam to previous ones, 70.8% said it was a better experience. The examination was found comfortable by 85.4% of the participants and 75.5% found the examination more comfortable compared to previous ones. Only 11.3% were anxious and 52.8% declared they were less anxious compared to previous examinations. Regarding the attractiveness of the new design, 66.9% declared they found the new design attractive, 39.7% found it more attractive than previous examinations, and 27.3% said the new design decreased anxiety. In the evaluation of impact of patient-assisted compression (PAC) on comfort, 80.2% said that they found it more comfortable and 64.2% said that PAC decreased anxiety. Furthermore, 72.6% said the exam was shorter.

Conclusion: Self-compression technique decreases pain and anxiety of women during mammography examinations and promises to enhance compliance of clients and patients with follow-up mammography recommendations.

Keywords: Mammography, self-compression, pain, patient satisfaction

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Introduction

Breast cancer is the most common cancer and the second leading cause of death due to cancer among women. The only proven method to decrease the mortality of breast cancer is screening mammography (1, 2). Mammography is a relatively inexpensive and widely available imaging technique. Stabilizing the breast by compression between a compression paddle and the detector housing during mammography examinations is required for many reasons (3-5). This application of force immobilizes the breast resulting in avoidance of motion blur and reduces breast thickness, which limits radiation scatter, resulting in improved image quality and also decreased overall radiation dose exposed to glandular tissue (5). Furthermore, it leads to a more homogeneous exposure from nipple to chest wall resulting in improved dynamic range (5). In addition, adequate compression can improve the diagnostic distinction between tumors and artifacts. However, breast compression is related with discomfort and pain (6), and some patients may experience anxiety or stress and hesitate about undergoing mammography. Sometimes the technician avoids adequate compression due to anxiety to hurt the patient. This results in poor image quality and increased radiation exposure. On the other hand, sometimes the technician applies too much compression to obtain good image quality, which results in the aversion of the examination, lack of compliance in periodic screening, and also discouragement of the participation of peers. There are no quantitative guidelines on the compression force a technologist should apply for acquisition of an adequate mammogram resulting in great variations among technologists and screening centers (1). The most adequate compression is the most compression the patient can endure. The breast tissue should be firm during an optimal compression and no indentation should appear when the tissue is pressed with fingers. To decrease patient anxiety and to reduce the pain and discomfort during the

mammography examinations various methods have been used including a thorough explanation of the procedure with verbal or written information, topical application of 4% lidocaine gel to the skin of the chest, self-controlled breast compression, the use of a radiolucent pad, administration of oral acetaminophen and ibuprofen, and decreasing the compression force (7-13).

Self-compression tool provides women a sense of control by letting them to manually adjust the degree of breast compression; patient-assisted compression (PAC). Guided by a technologist, the patient uses a hand-held wireless remote control to adjust the force of compression after breast positioning. This device gives patients control over the amount of compression for their exam. The technologist then guides the patient to gradually increase compression using the remote control until adequate compression is reached and checks the applied compression and breast positioning.

While it is not a new concept, to our knowledge there are only two reports in the English literature regarding breast compression by the patient during mammography (10, 11). The aim of this study was to evaluate the experience of patients on this next-generation mammography technology compared to previous exams with a questionnaire survey study.

Materials and Methods

Institutional Ethics Committee approval was obtained for this retrospective study (2018-12/8). Waived consent is obtained before all imaging procedures performed in our institution for research. The survey studies of 365 patients, aged 40-90 years, who underwent screening or diagnostic mammography (Senographe Pristina (GE Healthcare,

Chicago, IL) (Figure 1a), which has a PAC remote control (Dueta[®], GE Healthcare, Chicago, IL) (Figure 1b) between April 2017 and July 2017 at our center were reviewed retrospectively. The time of the previous examination is recorded in our institution for all mammography examinations. Women who never had a mammography before or who had a previous mammography examination more than 2 years ago or who did not want to use the self-compression device were excluded from the study. In total 106 women were included in the study.

Mammography procedure

The technologists or the radiologists in our department informed the patients about the presence of a self-compression system before undergoing the procedure. The technologists explained the procedure to each patient, with emphasis on breast compression. The relationship between breast compression, radiation dose, and image quality was explained briefly and basically. For the first breast (selected randomly), the technologist positioned the breast for the craniocaudal view and initiated a minimum compression of 3 dekanewton to immobilise the breast. Then, the patient used the PAC remote control to complete compression. The remote control is equipped with a '+' key to increase and a '-' key to decrease the amount of compression. This protocol was repeated for the other breast and also for both breasts for the mediolateral oblique views. The patient held the remote control on the other side of the compressed breast to provide easy management for PAC. PAC was under the technologist's control and observation and in case the compression performed by the patient was not found sufficient, she stepped in and supported the patient for further compression. The technologist also rechecked breast positioning including the positioning of the nipple and the pectoral muscle. Afterwards, acquisition of images was performed with 30-50 kV and 100-110 mAs.



Figure 1 a, b. Mammography device (a) and remote control of the patient-assisted compression device (b)

Table 1. Questionnaire

QUESTIONS	RESPONSES	RESULTS	
Q1. Number (n) of previous exams	n years	5.1±3.4 years	
		n	%
Q2. Experience compared to previous exams	Much worse experience	1	0.9
	Somewhat worse experience	3	2.8
	No difference	27	25.5
	Somewhat better experience	25	23.6
	Much better experience	50	47.2
Q3. Level of comfort	Uncomfortable	3	2.8
	Neither comfortable nor uncomfortable	13	12.3
	Comfortable	36	34.0
	Very comfortable	54	50.9
Q4. Level of comfort compared to previous exams	Much less comfortable	1	0.9
	Somewhat less comfortable	2	1.9
	No difference	23	21.7
	Somewhat more comfortable	28	26.4
	Much more comfortable	52	49.1
Q5. Level of anxiety	Not at all anxious	94	88.7
	Slightly anxious	11	10.4
	Very anxious	1	0.9
Q6. Level of anxiety compared to previous exams	Somewhat more anxious	6	5.7
	No difference	44	41.5
	Somewhat less anxious	7	6.6
	Much less anxious	49	46.2
Q7. Attractiveness	Not attractive	26	24.5
	Slightly attractive	9	8.5
	Somewhat attractive	50	47.1
	Very attractive	21	19.8
Q8. Attractiveness compared to previous	Somewhat less attractive	1	0.9
	No difference	63	59.4
	Somewhat more attractive	27	25.5
	Much more attractive	15	14.2
Q9. Impact of design on anxiety	It made me much less anxious	19	17.9
	It made me somewhat less anxious	10	9.4
	It made no difference	76	71.7
	It made me somewhat more anxious	1	0.9
Q10. Impact of PAC on comfort	Much less comfortable	3	2.8
	Somewhat less comfortable	4	3.8
	No difference	14	13.2
	Somewhat more comfortable	23	21.7
	Much more comfortable	62	58.5

Table 1. Questionnaire (Continued)

QUESTIONS	RESPONSES	RESULTS	
Q1. Number (n) of previous exams	n years	5.1±3.4 years	
		n	%
Q11. Impact of PAC on anxiety	Much less anxious	46	43.4
	Somewhat less anxious	22	20.8
	No difference	32	30.2
	Somewhat more anxious	5	4.7
	Much more anxious	1	0.9
Q12. Exam duration compared to previous exams	Much shorter than previous exams	27	25.5
	Somewhat shorter than previous exams	50	47.2
	No difference	27	25.5
	Somewhat longer than previous exams	2	1.8
N: number; PAC: patient-assisted compression			

Survey on the patient's experience

Each patient completed a survey subsequent to the mammography examinations. The participants were given a brief explanation on the survey by the mammography technician. The survey tool was a structured self-completed 12-item questionnaire on patient's experience with regards to physical pain, comfort, anxiety, and exam duration. It also included the number of previous mammography examinations. The questionnaire was available both in Turkish and in English.

Statistical Analysis

Response frequencies for each of the analytical items were analyzed by actual percentage responses to each of the multiple-choice options. Descriptive statistics were used. Continuous values were given by mean and standard deviation. $p < 0.05$ was considered statistically significant.

Results

The questions, responses and results are presented in Table 1.

The mean number of previous examinations is 5.1 ± 3.4 with a median of 4 (min 2-max 20).

In the evaluation of the experience compared to the previous ones, 47.2% of the participants declared that it was a much better experience compared to previous ones. For 70.8% of the participants it was a better experience compared to previous ones.

In the evaluation of the level of comfort, 84.9% of the participants found the examination comfortable; with 50.9% very comfortable. For 75.5% of the participants the examination was more comfortable compared to previous ones.

Only 11.3% of the participants declared that they were anxious and 52.8% of the participants declared that they were less anxious compared to previous examinations.

In the evaluation of impact of PAC on comfort; 80.2% of the participants declared that they found it more comfortable with 58.5% much more comfortable.

In the evaluation of impact of PAC on anxiety; 64.2% of the participants declared that the PAC decreased anxiety.

Mean duration time of the examination was 9.2 ± 1.4 minutes with a median of 10 minutes (min 5-max 10). In the evaluation of exam duration compared to previous exams; 72.6% of the participants declared that the exam was shorter than the previous exams.

Discussion and Conclusion

The results of our study showed that in general patient satisfaction on the experience of the new technology mammography device featuring patient-assisted compression was high. We believe that the presence of having control over the procedure may change their impression on mammography and increase their compliance to the screening programs.

A study by Kornguth et al. (14) reported that 91% of women had low-to-moderate degree of pain during a mammogram. This study provided predictors to pain and one of the variables that were shown to consistently predict pain was pain at the last mammogram. A more recent survey conducted by Padoan et al. (15) highlighted that "fear of pain" was a factor that affects screening compliance. These studies demonstrate the importance of previous mammography examinations in the participation of periodic screening. It has also been reported that the women who undergo mammography for the first time have higher anxiety levels (16, 17). A study conducted by Mendat et al. (18) regarding patient comfort from the technologist perspective showed that "proper communication of exam expectations" was rated to have significantly more impact on patient discomfort as compared to the other options. This indicates the importance of the psychological aspect of an examination.

Previous psychological studies have reported that self-control over a painful procedure helped women to adapt to pain more easily and felt less pain (19, 20). This can be applied to the mammography experience, especially the most distressing part of the examination, which is compression. Verbal control over the degree of compression can provide satisfactory control for some women. However, that may not be sufficient for certain women. To our knowledge there are only two reports in the English literature regarding breast compression by the patient during mammography, even though it is not a new concept. The

first study conducted by Kornguth et al. (10) including a pre-mammography survey of 30 and post-mammography survey of 10 items, reported that the pain experienced was significantly less when the patient controlled the compression paddle. In that study, one breast was initially compressed by the technologist and then the other breast was compressed by the patient herself with a hand-held button. They also demonstrated that there was no difference in adequacy of the images. A very recent study was reported by Balleyguier et al. (11) including 100 female patients using the same mammography device we used in our study. In that study, one breast was also initially compressed by the technologist and then the other breast was compressed by the patient herself with a remote control device. They reported that 70% of the patients assessed the overall procedure as painless. Discomfort and pain was stated by 17% and 13% of the patients, respectively. No significant difference was found in discomfort or pain felt between self-compressed and technologist compressed breast, however they also reported that 74% of the patients declared that this procedure made them more willing to return for their subsequent mammography examination. This supports our notion that self-control can re-construct the women's previous experience and perception of mammography leading to improved uptake and compliance. Also, 90% of the patients found this procedure useful. In that study, image quality was also evaluated and they compared image qualities obtained with PAC and technologist compression (TC). They reported that the image quality obtained by PAC was as good as TC with even higher compression levels, lower breast thickness, and diminished radiation dose.

There are several limitations to our study. Image quality assessment was not included, and image quality assessment including comparison with previous mammograms would make the manuscript stronger. Further studies with recording of breast tissue thickness with PAC and glandular dose for each woman with comparison to previous mammograms can be conducted. In addition, if one breast was initially compressed by the technologist and then the other breast was compressed by the patient herself; the patient could have more understanding of the amount of compression necessary to achieve an adequate compression. Also, a question regarding if they would like to come for another mammography examination after this experience would be useful to evaluate the effect of the new method on reattendance.

In conclusion, women may feel anxiety concerning mammography and self-compression/PAC may be a useful technique for decreasing pain during mammography examinations resulting in compliance of women with screening guidelines. Further studies should be conducted on the efficacy of self-compression to make sure that the image quality is not sacrificed for added patient comfort.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University School of Medicine (2018-12/8).

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

Peer-review: Externally peer-reviewed.

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

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What is the Diagnostic Performance of 18F-FDG-PET/MRI in the Detection of Bone Metastasis in Patients with Breast Cancer?

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ABSTRACT

Objective: To evaluate the diagnostic performance of 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/magnetic resonance imaging (MRI) in the detection of bone metastasis in patients with breast cancer.

Materials and methods: From August 2018 to January 2019, a total of 23 patients with pathologically confirmed invasive breast cancer underwent whole-body hybrid 18F-FDG-PET/MRI for initial staging and follow-up of their malignancies. The number of the bone metastasis was recorded for each patient. The total 18F-FDG-PET/MRI protocol was compared with PET only and the contrast enhanced fused (CE) component for the detection of bone metastasis.

Results: Eight (26%) of 23 patients had bone metastasis. Bone metastases were dominantly localized in the spine (63%) and pelvis (25%). In terms of the total number of detected bone metastasis, there was a statistically significant difference between 18F-FDG-PET/MRI (mean 3.57; median 0; range, 0-2) and PET only component (mean 2.87; median 0; range, 0-1) ($p=0.026$), but no statistically significant difference was detected between 18F-FDG-PET/MRI and whole-body CE MRI (mean 3.43; median 0; range 0-2) ($p=0.083$).

Conclusion: Whole-body hybrid 18F-FDG-PET/MRI is superior to PET component only, but no statistically significant difference between hybrid 18F-FDG-PET/MRI and whole-body CE MRI is found for the detection of bone metastasis in patients with breast cancer.

Keywords: 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/magnetic resonance imaging (MRI), breast cancer, bone metastasis

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Introduction

Breast cancer is the most frequent cancer in women and initial staging and follow-up is very important for treatment and survival. The presence of distant metastases at the initial examination changes the treatment strategy and options. The most frequent locations for breast cancer metastasis include the liver, lungs, and bone (1). 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) and whole-body magnetic resonance imaging (MRI) are generally used for initial staging or when distant metastases are suspected (2-4). Whole-body hybrid FDG-PET/MRI is another modality that provides initial staging and may also improve the detection of metastases and recurrent disease (5-11). PET/MRI scanners have the potential to become an effective tool for the evaluation of oncology patients and influence patient management (12, 13). FDG-PET/MRI combines the sensitivity of molecular imaging of PET and the superior radiologic diagnostic capabilities of MRI. In addition, FDG-PET/MRI provides detailed background anatomic landmarks from MRI images.

Bone metastases are seen in 8% of all patients with breast cancer and the percentage increases with advanced disease (14-16). Tumor cells spread hematogenously and at the beginning intramedullary lesions are found in the red marrow. The lesions can be osteolytic, osteoblastic or mixed (17). Bone scintigraphy is used widely for its low cost and ability to cover whole-body (18). However, FDG-PET/CT has been shown to be an effective tool for the staging and detection of bone metastasis (19-21). Whole-body CE MRI, with its bone marrow-sensitive techniques, has been shown to have higher sensitivity than FDG-PET/CT for the detection of bone metastasis. Hence, a combination of metabolic information provided by FDG-PET/CT and the high soft tissue resolution of MRI increases the detection rate of bone metastasis.

Materials and Methods

In our study, we retrospectively evaluated 23 patients with invasive breast cancer from August 2018 to January 2019. The Bilim University Institutional review board approved the study; the requirement of informed consent was waived because the study was a retrospective investigation. Inclusion criteria were newly diagnosed or recurrent breast cancer with clinical indication for staging and follow-up. Exclusion criteria were MRI general contraindications, pregnancy and patients with less than 12 months follow-up and no pathology reports. Six of the patients had prior FDG PET/CT and 3 of them had bone scintigraphy in other institutions. Also, 3 of the patients had CE MRI and 1 of them had FDG-PET/MRI in our institution. We extracted the results from their reports. For the rest of 10 patients, FDG-PET/MRI was the initial imaging for staging and follow-up.

All patients fasted for at least 6 hours before imaging. The blood glucose level was assessed with a blood glucose meter (OneTouch Vita; LifeScan, Milpitas, California, USA) before imaging to ensure that it was less than 140 mg/dL (7.77 mmol/L).

18F-FDG-PET/MRI was performed 60±6 minutes after the injection of FDG (mean dose, 4.54 MBq per kilogram of body weight±1; range, 370–400 MBq). The images were acquired with the patient in the supine position on a 3 Tesla Biograph mMR scanner (Siemens Healthcare, Erlangen, Germany) using a 16-channel head and neck surface coil and three 12-channel body coils. The whole-body images

were obtained in five to six bed positions according to the size of the patient. PET acquisition occurred simultaneously during the whole-body MRI acquisition. In all patients, the whole-body FDG-PET/MRI covered the entire body from head to knee. PET attenuation correction was performed using four-compartment model attenuation map calculated from a Dixon-based VIBE (volumetric interpolated breath-hold examination) sequence. The MRI protocol consisted of T2-weighted single-shot echo train (HASTE) (TR/TE, 1500 msec / 87 msec) in the coronal plane, T1-weighted slice-selective Turbo Flash (TR/TE, 1600 msec / 2.5 msec) and free breath diffusion-weighted imaging using the Eoplanar Imaging technique (EPI) (TR/TE, 12000 msec / 78 msec, b=0 s/mm² and b800 s/mm²) in the axial planes. After the non-contrast enhanced (NCE) protocol was performed, a weight-adapted dose of a gadolinium-based contrast agent (was administered, and serial CE images were obtained using breath-hold 3D VIBE (TR/TE, 4.56 msec / 2.03 msec) in the arterial, portal venous, and equilibrium phases covering the upper abdomen in the axial plane. After the serial CE images were acquired, continuous breath-hold 3D VIBE images were obtained from head to knee in the axial plane. All sections were then combined, resulting in uninterrupted whole-body coverage.

Images were evaluated by a radiologist with 10 years' experience in body MRI reading and 5 years' experience in hybrid imaging. The data were analyzed on a dedicated workstation (Syngo Via; Siemens Healthcare, Erlangen, Germany). The number of bone metastasis was recorded for each patient.

Statistical analyses were performed using Statistical Package for Social Sciences for Windows software version 25 (IBM Corp.; Armonk, NY, USA). The variables were investigated using the Kolmogorov-Smirnov test to determine whether the distribution was normal. Due to the fact that most variables except for age were not normally distributed, Friedman's test was conducted to evaluate whether there was a significant change in the total number of detected bone metastasis among the different sequences. Pairwise comparisons were performed using the Wilcoxon signed-rank test. A p-value of less than or equal to 0.05 was accepted as statistically significant.

Results

Twenty-three women with pathologically confirmed breast cancer were included in our study. The women were aged between 23–80 (mean ± standard deviation, 47.7±12.9) years. All patients included in the study were stage 3 or higher at the time of diagnosis. Eight of the 23 patients had bone metastasis (26%). Bone metastases were dominantly localized in the spine (63%) and pelvis (25%).

Breast carcinoma was histopathologically confirmed in surgical specimen or using a tru-cut biopsy for every patient. Three patients (13%) were determined to have bone metastases after histopathologic confirmation through surgery and Tru-cut biopsy. The other 20 (87%) patients had prior 18F-FDG-PET/CT, bone scintigraphy, CE MRI, 18F-FDG-PET/MRI for follow-up and the metastases were recorded as malignant after a comparison of these modalities. For cases without pathology results the mean follow up period was 18.5 months (range: 12–36 months) and was used as the standard of reference. The number of metastases detected using 18F-FDG-PET/MRI (mean 3.57; median 0; range, 0–2) was significantly higher than in the PET component only (mean 2.87, median 0; range, 0–1) (p=0.026) (Figure 1). There was no statistical difference between the bone metastases detected with FDG-PET/MRI (mean 3.57; median 0; range 0–2) and CE MRI

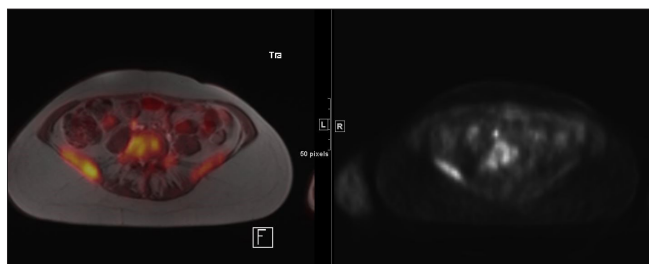


Figure 1. a, b. PET/MR (a, b) of a 37-year-old patient with grade 3 invasive ductal carcinoma. The axial plane PET/MR fusion image (a) shows bilateral iliac and vertebral body metastatic lesions; the corresponding PET image does not show the left iliac metastatic lesion

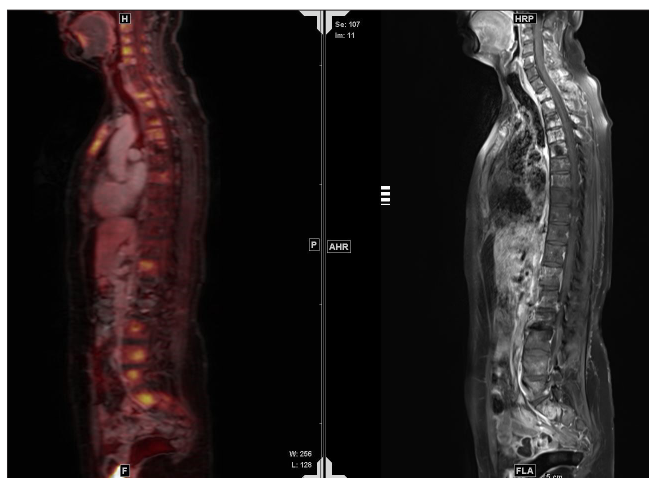


Figure 2. a, b. A 35-year-old patient with grade 3 invasive ductal carcinoma of the left breast. Fused PET/MR and sagittal Dixon T1W MR images (a, b) both show similar metastatic lesions

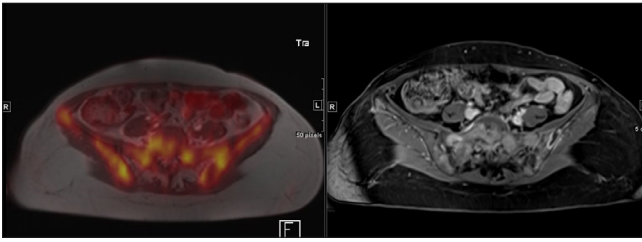


Figure 3. a, b. PET/MR (a, b) of the same patient with grade 3 invasive ductal carcinoma. The axial plane PET/MR fusion image (a) shows bilateral iliac, sacral and vertebral body metastases and the corresponding axial Dixon T1W MR shows similar metastatic lesions

(Figure 2, 3) (mean 3.43; median 0; range 0-2) ($p=0.083$). CE MRI superior to PET for the detection of bone metastasis, but the statistical significance was not as high as with FDG-PET/MRI ($p=0.042$).

Discussion and Conclusion

The presence of bone metastasis has an important effect on morbidity and mortality (22). Early stage breast cancer incidence is increasing with improved screening techniques and diagnosis of cancer at in situ stage increases survival. Therefore, optimal assessment for treatment planning may avoid unnecessary chemotherapy and early detection enables accurate staging and management of therapy (23, 24). 18FDG-PET/MRI is a new and promising tool in oncologic imaging and may improve the detection of early bone marrow infiltration and increase diagnostic confidence in the assessment of bone metastasis (25).

Our data showed that the combined evaluation of PET and MRI with post-contrast VIBE images increased the detection rate of bone metastases. Previous studies have shown that CE MRI and DWI have similar sensitivities for the assessment of bone metastases (26), but only FDG-PET/CT has lower sensitivity than these modalities. FDG-PET is not sensitive for hypometabolic metastasis and increased bone marrow activity after chemotherapy (27-29). Therefore, in PET/MRI, even in cases of low FDG activity, the likelihood of correct detection and staging seems to be higher than PET/CT. (30).

The metabolic information from PET data together with the diagnostic accuracy of CE whole-body MRI without radiation exposure may increase the sensitivity of detection. FDG-PET/MRI showed superior lesion detection than only PET component in our study and this may reflect the superiority of PET/MRI over PET/CT with its ability to assess early infiltration of bone marrow with malignant tissue, as mentioned in the literature (31). However, we found no significant difference between CE MRI and FDG-PET/MRI, probably because of the absence of hypometabolic metastases in our study group.

Diagnostic ability of the various radiopharmaceuticals depends on the type of the metastases. 18F-FDG is superior to other tracers in the detection of osteolytic pattern, while sclerotic lesions show low glycolytic activity are well identified by 18F-NaF PET and bone scintigraphy. The low specificity and planar resolution of planar scintigraphy and SPECT are the limitations that may decrease the ability of these techniques to identify early bone infiltration. 18F-NaF PET and other bone-seeking radiopharmaceuticals identify osteoblastic reaction around the metastatic lesion of the bone and is not tumor specific (32-34). Sonni et al. (35) found that the ability of Na[18F]F/[18F]FDG PET/MRI is superior than ^{99m}Tc -MDP WBBS and Na[18F]F/[18F]FDG PET/MRI is a promising tool for the evaluation of metastatic and extra-skeletal lesions.

Our study has limitations, including the limited number of patients and lack of histopathologic confirmation for every lesion. The results should be considered as preliminary and larger studies are needed to show the potential of FDG-PET/MR.

In conclusion, our results showed that FDG-PET/MRI may be beneficial over PET/CT and bone scintigraphy in breast cancer patients with only few early bone metastasis without radiation exposure.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Bilim University Institutional Review Board (No. 28.06.2016/51-06).

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

Peer-review: Externally peer-reviewed.

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Oncological Safety of Lipofilling in Healthy BRCA Carriers After Bilateral Prophylactic Mastectomy: A Case Series

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ABSTRACT

Objective: The germline breast cancer gene (BRCA) mutation confers a lifetime high risk for breast cancer (BC) and bilateral prophylactic mastectomy is the procedure which allows the highest risk reduction rate. Among other techniques, lipofilling (LF) can be used for breast reconstruction of these patients. However, there are some oncological safety concerns on the subject. The purpose of this study was to assess the oncological risk of LF in BRCA healthy patients.

Materials and Methods: A single institution case series was built including BRCA I/II mutated patients with no previous history of BC, who underwent bilateral prophylactic mastectomy followed by breast reconstruction with exclusive LF or combined with implants or latissimus dorsi flap. Data were collected regarding patient demographics, clinical information, reconstruction techniques used, and fat grafting details.

Results: From September 1999 till November 2017, we identified 18 BRCA carriers with no history of BC who had undergone bilateral prophylactic mastectomy, followed by breast reconstruction with LF. A total of 36 LF procedures were performed following an implant or latissimus dorsi flap, or as an exclusive fat grafting breast reconstruction. The average number of LF sessions was 1.4 with a mean volume of 108.8cc per breast. Median follow-up was 33.0 months after mastectomy and 24.5 months after the last LF intervention; no patients were diagnosed with BC during follow-up.

Conclusion: Germline BRCA mutation is a high-risk plight for BC. However, despite the limited follow-up, no BC was detected.

Keywords: BRCA mutation, breast cancer, prophylactic mastectomy, fat grafting, lipofilling, breast reconstruction

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Introduction

The breast cancer genes (BRCA) I and II are two different tumour suppressor genes responsible for the repair of damaged deoxyribonucleic acid (1). When mutated, they carry a breast cancer (BC) lifetime risk up to 72% for BRCA I and 69% for BRCA II (2). Nowadays, identifying a BRCA-mutated patient has multiple implications, since it determines how the oncological team may individualize treatment of an affected patient, and provides the cancer-free related family members with access to preventive professional guidance (3, 4). Therefore, management strategies for non-affected germline BRCA carriers must be weighted, with the decision-making process involving a pivotal plight between closer clinical surveillance and prophylactic interventions. Amidst definitive procedures, bilateral prophylactic mastectomy (BPM) conceives the highest protection for BC, with a risk-reduction of more than 90% (5, 6).

Patients who undergo BPM procedures are driven by the distress of cancer risk and reconstructive techniques are offered to balance surgical burden (7). These reconstruction strategies are based on implants devices, autologous tissues or the combination of both procedures (8). More recently, lipofilling (LF) has become widely popular among surgeons. The technique has been demonstrated to be effective in breast reconstruction and can be used exclusively or associated with implants and flaps. Its versatility stems from correction of moderate sequelae until complete reconstruction of the breast contour (9-11).

Besides the comprehensive debate over the oncological safety of LF, actual data does not condemn this procedure (12-17). Nonetheless, there is currently a lack of knowledge pertaining to the subject. Additionally, the relation between LF and high-risk patients such as healthy mutated carriers is yet to be fully described. Bearing this in mind, the purpose of this study was to evaluate the oncological safety of LF on unaffected BRCA carriers, who experienced prior BPM.

Materials and Methods

This is a non-analytical observational study. Data was collected from prospectively maintained medical records. Study approval was granted by the Institut du Sein des Deux Rives – Clinique Rhena Ethical Committee before the study. Written informed consent was obtained from all patients.

Study population

Between September 1999 and November 2017, unaffected BRCA mutated women who had undergone BPM followed by LF, were elected to this cohort. Patients genetically classified as having a BRCA variant of unknown significance were excluded from the analysis, as were those found to have an occult breast carcinoma on the final pathology report after the BPM. All patients included underwent prophylactic and reconstructive surgical procedures at our institution. The study group included patients who had undergone BPM followed by immediate breast reconstruction, whether it be implant-based, with autologous tissue, or combination of both. Patients who had undergone expander and posterior final implant placement were included. The autologous flap employed was the latissimus dorsi (LD) flap. Fat grafting was used as a secondary technique, always performed when the previous reconstruction technique used did not need further re-interventions. The only exception was the complete fat grafting reconstruction, in which LF was the first procedure after the BPM.

Data research

Clinical files were reviewed to collect patient demographics, risk factors, BRCA statements, any previous oophorectomy procedures, prophylactic mastectomy and breast reconstruction details. Recipient and donor site complications were also reviewed. The follow-up was stated as the time between the last LF procedure and the last clinical visit. Clinical assessments and registered exams were analysed.

Technical aspects

The preoperative assessment included clinical interview and physical examination. Eligible patients underwent a preoperative imaging survey with mammography, breast ultrasound and breast magnetic resonance. All images were reviewed and approved by a radiologist.

All procedures were conducted under general anaesthesia. In order to formulate an individual surgical plan for each patient, the surgeon examined the morphology of the patient and explored the best possibilities for mastectomy and subsequent reconstruction in accordance with the individual characteristics of the patient. This was followed by a shared decision-making process. Both total and skin-sparing mastectomies (skin and nipple) were performed. For immediate reconstruction only, expanders, direct-to-implants and LD flaps were used. Exclusive LF was offered in a delayed timing of the procedure. We do not routinely perform sentinel node biopsy for prophylactic mastectomy.

Follow-up regimen for postoperative imaging and surveillance was scheduled with clinical visits at 1, 2, 6 and 12 months during the first year after BPM or LF procedures. Subsequently, clinical assessment was biannual. Imaging surveillance included magnetic resonance and mammogram, which were performed alternately every six months.

LF technique

The technique employed is a modified version of that described by Coleman (18). The choice of the donor site depended on each patient's morphologic distribution, and no previous subcutaneous infiltration was performed. The fat was primarily harvested from abdo-

men, thighs and lumbar areas. The donor site was then infiltrated with a solution composed of 500ml of saline, 1mg of epinephrine tartrate (Adrenaline Renaudin® 1mg/mL; Renaudin Laboratoire, Ixassou, Nouvelle-Aquitaine, France) and 150 mg of chlorhydrate of ropivacaine (Naropin® 7.5 mg/mL; AstraZeneca, Courbevoie, France). The collected fat was centrifuged for 20 – 30 seconds at 3000 rpm, isolating blood cells and plasma from the specimen. The purified fat was separated from the other contents and set for injection in 10mL BD Luer-Lok syringes (BD Plastipak™; Becton Dickinson, Grenoble, France). A 2 mm cannula was used for LF injection in both subcutaneous and muscle layers.

Statistical Analysis

Descriptive statistics such median, interquartile and range, or means and standard deviations were used to describe continuous values considering variable normality (assessed by graphical analysis and Shapiro-Wilk test) and outliers. Categorical variables are presented by their frequencies and proportions. Statistical analyses were conducted using Statistical Package for Social Sciences for Windows version 23.0 (IBM Corp.; Armonk, NY, USA) for Windows.

Results

General aspects

A background analysis identified 18 germline BRCA patients with no history of BC submitted to BPM and breast reconstruction with LF. The BPM and LF procedures were performed respectively from September 1999 until June 2016, and from October 2010 until February 2017. There were 77.8% (14/18) BRCA I patients and 22.2% (4/18) BRCA II. The patients' median age was 43 years (interquartile range [IQR], 36 – 49 years) at the first LF intervention. The median follow-up was 33.0 months after mastectomy, 4.5 months between BPM and LF, and 24.5 months after the last LF procedure. No primary BC was reported during follow-up surveillance. (Table 1)

Prophylactic mastectomy and immediate reconstruction details

Regarding the prophylactic procedures, there were 55.6% (10/18) nipple-sparing mastectomies, 38.9% (7/18) skin-sparing mastectomies and one 5.6% (1/18) total mastectomy. For immediate reconstruction, 44.4% (8/18) patients received expanders, 33.3% (6/18) went directly for implants, 16.7% (3/18) underwent LD flaps (no implant associated), and 5.6% (1/18) went exclusively for LF. All the patients that primarily received an expander, then proceeded to definitive silicone implant placement in a subsequent procedure. The mean breast weight was 472g ± 318g. No occult BC was detected on the final pathological analysis.

Lipofilling details

Most of the breasts (72.2%) (26/36) underwent only one LF intervention, and the mean session volume was 135±78cc per breast. Patients submitted for implants needed one (85.7%), two (3.6%) or three (10.7%) LF sessions. Patients submitted for LD flap reconstruction needed one (33.3%) or two (66.7%) sessions of LF and the exclusive reconstruction with fat required four interventions with a mean volume injected per session of 118cc, achieving a total of 474cc. Concerning the final reconstruction, the total mean volume injected per breast was 194±150cc, with an average total volume of 124±60cc for prosthesis and 429±117cc for LD flaps. (Table 2)

All the patients presenting with regular donor and receptor site hematoma were clinically assisted. No other complications were reported.

Table 1. Patients characteristics

Variable	All (n=18)
Age, yr (IQR)	43.8 (36–49)
BMI, (kg/m ² – mean±SD)	26.6±6.4
Diabetes	–
Hypertension	–
Smoking	1 (5.6)
Allergy	2 (11.1)
Type of mastectomy	
NSM	10 (55.5)
SSM	7 (38.9)
Total Mastectomy	1 (5.6)
Mastectomy weight, gr – mean±SD	472±318
Type of reconstruction	
Implant	14 (77.7)
LD flap	3 (16.7)
LF exclusive	1 (5.6)
Definitive implant volume, cc – mean±SD	367±124
FU after mastectomy, mo – median	33
FU from mastectomy to first LF, mo – median	4.5
FU after last LF, mo – median	24.5
All data presented as N (%) unless otherwise specified SD: standard deviation; BMI: body mass index; NSM: nipple sparing mastectomy; SSM: skin sparing mastectomy; LD: latissimus dorsi; LF: lipofilling; FU: follow-up	

Discussion and Conclusion

To date, the only study regarding LF in healthy BRCA patients was published by Kronowitz et al. (19) in 2016. This matched cohort described a group of thirty-three healthy BRCA patients submitted to BPM and LF reconstruction. They reported a mean follow-up of 33.6 and 18.4 months after BPM and LF, respectively, and no primary BC was detected during vigilance. Kronowitz analysed a group that underwent BPM and LF, respectively from 1981 until 2013, and from 2001 until 2014 (19). Other than the distant historical times between BPM and LF presented in their study, the results were consistent with those presented by our descriptive analysis (36.0 and 26.2 mean follow-up months after BPM and LF, respectively). As a natural response to the lack of data, specialties societies still recommend caution when performing LF on high-risk patients, particularly mutation carriers (20, 21).

To determine the oncological risk of LF on BRCA healthy individuals, it is crucial to discern the microenvironment path from normal to cancer cells and to identify which factors are related. Fat tissue is a known rich source of multipotent mesenchymal stem cells (MSCs), termed adipose stem cells, (22) and one of the physiological roles of the MSCs is the homing ability of being recruited to repair injured tissues (23). Several studies have suggested that MSCs have the ability to participate in primary and metastatic tumour development, thus playing an important role in tumour progression (24, 25). This is theoretically related to the similar microenvironment mechanism of wound healing and cancer cell proliferation (26). Cytokines and growth factors, such as platelet-derived growth factor and vascular endothelial growth factor, mediate a crosstalk between epithelial cells and surrounding stromal cells that are crucial for cancer initiation, progression and metastases (27). In a study by Massa et al. (28), an in vitro evaluation was performed with three BC cell lines in direct contact with human fat tissue and bone marrow fibroblasts. They observed a high proliferation

Table 2. Lipofilling characteristics (per breast)

Variable	Primary Reconstruction Procedures			
	All (n=36)	Implant (n=28)	LD flap (n=6)	LF exclusive (n=2)
Number of sessions – mean±SD	1.5±0.9	1.3±0.6	1.7±0.5	4.0±0.0
1	26 (72.2)	24 (85.7)	2 (33.3)	–
2	5 (13.9)	1 (3.6)	4 (66.7)	–
3	3 (8.3)	3 (10.7)	–	–
4	2 (5.6)	–	–	2 (100.0)
Volume injected per sessions, cc – mean±SD	135±78	107±48	270±65	118±1
Total volume injected, cc – mean±SD	194±150	124±60	429±117	474±2
<100 cc	11 (30.6)	11 (39.3)	–	–
101–200 cc	15 (41.7)	15 (53.6)	–	–
201–300 cc	2 (5.6)	2 (7.1)	–	–
301–400 cc	3 (8.3)	–	3 (50.0)	–
401–500 cc	3 (8.3)	–	1 (16.7)	2 (100.0)
>501 cc	2 (5.6)	–	2 (33.3)	–
All data are presented as N (%) unless otherwise specified LD: latissimus dorsi; LF: lipofilling; SD: standard deviation				

rate of BC cells in contact with unprocessed lipoaspirate tissue (2.31 folds in 48 hours) and apparently, no interaction between bone marrow fibroblasts and cancer cells (28).

The final LF injected specimen contains fibroblasts, adipose stem cells and preadipocytes at a different maturation stage. The act of infiltration provokes an injury at the receptor tissue site, which induces the adipose stem cells to differentiate and set up the wound healing micro-environment (22). It is considered perilous to perform this procedure on a site with the risk of containing dormant cancer. However, when LF procedures were performed in patients previously treated for BC, the cancer recurrence rates did not increase. In addition, it is worthy of note that regardless of the surgical treatment type, with lumpectomy or mastectomy, the result in terms of oncological control was the same (12-17). For instance, Petit et al. (16) published a large retrospective study with 513 patients submitted to LF after BC, in which 370 women underwent mastectomy, and the local regional recurrence rate was 1.38% with a mean follow-up of 19.2 months after LF. Consistent with this data, Silva-Vergara et al. (15) reported a 1:2 case-controlled study with 147 patients submitted for mastectomy followed by LF, and the cumulative relapse rate was 3.4% and 4.2% in cases and controls groups, respectively.

The liaison between adipose tissue and tumour cells is far more complex than expected. Cancer proliferation support apparently relies on mesenchymal stromal surroundings, which chemotactically sense the hypoxia and inflammatory activity of the tumour cells, and collectively enhance the cancer trophic environment. Besides the induction of collagen matrix deposit and vascular proliferation, there is a favourable ambiance which blocks anti-tumour immune response, secretes anti-apoptotic factors and provides a propitious mitogenic context (14, 29). Concerning the aforesaid pathways, there is lack information about the trigger mechanism of silent tumour cells. In fact, the scientific knowledge so far indicates that the synergy between fat tissue, its stem cells, adipokines and vascular-inducing factors seems to organize and differentiate the adjacency tissue, and not induce the activation of dormant cancer cells (30).

The adipocyte microenvironment and its capacity to induce the replication of silent tumour cells is the tight-spot question for high-risk mutated patients. BRCA-affected patients are often submitted for other clinical treatments and the interaction between adipocytes and cancer cells may be underestimated in a mutated healthy patient. Without sustainable knowledge about subcutaneous tissue behaviour, its paracrine loop and influence on cells replication pathways, a definitive medical statement is still unwise.

In addition, some limitations should be mentioned. Firstly, this is a non-analytical study without a control group. In France, the consensus recommendation for LF in BRCA patients that had a history of BC presents some strict indications and should be performed with a minimum of two years' delay. Having said that, the affected sample taken from our database was limited and most patients were lost during follow-up. Secondly, the restricted sample size presented compromised statistical measurements and precluded significant relationships based on the collected data. Thirdly, there is a limited number of publications about the subject, which compromised the final statements.

To incorporate LF as a safe procedure, it is essential to be familiar with the physiology of the adipocyte microenvironment and whether it acquires a silent tumour replication capacity or not. Currently, LF does

not seem to increase BC incidence in patients with germline BRCA mutation who previously underwent BPM. It is important for patients to be aware that despite the LF being considered a low-risk procedure and our positive result, more data is needed to guide the oncological safety of LF for BRCA patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Institut du Sein Des Deux Rives - Clinique Rhena.

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

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Comparison of Clinical Features and Treatment Results of Mix Mucinous Carcinomas and Other Atypical Carcinomas of the Breast

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ABSTRACT

Objective: There are multiple subtypes of breast cancer with different biological and pathological features and accordingly exhibit different clinical behaviors. The aim of this study was to compare the treatment modalities, clinical features and prognostic characteristics of Mix Mucinous Carcinomas (MMBC) and other rare tumors of the breast.

Materials and Method: A total of 2152 patients who were operated on for breast cancer in our clinic between 2010-2019, with pathological diagnoses of tubular, pure mucinous, mix mucinous or papillary carcinoma were enrolled in the study. Patients were divided into two groups as mix mucinous patients (Group1) and other rare tumors (Group2). The demographic, clinical and prognostic characteristics and treatment approaches were compared between Groups, and additionally between the subtypes of Group 2.

Results: 42 patients participated in our study. Group 1 consisted of 7 patients, and Group2 consisted of 35 patients. The subtypes in Group2 were papillary (n=21), pure mucinous (n=10) and tubular (n=4). Progesterone Receptor Positivity was found to be significantly higher in Group 2 patients than in Group1 patients (p=0.005, p<0.05). Multicentricity rates in the tumors of the patients in Group1 were found to be statistically significantly higher than the patients in Group 2 (p=0.024, p<0.05). In subtype analysis in Group2, there were no statistically significant differences parameters in the subgroups (p>0.05). Mean survival was 19.5+5.6 (8.5-30.5) months in Group 1 and 46.3+5.2 (36.1-56.6) months, in Group2 when evaluated separately (p:0.002).

Conclusion: The prognosis of pure mucinosis (PMBC) and other atypical cancers of the breast compared to the (MMBC) is quite good. Rare pathological types of breast cancer can have favorable outcomes when treated with necessary oncological principles.

Keywords: Breast neoplasms, pure mucinous breast carcinoma, mix mucinous breast carcinoma

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Introduction

Breast cancer accounts for about 23.8% of all cancers seen in women around the world with around 1,380,600 new cases and 458,000 deaths per year. Looking at the statistics of Turkey in 2015, breast cancer is the most common cancer in women and the incidence is 43.8/100,000 (1, 2).

According to the World Health Organization (WHO) classification, breast cancer can be classified into 21 distinct histological types based on cell morphology, growth and architecture patterns (3). Histopathological classification has a prognostic value. The most common histological type is invasive ductal breast (4).

Invasive papillary carcinoma of the breast constitutes approximately 0.5% of all new breast cancer diagnoses and is the most common breast cancer, usually seen in postmenopausal women. Invasive papillary carcinoma (IPC) is defined as having papillary architecture in >90% of the invasive component (5, 6).

Tubular carcinoma is a well-differentiated breast carcinoma and constitutes less than 2% of all breast carcinomas. This tumor is composed of distinct, well-differentiated tubular structures with open lumens that are lined by a single layer of epithelial cells (3, 7).

Mucinous breast carcinoma, also known as colloid or gelatinous carcinoma, is a rare type and constitutes 1-6% of breast carcinomas. In histopathological examination, small cell islands and glandular structures consisting of uniform cells floating in large extracellular mucin lakes are seen. Hormone receptors are usually positive, the human epidermal growth factor (HER-2/neu) is usually negative (8). Mucinous is defined as a tumor with a mucinous component of 50% or more and divided into pure and mixed subgroups according to the amount of cellularity.

Prognosis of pure mucinosis (PMBC) and Mix Mucinous Carcinomas (MMBC) have a significant distinction between tumor behavior and treatment outcomes. PMBC has a favorable prognosis due to slow growth rates, reduced tumor cell load per unit volume and low lymph node metastases rates, whereas MMBC usually has a worse prognosis, similar to invasive ductal carcinomas. Most studies have reported that PMBC has a slower growth rate and a better prognosis with lower frequency of axillary lymph node metastasis than MMBC (9-11). The 10-year survival reported for PMBC is 87-90%, and for MMBC it is 54-66% (8).

The aim of this study was to compare the treatment modalities, clinical features and prognostic characteristics of MMBC and other rare tumors of the breast.

Materials and Method

A total of 2152 patients who were operated on for breast cancer in Erciyes University General Surgery Department between 2010-2019 were enrolled in the study, after the obtainment of the informed and numbered approval from the Erciyes University School of Medicine Ethics Committee. The final pathological diagnoses of the patients were retrospectively reviewed from the pathology records. Forty-two patients with Tubular, Pure Mucinous, Mix Mucinous or Papillary carcinoma were included in the study. Tumor typing was made according to the World Health Organization criteria (3). Patients were divided into two groups as mix mucinous patients (Group 1) and other rare tumors (Group 2). A common database was created by examining patient files and hospital information system and breast council records. Patient data were evaluated retrospectively using this database. Group 1 and Group 2 were compared. Additionally, the subtypes in Group 2 were compared. The compared parameters include the following; demographic characteristics, comorbid diseases, family history of breast cancer, oral contraceptive use, neoadjuvant chemotherapy status, Breast Imaging and Data System (BI-RADS) as the radiological scoring system (12), tumor localization, multicentricity, multifocality, applied surgical procedure, number of axillary pathological lymph nodes, tumor diameter, receptor status, HER2/neu gene over expression status and pathological stage. Breast cancer was staged according to the sixth edition of the American Joint Committee on Cancer Staging Manual (13). Neoadjuvant treatment was given to locally advanced tumors. Histological diagnosis was confirmed by surgery core-needle biopsy or frozen section during surgery. SLNBs were performed using blue dye and radiocolloid injections. All patients received a lymphoscintigraphy on the day of surgery. The dose of the injected radioisotope was 10-12 MBq (on the day of surgery). Patients were surgically treated by either total mastectomy or breast-conserving surgery. ALND was performed for Level I and II LNs if any macrometastases or micrometastases in SLN were detected in the frozen section analysis. Multifocal breast cancer is defined as a case in which multiple invasive foci existed in the same quadrant, and multicentric cancer was defined as one in which

the multiple invasive lesions were interspersed in the pleural quadrants. Treatment decision making was made in a multidisciplinary tumor board setting attended by surgeons, medical oncologists, and radiation oncologists specializing in breast cancer ER, PR, and HER2 receptor statuses were established on the resected primary tumor or on the core biopsy sample. PR and ER statuses were assessed by Allred scores, with an Allred score of 3 or more indicating ER or PR positivity (14, 15). HER2 expression was examined by immunohistochemical (IHC) analysis. A gene amplification assay using fluorescence in situ hybridization was used in cases where it was difficult to decide the HER2 status by IHC. The mean survival duration and cause of mortality were obtained from the population registry information. Statistical Package for the Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA) package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as means and standard deviations (median and minimum-maximum where necessary). Chi Fisher test statistics were used to compare categorical variables. In the comparison of continuous measurements between the groups, the distributions were controlled and Student T test was used for the parameters that normally distributed according to the number of variables. Mann-Whitney U test was used for the parameters not showing normal distribution. Kaplan-Meier analysis and Log Rank test were used for survival analysis. Statistical significance level was taken as 0.05 in all tests. This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Before the operation, patients were informed about the operation and a written consent was obtained.

Invasive ductal carcinoma (IDC), invasive lobular carcinoma, rare non-invasive tumors and patients whose data were not available were excluded from the study.

Results

42 patients participated in our study. Group 1 (mix mucinous) consisted of 7 patients, and Group 2 (other rare tumors) consisted of 35 patients. The subtypes in Group 2 were papillary (n=21), pure mucinous (n=10) and tubular (n=4). There were no statistically significant differences between Group 1 and Group 2 in terms of the age of patients, estrogen receptor status, history of oral contraceptive use, family history of breast cancer, radiological BI-RADS, tumor localization, multifocality, neoadjuvant therapy, surgical treatment method, tumor diameter, pathological lymph node number, pathological stage, postoperative duration of stay, postoperative radiotherapy, chemotherapy, endocrine therapy and targeted treatment (Table 1).

Progesterone Receptor Positivity was found to be significantly higher in Group 2 patients than in Group 1 patients ($p=0.005$, $p<0.05$) (Table 1). Comorbid diseases were found to be statistically significantly higher in Group 1 than in Group 2 patients ($p=0.038$, $p<0.05$) (Table 1).

The rate of patients with breastfeeding history in Group 2 was found to be significantly higher than the patients in Group 1 ($p=0.048$, $p<0.05$) (Table 1). In the history of surgery variable, the patients in Group 2 had a significantly higher rate of appendectomy, TAH + BSO (total abdominal hysterectomy with bilateral salpingo-oophorectomy) and those without any surgical history than those in Group 1 ($p=0.031$, $p<0.05$). Multicentricity rates in the tumors of the patients in Group 1 were found to be statistically significantly higher than the patients in Group 2 ($p=0.024$, $p<0.05$).

Table 1. Patient, tumor, and treatment characteristics

Measurements		Group 1 n: 7	Group 2 n: 35	p*
Age (min-max)		56.7+11.6 (38-73)	56.6+12.3 (34-85)	0.982
Estrogen	Negative	0 (0.0)	2 (5.7)	0.691
	Positive	7 (100.0)	33 (94.3)	
Progesterone	Negative	6 (85.7)	9 (25.7)	0.005
	Positive	1 (14.3)	26 (74.3)	
Her2/neu	Negative	7 (100.0)	25 (71.4)	0.125
	Positive	0 (0.0)	10 (28.6)	
Comorbidity	No comorbid disease	2 (28.6)	24 (68.6)	0,038
	Singular disease	4 (57.1)	5 (14.3)	
	Double disease	1 (14.3)	6 (17.1)	
Oral contraceptive	Yes	0 (0.0)	4 (11.4)	0.468
	No	7 (100.0)	31 (88.6)	
Breastfeeding history	Yes	4 (57.1)	32 (91.4)	0.048
	No	3 (42.9)	3 (8.6)	
Family history	Yes	0 (0.0)	3 (8.6)	0.570
	No	7 (100.0)	32 (91.4)	
Surgical history	Appendectomy	0 (0.0)	1 (2.9)	0.031
	BCS	1 (14.3)	0 (0.0)	
	TAH+BSO	1 (14.3)	6 (17.1)	
	Total Thyroidectomy	1 (14.3)	0 (0.0)	
	None	4 (57.1)	28 (80.0)	
Pre-op Imaging BI-RADS	3	1 (14.3)	1 (2.9)	0.136
	4	0 (0.0)	1 (2.9)	
	4A	2 (28.6)	6 (17.1)	
	4B	0 (0.0)	1 (2.9)	
	4C	0 (0.0)	18 (51.4)	
	5	4 (57.1)	8 (22.9)	
Localization	Bilateral	0 (0.0)	1 (2.9)	0.800
	Right	3 (42.9)	18 (51.4)	
	Left	4 (57.1)	16 (45.7)	
Multicentricity	Yes	2 (28.6)	0 (0.0)	0.024
	No	5 (71.4)	35 (100.0)	
Multifocality	Yes	0 (0.0)	3 (8.6)	0.570
	No	7 (100.0)	32 (91.4)	
Neoadjuvant	Yes	0 (0.0)	2 (5.7)	0.691
	No	7 (100.0)	33 (94.3)	
Surgery	Mastectomy	4 (57.1)	9 (25.7)	0.118
	BCS	3 (42.9)	26 (74.3)	
Tumor diameter	T1	2 (28.6)	14 (40.0)	0.170
	T2	3 (42.9)	19 (54.3)	
	T3	2 (28.6)	2 (5.7)	

Table 1. Patient, tumor, and treatment characteristics (continued)

Measurements		Group 1 n: 7	Group 2 n: 35	p*
Lymph nodes	N0	5 (71.4)	28 (80.0)	0.152
	N1	1 (14.3)	6 (17.1)	
	N2	0 (0.0)	1 (2.9)	
	N3	1 (14.3)	0 (0.0)	
Stage	1A	2 (28.6)	10 (28.6)	0.603
	2A	3 (42.9)	20 (57.1)	
	2B	1 (14.3)	4 (11.4)	
	3A	1 (14.3)	1 (2.9)	
Postoperative duration of stay ((Mean+SD)(min-max)		3.0+2.2 (2-8)	2.4+1.0 (2-6)	0.323
Postoperative Radiotherapy	Yes	6 (85.7)	29 (82.9)	0.670
	No	1 (14.3)	6 (17.1)	
Postoperative Chemotherapy	Yes	3 (42.9)	6 (17.1)	0.155
	No	4 (57.1)	29 (82.9)	
Postoperative Endocrine treatment	Yes	4 (57.1)	16 (45.7)	0.444
	No	3 (42.9)	19 (54.3)	
Postoperative Targeted treatment	Yes	0 (0.0)	3 (8.6)	0.570
	No	7 (100.0)	32 (91.4)	

BCS: Breast-conserving surgery; TAH+BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; SD: Standard deviation

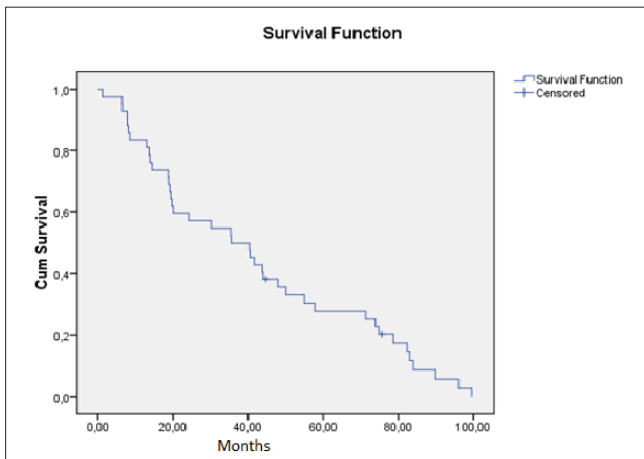
Table 2. Patient, tumor, and treatment characteristics, Group 2 subtypes

Measurements		Papillary (n: 21)	Pure Mucinous (n: 10)	Tubular (n: 4)	p*
Age (min-max)		57.7+12.3 (38-85)	52.6+13.0 (34-76)	60.5+10.5 (51-72)	0.452
Estrogen	Negative	2 (9.5)	0 (0.0)	0 (0.0)	0.493
	Positive	19 (90.5)	10 (100.0)	4 (100.0)	
Progesterone	Negative	8 (38.1)	1 (10.0)	0 (0.0)	0.113
	Positive	13 (61.9)	9 (90.0)	4 (100.0)	
Her2/neu	Negative	13 (61.9)	9 (90.0)	3 (75.0)	0.266
	Positive	8 (38.1)	1 (10.0)	1 (25.0)	
Comorbidity	No comorbid disease	13 (61.9)	8 (80.0)	3 (75.0)	0.676
	Singular disease	3 (14.3)	1 (10.0)	1 (25.0)	
	Double disease	5 (23.8)	1 (10.0)	0 (0.0)	
Oral contraceptive	Yes	3 (14.3)	0 (0.0)	1 (25.0)	0.335
	No	18 (85.7)	10 (100.0)	3 (75.0)	
Breastfeeding history	Yes	20 (95.2)	8 (80.0)	4 (100.0)	0.297
	No	1 (4.8)	2 (20.0)	0 (0.0)	
Family history	Yes	2 (9.5)	0 (0.0)	1 (25.0)	0.310
	No	19 (90.5)	10 (100.0)	3 (75.0)	
Surgical history	Appendectomy	0 (0.0)	1 (10.0)	0 (0.0)	0.371
	BCS	0 (0.0)	0 (0.0)	0 (0.0)	
	TAH+BSO	5 (23.8)	1 (10.0)	0 (0.0)	

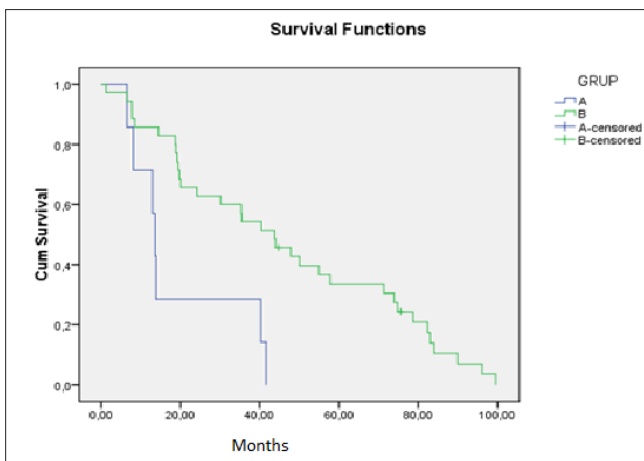
Table 2. Patient, tumor, and treatment characteristics, Group 2 subtypes (continued)

Measurements		Papillary (n: 21)	Pure Mucinous (n: 10)	Tubular (n: 4)	p*
Pre-op Imaging BI-RADS	Total Thyroidectomy	0 (0.0)	0 (0.0)	0 (0.0)	0.632
	None	16 (76.2)	8 (80.0)	4 (100.0)	
	3	0 (0.0)	1 (10.0)	0 (0.0)	
	4	1 (4.8)	0 (0.0)	0 (0.0)	
	4A	4 (19.0)	2 (20.0)	0 (0.0)	
	4B	0 (0.0)	1 (10.0)	0 (0.0)	
	4C	10 (47.6)	5 (50.0)	3 (75.0)	
	5	6 (28.6)	1 (10.0)	1 (0.0)	
Localization	Bilateral	1 (4.8)	0 (0.0)	0 (0.0)	0.775
	Right	12 (57.1)	4 (40.0)	2 (50.0)	
	Left	8 (38.1)	6 (60.0)	2 (50.0)	
Multifocality	Yes	1 (4.8)	2 (20.0)	0 (0.0)	0.297
	No	20 (95.2)	8 (80.0)	4 (100.0)	
Neoadjuvant	Yes	1 (4.8)	1 (10.0)	0 (0.0)	0.734
	No	20 (95.2)	9 (90.0)	4 (100.0)	
Surgery	Mastectomy	7 (33.3)	2 (20.0)	0 (0.0)	0.334
	BCS	14 (66.7)	8 (80.0)	4 (100.0)	
Tumor diameter	T1	5 (23.8)	5 (50.0)	4 (100.0)	0.053
	T2	14 (66.7)	5 (50.0)	0 (0.0)	
	T3	2 (9.5)	0 (0.0)	0 (0.0)	
Lymph nodes	N0	15 (71.4)	10 (100.0)	3 (75.0)	0.437
	N1	5 (23.8)	0 (0.0)	1 (25.0)	
	N2	1 (4.8)	0 (0.0)	0 (0.0)	
	N3	0 (0.0)	0 (0.0)	0 (0.0)	
Stage	1A	2 (9.5)	5 (50.0)	3 (75.0)	0.067
	2A	14 (66.7)	5 (50.0)	1 (25.0)	
	2B	4 (19.0)	0 (0.0)	0 (0.0)	
	3A	1 (4.8)	0 (0.0)	0 (0.0)	
Postoperative duration of stay ((mean+SD)(min-max))		2.6+1.3 (2-6)	2.1+0.3 (2-3)	2.2+0.5 (2-3)	0.364
Postoperative Radiotherapy	Yes	17 (81.0)	8 (80.0)	4 (100.0)	0.625
	No	4 (19.0)	2 (20.0)	0 (0.0)	
Postoperative Chemotherapy	Yes	3 (14.3)	3 (30.0)	0 (0.0)	0.348
	No	18 (85.7)	7 (70.0)	4 (100.0)	
Postoperative Endocrine treatment	Yes	8 (38.1)	5 (50.0)	3 (75.0)	0.378
	No	13 (61.9)	5 (50.0)	1 (25.0)	
Postoperative Targeted treatment	Yes	3 (14.3)	0 (0.0)	0 (0.0)	0.335
	No	18 (85.7)	10 (100.0)	4 (100.0)	

BCS: Breast-conserving surgery; TAH+BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; SD: standard deviation



Graphic 1. Mean survival



Graphic 2. Survival in groups

Mean survival was 41.9 ± 4.6 (32.6-51.1) months in all patients (Graphic 1), and 19.5 ± 5.6 (8.5-30.5) months and 46.3 ± 5.2 (36.1-56.6) months ($p:0.002$) in Group 1 and Group 2, respectively, when they were evaluated separately (Graphic 2).

Discussion and Conclusion

Mucinous carcinoma of the breast is rare in clinical practice and includes approximately 4% (1% to 6%) of all invasive breast cancers. It is more common especially in the peri-menopausal and postmenopausal age groups (16). Pure mucinous tumors have a good prognosis. Mix mucinous cancers have a poor prognosis because of their clinical characteristics and survival characteristics, which are similar to those of (IDC). It is important to distinguish mix mucinous tumors from pure mucinous tumors and other rare types.

Axillary lymph node involvement remains as an important prognostic factor. Axillary lymph node positivity is reported in the literature as 20-53% in mix mucinous carcinoma, as 4-17% in pure mucinous carcinoma (9, 17-21), as 3-18% in tubular carcinoma (19, 22, 23) and as 11% in papillary carcinoma (24). In our series, it was 29% for mix mucinous patients. When we evaluated the other rare tumors together, it was 20%. When we evaluated them separately, it was 0% in pure mucinous carcinoma, 25% in tubular carcinoma and 28.6% in papillary carcinoma. The lymph node involvement of mix mucinous tumors in our series were similar to that of papillary carcinoma.

In the treatment of mixed mucinous breast carcinoma and other rare tumors of the breast, the primary treatment protocol is surgery with postoperative adjuvant therapy. We performed mastectomy on 57% of the patients in Group 1, and 25.7% of the patients in Group 2. In our series, multicentricity, tumor diameter and patient request played a part in the decision of mastectomy. While no patient received neoadjuvant treatment in the mix mucinous group, 2 patients in the other group received it. Axillary lymph node involvement and tumor size played a role in the selection of neoadjuvant treatment. Adjuvant therapies after mastectomy were planned considering the recommendations of St. Gallen (25).

Radiotherapy was given to all patients after breast-conserving surgery, and axillary lymph node involvement and tumor size were affected in patients receiving radiotherapy after mastectomy. Adjuvant endocrine therapy is indicated for hormone responsive tumors. Almost all mucinous carcinomas are positive for estrogen and/or progesterone receptors, which means that hormonal therapy can be an effective treatment (26).

Human epidermal growth factor receptor (HER-2 / neu) is generally negative for mucinous tumors (18, 27). In our series, all of the mixed mucinous tumors were negative and 1 case was positive in pure mucinous tumors. When other rare tumors were examined, papillary carcinoma was 38% positive and tubular carcinoma was 25% positive. The presence of HER2 is important for agents targeting HER2, as in other breast cancers. While no patient received targeted therapy in the mix mucinous carcinoma group, 8.6% of the other rare tumors group received targeted treatment.

Di Saverio (27) described tumor size as an independent prognostic indicator. Tumor diameter was reported in the literature to be above 5 cm in 48% of mix mucinous tumors and in 22% of pure mucinous tumors. Tumor diameter in mix mucinous tumors was greater than pure mucinous tumors and other rare tumors, in many series (17, 28). In our series, there were 2 patients with a tumor diameter above 5 cm in the mix mucinous group, and the tumor diameter was not greater than 5 cm in any patient in the pure mucinous group.

In comparison of radiological imaging methods in literature, it has been reported that in mucinous tumors with mix pattern, BI-RADS 5 is more predominant than in pure and other types (29). In our series, 5 patients with mix mucinous tumor, 1 patient with pure mucinous tumor, and 6 patients with papillary carcinoma were BI-RADS 5.

Pure mucinous carcinoma of the breast and other rare tumors have a favorable prognosis because of low lymph node metastases, small tumor diameter and high hormone receptor positivity. Mix mucinous breast cancer has a worse prognosis because of their high incidence, large tumor size, high axillary lymph node metastases. Rare pathological types of breast cancer can have favorable outcomes when treated with necessary oncological principles.

Our study has several limitations. The major limitations of this study are the retrospective design and the small number of selected patients in each group.

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

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - U.T., M.G., B.Ö.; Design - M.G., U.T.; Supervision - A.C.A., E.M.S., H.A.; Resources - U.T., H.A.; Materials - U.T., H.A.; Data Collection and/or Processing - U.T., M.G., B.Ö.; Analysis and/or Interpretation - U.T., M.G., B.Ö.; Literature Search - E.M.S., A.C.A.; Writing Manuscript - U.T.; Critical Review - M.G., B.Ö., A.C.A., E.M.S., H.A.

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Association of Retrospective Peer Review and Positive Predictive Value of Magnetic Resonance Imaging-Guided Vacuum-Assisted Needle Biopsies of Breast

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ABSTRACT

Objective: To evaluate the association between retrospective peer review of breast magnetic resonance imaging-guided vacuum-assisted needle biopsies and positive predictive value of subsequent magnetic resonance imaging-guided biopsies

Materials and Methods: In January, 2015, a weekly conference was initiated in our institution to evaluate all breast magnetic resonance imaging-guided vacuum-assisted needle biopsies performed over January 1, 2014-December 31, 2015. During this weekly conferences, breast dynamic contrast-enhanced magnetic resonance imaging findings of 6 anonymized cases were discussed and then the faculty voted on whether they agree with the biopsy indication, accurate sampling and radiology-pathology correlation. We retrospectively reviewed and compared the magnetic resonance imaging indication, benign or malignant pathology rates, lesion types and the positive predictive value of magnetic resonance imaging-guided vacuum-assisted needle biopsy in the years before and after initiating this group peer review.

Results: The number of dynamic contrast-enhanced magnetic resonance imaging and magnetic resonance imaging-guided vacuum-assisted needle biopsies before and after initiating the review were 1447 vs 1596 ($p=0.0002$), and 253 (17.5%) vs 203 (12.7%) ($p=0.04$), respectively. There was a significant decrease in the number of benign biopsies in 2015 ($n=104$) compared to 2014 ($n=154$, $p=0.04$). The positive predictive value of magnetic resonance imaging-guided biopsy significantly increased after group review was implemented (Positive predictive value in 2014= $\%39.1$ and positive predictive value in 2015= $\%48.8$) ($p=0.03$), although the indications ($p=0.49$), history of breast cancer ($p=0.14$), biopsied magnetic resonance imaging lesion types ($p=0.53$) were not different. Less surgical excision was performed on magnetic resonance imaging-guided vacuum-assisted needle biopsy identified high-risk lesions in 2015 ($p=0.25$).

Conclusion: Our study showed an association between retrospective peer review of past biopsies and increased positive predictive value of magnetic resonance imaging-guided vacuum-assisted needle biopsies in our institution.

Keywords: Breast, dynamic contrast-enhanced magnetic resonance imaging, magnetic resonance imaging-guided vacuum-assisted needle biopsy, positive predictive value

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Introduction

With rising health care costs, recent initiatives have focused on appropriate ordering of tests by physicians, to minimize waste and to improve quality of care (1-7). National campaigns such as 'Choosing Wisely' have gained significant following to improve the utilization of high-cost imaging. Dynamic contrast-enhanced magnetic resonance imaging (MRI) of breast is an important tool for screening high-risk women and for the diagnosis, staging, and evaluation of breast malignancies (8-21). While MRI is highly sensitive (range, 89-100%), it has moderate to low specificity (range, 37-70%) (22-34), resulting in a significant increase in unnecessary needle biopsies (35-37). More than half of MRI detected abnormalities cannot be identified with an MRI directed, or "second-look" ultrasound (38-52), leading to an increased need for MRI-guided biopsies. MRI-guided vacuum-assisted needle biopsy is a costly and time-consuming procedure with a moderate yield of malignancy (range, 14-35%) and can be stressful procedure for patients due to claustrophobia and positioning, even occasionally requiring sedation.

In an effort to educate and inform our dedicated breast radiology group, a retrospective peer review system was initiated at our institution to evaluate the indication, technical adequacy, and radiology-pathology correlation of previously performed MRI-guided vacuum-assisted needle biopsies and their outcomes. In this study, we present the outcomes of MRI guided biopsies in our tertiary healthcare institution before and after the implementation of our MRI-guided vacuum-assisted needle biopsy peer-review process.

Materials and Methods

This was an institutional review board approved, Health Insurance Portability and Accountability Act (HIPAA) compliant, retrospective case review in which the requirement for patient informed consent was waived. We searched our tertiary imaging center's MRI database for patients who underwent breast MRI-guided vacuum-assisted needle biopsy between January 1, 2014 and December 31, 2014, before initiating the peer review, and between January 1, 2015 and December 31, 2015, after its implementation.

Dynamic contrast-enhanced MRI Technique and MRI-guided vacuum-assisted needle biopsy

All MR imaging studies were performed using a wide bore 3-Tesla MRI unit. (Discovery MR750 GE Healthcare, Waukesha, WI) The protocol consisted of T1-weighted sequence, followed by dynamic contrast-enhanced sequence, T2 weighted sequence and a diffusion weighted imaging sequence. Pulse sequence parameters are outlined in Table 1. Depending on patient size and scanned area, average scan time ranges from 38 minutes to 60 minutes. There is no change in protocol between January 1, 2014 and December 31, 2015. The standard protocol is applied to all patients with a clinical indication to undergo breast MRI for further evaluation between aforementioned dates. MRI-guided vacuum-assisted needle biopsy is recommended for 401 patients.

All MRI-guided vacuum-assisted needle biopsies were performed in a dedicated prone table (*Invivo* Gainesville FL) using a 9-gauge vacuum-assisted needle (ATEC; Hologic, Bedford, Mass). Some of the patients in our study had more than one biopsy performed and each biopsy was considered as a separate entity.

Peer Review Process

In January, 2015, a weekly conference was initiated to evaluate all MRI-guided vacuum-assisted needle biopsies performed over January 1, 2014-December 31, 2015. During each weekly conference, 6 ano-

nymized cases were presented by a breast imaging faculty member of 5-16 years of experience with breast MRI interpretation to an audience of breast imaging faculty comprising our entire group and the breast imaging fellows. The MRI findings and the biopsy indications of the lesions were discussed and then the breast imaging faculty voted on whether they agree with (a) the biopsy indication (b) appropriate sampling (c) radiology-pathology correlation (d) final recommendation.

Below data was collected from the electronic health record of each patient (a) patient age at the time of biopsy, (b) the indication for the study, (c) whether the patient had a new breast cancer or was treated for breast cancer in the past, and if so, whether the cancer was ipsilateral or contralateral to the biopsy site, (d) lesion type (mass or non-mass) and size. The pathology results were reviewed and categorized into benign, high-risk [atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, atypical papilloma, and radial scar (including complex sclerosing lesion, complex sclerosing adenosis, and radial sclerosing lesion)] or malignant. Cancers were further classified into invasive or pure ductal carcinoma in situ based on their final surgical histopathology. In our institution, short-term MRI follow up or excision is not performed for lesions revealing benign and concordant results, in line with recent literature (53). Lesions revealing atypia are routinely reviewed in a multidisciplinary Clinical Management Conference, comprised of representatives from breast radiology, pathology, surgery departments and primary care providers who make a consensus management recommendation.

To control for possible radiologist interpretation differences between the two years, MRI-guided vacuum-assisted needle biopsy recommendations of radiologists who joined our group in 2014 and 2015 were excluded, and only the readings and recommendations by the same group of radiologists (n=12) at our institution were included in the analysis.

Statistical Analysis

Total number of MR imaging performed, number of biopsies, patient and tumor characteristics were summarized using frequencies and percentages. Biopsy rate was estimated along with 95% confidence interval (CI) for 2014 and 2015. Fisher's exact test was used to compare MRI-guided vacuum-assisted needle biopsy rates and patient characteristics of biopsied cases between these years. All tests were two-sided and p-values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using SAS version 9 (SAS Institute, Cary, NC).

Table 1. Dynamic contrast-enhanced breast MRI protocol

Pulse Sequence Parameters	Protocol Pulse Sequences				
	Pre-contrast T1-Weighted	DCE (1 pre+5 post contrast)	T1-Weighted Sagittal	T2-Weighted	DWI
Average scan time (min)	5	10	7	10	6
TR/TE	5.4/2.1ms	5.4/2.2ms	7.5/2.1ms	~5000/100ms	~5000/60ms
Flip Angle	10°	10°	10°	90°	90°
Slice	1.8/-0.9mm	1.8/-0.9mm	2.4/-1.2mm	5/1mm	4/0mm
FOV	~30cm	~30cm	~22cm	~30cm	~36cm
Matrix	384x384	480x384	384x320	384x224	170x224

TR: Repetition Time; TE: Echo Time; FOV: field of view

Results

Of 459 MRI-guided vacuum-assisted needle biopsy procedures performed in the defined two-year time frame, 253 occurred between January 1, 2014-Jan 1, 2015 and 203 between Jan 1, 2015 and December 31, 2015. A single lesion was biopsied in each patient.

In the defined timeframe, significantly more dynamic contrast-enhanced MRIs were performed in 2014 compared to 2015 (1447 vs 1596, $p=0.0002$) while a lower biopsy rate was observed (17.5% vs 12.7% $p=0.04$).

There were no significant differences between patient age [median 50 vs 51 years, ($p=0.8$)], MRI indication ($p=0.49$), history of ipsilateral or contralateral breast cancer ($p=0.14$) or MRI lesion types (mass vs non-mass like enhancement, $p=0.53$) between the two groups. In 2014 there was a significantly higher benign biopsy rate (154 of 253, 60.9%) compared to 2015 (104 of 203, 51.2%) ($p=0.04$). The malignancy rates were similar (26.09% in 2014 and 26.11% in 2015), there was

a higher rate of high-risk lesions identified in 2015 (21.7% vs 12.7%) ($p=0.03$). There was a slight but significant increase in the positive predictive value of MRI-guided vacuum-assisted needle biopsies in 2015 [48.8% (97/203)] compared to those in 2014 [39.1% (98/253)] ($p=0.04$) (Table 2).

Clinical parameters including breast MRI indication, lesion type on MRI (mass vs non-mass), were not significantly different (Table 3).

Discussion and Conclusion

Magnetic resonance imaging is an important diagnostic tool for breast cancer and for screening high-risk patients. MRI has a high sensitivity for the detection of breast lesions however its specificity is low (22-34), increasing the false positive results and leading to costly, time and resource consuming interventions like MRI-guided vacuum-assisted needle biopsy. MRI-guided vacuum-assisted needle biopsy can be done in an outpatient office for half of a surgical biopsy cost without the need for anesthesia and hospitalization (54). However, this cost is approximately twice as much as an ultrasound image-guided biopsy or a stereotactic image-guided biopsy (55).

In our study, despite an increase (10.3%, $p=0.0002$) in the overall number of dynamic contrast-enhanced breast MRIs between pre-PRS and post-PRS periods, there was a significant decrease ($p=0.0002$) in the overall number of MRI-guided vacuum-assisted needle biopsies recommended by the same group of radiologists, without significant differences in the MRI indication ($p=0.49$) or MRI lesion type ($p=0.53$). Less benign biopsies occurred in 2015 compared to 2014 ($p=0.0002$). There was a statistically significant increase in positive predictive value of MRI-guided vacuum-assisted needle biopsy after the initiation of PRS in January 1, 2015 ($p=0.046$), although the same group of radiologists made the decision of biopsy.

The overall malignancy rate of breast lesions underwent MRI-guided vacuum-assisted needle biopsy was 26.1% in 2014 and 26.1% in 2015. Our results are similar to the malignancy rates of previous reports, which range between 20-43% (22, 24, 56-60). Our malignancy rate is at the lower end of the spectrum, because all suspicious mass-like enhancements –which are more likely to yield malignancy (48)–undergo MRI-directed ultrasound in our institution.

The upgrade rate for high-risk breast lesions identified at MRI-guided vacuum-assisted needle biopsy ranges between 3-21.5% (28, 61-62). In our study, 62.5% (20/32) of high-risk lesions were excised in 2014, this ratio was 45.5% (20/44) in 2015 ($p=0.17$). None of these high-risk lesions were upgraded into malignancy upon surgical excision. Surgical excision rate of high-risk lesions decreased in 2015, although the difference was not statistically significant ($p=0.25$).

Our study has some limitations. First, this is retrospective study performed in a single institution. The small number of patients included decreases the power of the statistical results. Further, for mass-like MR enhancement, we start our work up with MRI-directed ultrasound, and if a correlate is identified, perform ultrasound-guided needle biopsy. Non-mass like enhancement and masses with no ultrasound correlate are subjected to MRI-guided biopsy. MRI-directed ultrasound, and ultrasound guided biopsy rates are not included in this study. However, our primary goal was to investigate the rate of MRI-guided biopsies since ultrasound guided biopsy does not involve contrast or require magnet time, is much better tolerated and less costly compared to MRI-guided vacuum-assisted needle biopsy.

Table 2. Pathology results of the biopsied lesions in 2014 and 2015

	MRI Year				*p
	2014		2015		
	n	%	n	%	
Benign	154	60.87	104	51.23	0.046
Cancer	66	26.09	53	26.11	
High Risk	32	12.65	44	21.67	0.03
All	253	100.00	203	100.00	
Positive predictive value	39.13%		48.77%		0.046

Table 3. Breast MRI indications and findings of the biopsied lesions in 2014 and 2015

	MRI Year				*p
	2014		2015		
	n	%	n	%	
Breast Cancer					
Extent of Disease	131	51.78	115	56.65	0.49
High-risk screening	53	20.95	39	19.21	
Other	15	5.93	12	5.91	
Breast Cancer					
Surveillance	18	7.11	7	3.45	
*Problem solving	36	14.23	30	14.78	
MRI finding					
Asymmetry	1	0.40	0	0	0.53
Mass enhancement	107	42.29	94	46.31	

*p-values by Fisher's exact test

*Problem solving: further evaluation due to abnormal mammography, ultrasonography, nipple retraction

Our weekly all-radiologist review of MRI-guided vacuum-assisted needle biopsies was associated with an increase in positive predictive value of biopsies over time independent of lesion type, indication or history of breast cancer. Peer-review was associated with significantly less surgical excisions for high-risk lesions identified on MRI-guided vacuum-assisted needle biopsy.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of MD Anderson Cancer Center.

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

Peer-review: Externally peer-reviewed.

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Correlation between the Expression of PD-L1 and Clinicopathological Parameters in Triple Negative Breast Cancer Patients

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ABSTRACT

Objective: Triple-negative breast cancer (TNBC) is a heterogenous group of tumors with no estrogen receptor (ER), progesterone receptor (PR) and Cerb-B2/HER2 expression. Programmed death ligand-1 (PD-L1) is a transmembrane protein located on both non-tumor and tumor cells and it has been shown to be associated with the escape of tumor cells from the immune system. PD-L1-targeted therapy alone or in combination is now an alternative strategy in several aggressive tumor types. In this respect, TNBC is a potential candidate having limited treatment options and poor outcome.

Material and Methods: Sixty-one breast cancers with no expression of ER, PR and Cerb-B2/HER2 were chosen to study PD-L1 immunohistochemistry. PD-L1 staining and its correlation with main clinicopathological parameters were evaluated.

Results: The percentage of PD-L1 positivity was 37.7% and 47.5% in tumor and tumor microenvironment, respectively. The positivity rate was higher in breast carcinomas with medullary features (83.3%) and metaplastic carcinoma (66.6%) subgroups. PD-L1 expression of tumors was positively correlated with their Ki-67 score and PD-L1 positivity of the tumor microenvironment. No significant relationship was found between the other variables.

Conclusion: PD-L1 expression rate was remarkable both in the tumor and the tumor microenvironment of TNBCs. Larger cohorts of TNBC are required to further describe their PD-L1 expression characteristics and help standardize PD-L1 immunohistochemistry assays in these tumors.

Keywords: PD-L1, breast cancer, triple-negative breast cancers, immunohistochemistry, monoclonal antibody

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Introduction

Breast cancer is the most common malignancy and the second most common cause of cancer-related death in women (1). The widespread use of mammographic screening in recent years has increased the awareness of breast cancer (1). Targeted therapies against the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) have provided significant improvement in breast cancer prognosis (2). However, tumors lacking ER, PR and HER2 expression, called triple-negative breast cancers (TNBC), have a poor prognosis and unsatisfactory treatment options (3).

Programmed death ligand-1 (PD-L1) encoded by the CD274 gene on the chromosome 9 is a 40 kDa transmembrane protein found in a number of normal tissue cells such as natural killer cells, macrophages, myeloid dendritic cells, B-cells, epithelial cells and vascular endothelial cells (4). Recent studies on a wide variety of epithelial tumors have shown that tumoral escape from the host immune system is enhanced by the PD-1 (Programmed Death Receptor 1)/PD-L1 signal pathway by the interaction of the PD-1 expressed on tumor-infiltrating lymphocytes (TIL) and the PD-L1 expressed on tumor cells (4).

Expression of PD-L1 in tumor cells is one of the most important mechanisms associated with tumors' defense against immune system attacks (4). Studies have demonstrated that PD-L1 expression is evident in malignant melanoma, renal cell carcinoma, non-small cell lung cancer, colorectal carcinoma, gastric carcinoma, pancreatic carcinoma, some breast carcinomas and various hematological malignancies (5). These tumors are potential targets for PD-1/PD-L1 inhibitor therapies (5). However, data on PD-L1 expression of breast cancers has been limited. There is conflicting data on the possible effect of PD-L1 expression on breast cancer prognosis; some reports indicate PD-L1 to be a favorable factor (6-8), while others consider it unfavorable (2, 4, 9) or of no effect (10, 11).

In this study, we analyzed PD-L1 expression of 61 TNBC cases and correlated them with major clinicopathological parameters.

Materials and Methods

Case selection and patient data

Triple negative breast cancers diagnosed in our Pathology Department between January 2009 and July 2017 were retrieved from pathology archives. Sixty one cases had paraffin blocks available for the study. The grades and histotypes of tumors were reviewed by two pathologists using American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) breast cancer guidelines. The slides with hematoxylin and eosin (H&E), ER, PR, HER2 and Ki-67 stainings were evaluated. Clinicopathological information including patient age, tumor size, TNM stage, type of surgery, date of the last follow-up and date of recurrence were collected from the medical records retrospectively. The Şişli Hamidiye Etfal Training and Research Center, University of Health Sciences Ethics Committee approval has been received beforehand. Patient consent forms were deemed nonessential.

Immunohistochemical studies

Immunohistochemical staining for PD-L1 antibody (rabbit monoclonal antibody, #13684, clone: E1L3N, cell signalling technologies, USA, 1:400) was performed using the DAB peroxidase method on a (Leica Bond III) device. Other primary antibodies used for immuno-

histochemical assays are as follows: ER, PR, HER2 and Ki-67. Three-micron thick sections were taken from the paraffin embedded blocks for immunohistochemical assays.

Immunostaining procedure was performed on a (Leica Bond III) device after slides were incubated at 80°C for 3 hours. Briefly, Bond-Dewak solution was applied for 10 minutes at 60°C, slides were then deparaffinized and rehydrated through graded ethanol solutions. Antibody retrieval was carried out by applying ER1 at 96°C for 20 minutes, followed by H₂O₂ blocking for 13 minutes at room temperature. The primary antibody (PD-L1, rabbit monoclonal antibody, #13684, clone: E1L3N, cell signalling technologies, USA, 1:400) was applied for 30 minutes, then it was washed and secondary antibody was applied for 8 minutes at room temperature. DAB was used as a chromogen and hematoxylin was used for counterstaining. Coverslipping followed graded alcohols and xylene.

Immunohistochemical evaluation

Programmed death ligand-1 immunohistochemical staining was evaluated both in the tumor and the peritumoral microenvironment. Tumoral PD-L1 staining was designated as positive when clear membranous or cytoplasmic staining was present in at least 1% of tumor cells. The extent of tumor staining was further classified into the following subcategories: <1%: score 0, 1% to 5%: score 1, 6% to 50%: score 2 and >50%: score 3 (Figure 1). Scores 1 to 3 were considered as posi-

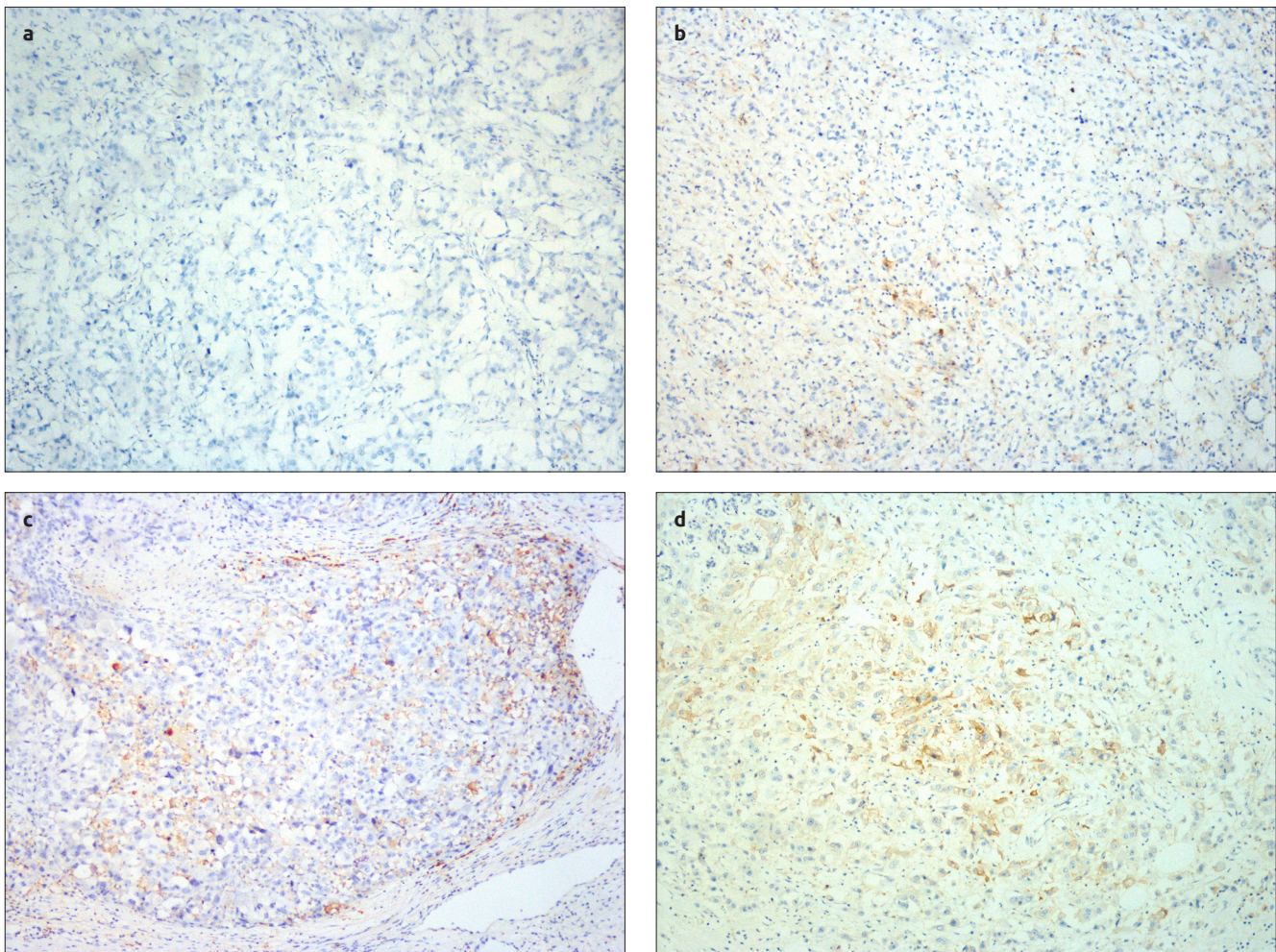


Figure 1. a-d. Tumoral PD-L1 scoring. Score 0: no staining, x100 (a). Score 1: 1-5% tumoral staining, x100 (b). Score 2: 6-50% tumoral staining, x100 (c). Score 3: >50% tumoral staining (d)

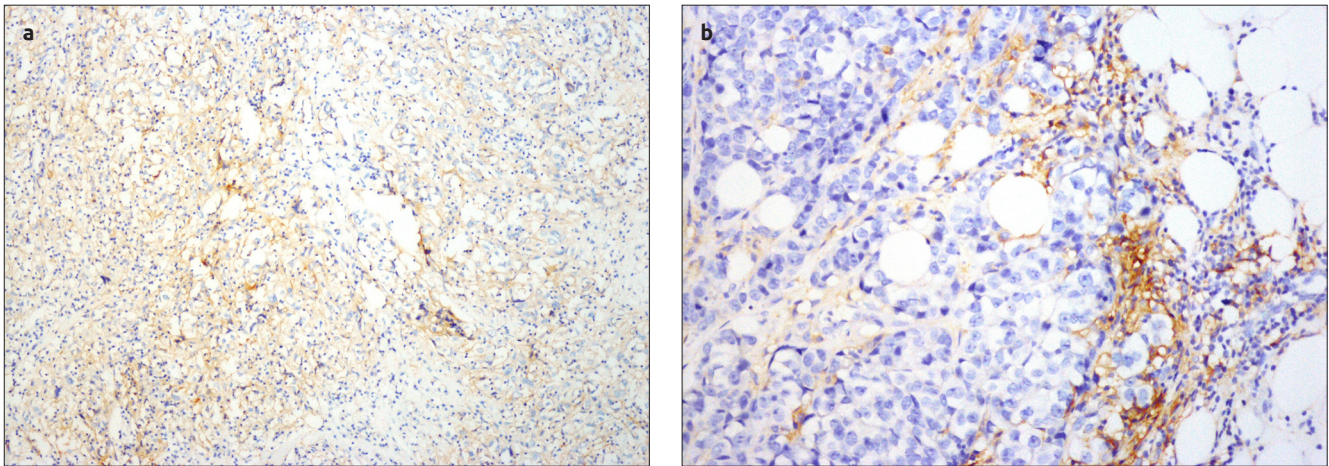


Figure 2. a, b. PD-L1 positivity of tumor and tumor microenvironment. PD-L1 immunostaining in tumor and tumor microenvironment, x100 (a). Marked PD-L1 expression in tumor microenvironment, x200 (b)

Table 1. Clinicopathological features of triple negative breast cancer cases

		Mean±SD (Min-Max)	
Age		50.2±12.0 (26-95)	
Mean Ki-67 score (%)		38.6±23.8 (5-80)	
Tumor diameter (cm)		4.2±3.3 (0.7-15)	
		n	%
Tumor site	UOQ	28	45.9
	UIQ	13	21.3
	LOQ	8	13.1
	Multiple quadrants	5	8.2
	LIQ	4	6.6
	Retroareolar	3	4.9
Histologic type	Invasive carcinoma, NST	42	68.9
	Invasive carcinoma with medullary features	6	9.8
	Metaplastic carcinoma	6	9.8
	Apocrine carcinoma	3	4.9
	Invasive lobular carcinoma	2	3.3
	Mixed carcinoma	1	1.6
	Secretory carcinoma	1	1.6
Histologic grade	1	3	4.9
	2	8	13.1
	3	50	82.0
Nuclear grade	1	1	1.6
	2	11	18.0
	3	49	80.3
Pathologic stage	1	13	21.3
	2	33	54.1
	3	9	14.8
	4	6	9.8
Lymph node metastasis		31	50.8
Lymphovascular invasion		30	49.2
DCIS		22	36.1
Neoadjuvant therapy		16	26.2
Recurrence/distant metastasis		18	31.0

SD: Standard deviation; UOQ: Upper outer quadrant; UIQ: Upper inner quadrant; LOQ: Lower outer quadrant; LIQ: Lower inner quadrant; NST: No special type; DCIS: Ductal carcinoma in-situ

Table 2. PD-L1 expression in tumor and tumor microenvironment

	n	%
Tumoral positivity of PD-L1	23	37.7
Tumoral PD-L1 score		
0 (-)	38	62.3
1 (1-5%)	6	9.8
2 (5-50%)	11	18.0
3 (>50%)	6	9.8
Microenvironment positivity of PD-L1	29	47.5
Tumoral or microenvironment positivity of PD-L1	36	59

tive and score 0 as negative. Peritumoral PD-L1 expression was scored as positive or negative where “positive” noted $\geq 5\%$ PD-L1 staining (Figure 2).

Expressions of ER and PR were considered negative when less than 1% of tumor cells were stained (12). HER2 staining of the tumors were evaluated according to ASCO/CAP recommendations (13). HER2 slides were scored as 0, no staining or faintly seen incomplete membranous staining within <10% of tumor cells; 1+, faintly seen incomplete membranous staining within >10% of tumor cells; 2+, weak/moderate incomplete membranous staining within >10% of tumor cells or complete circumferential membranous staining within <10% of tumor cells; and 3+, complete circumferential membranous staining within >10% of tumor cells (13). HER2 expression was regarded negative if the score was 1 or lower. Microscopic evaluation of the immunohistochemically stained slides were made by two pathologists (RU, CT).

Table 3. Correlation of tumoral PD-L1 positivity with clinicopathologic parameters

		Tumoral PD-L1 positivity				p
		Positive (n=23)		Negative (n=38)		
		n	%	n	%	
Histologic type	Invasive carcinoma, NST	10	43.5	32	84.2	0.004
	Invasive carcinoma with medullary features	5	21.7	1	2.6	
	Metaplastic carcinoma	4	17.4	2	5.3	
	Invasive lobular carcinoma	1	4.3	1	2.6	
	Apocrine carcinoma	1	4.3	2	5.3	
	Mixed carcinoma	1	4.3	0	0.0	
	Secretory carcinoma	1	4.3	0	0.0	
Histologic grade	1	0	0.0	3	7.9	0.440
	2	4	17.4	4	10.5	
	3	19	82.6	31	81.6	
Nuclear grade	1	0	0.0	1	2.6	1.000
	2	4	17.4	7	18.4	
	3	19	82.6	30	78.9	
Pathologic stage	1	4	17.4	9	23.7	0.545
	2	11	47.8	22	57.9	
	3	5	21.7	4	10.5	
	4	3	13.0	3	7.9	
Lymph node metastasis	present	11	47.8	20	52.6	0.716
	absent	12	52.2	18	47.4	
Lymphovascular invasion	present	13	56.5	17	44.7	0.372
	absent	10	43.5	21	55.3	
DCIS	present	10	43.5	12	31.6	0.348
	absent	13	56.5	26	68.4	
Microenvironment positivity of PD-L1	present	16	69.6	13	34.2	0.007
	absent	7	30.4	25	65.8	
		Mean±SD (Median)		Mean±SD (Median)		p
Mean Ki-67 score (%)		47.8±26.4 (50)		33.0±20.4 (30)		0.017
SD: Standard deviation; NST: No special type; DCIS: Ductal carcinoma in-situ						

SD: Standard deviation; NST: No special type; DCIS: Ductal carcinoma in-situ

Statistical Analysis

The software Statistical Package for the Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA) was used for the statistical analysis. Independent two-group comparisons were made by Student's *t* test when the variables provided normal distribution and Mann Whitney U test was used when the variables did not display a normal distribution. Comparisons of ratios in independent groups were performed with Chi-Square Analysis. P values lower than 0.05 were considered statistically significant.

Disease-free survival (DFS) was measured as the time between the date of the initial diagnosis and the date of metastasis or relapse whichever

was earlier. The duration of follow-up was the period between the date of diagnosis to the the last follow-up date.

Results

Clinical and histopathological findings

Sixty one TNBCs were included in the study. The mean age was 50.2 ± 12.0 years (range 26-95 years). The mean tumor size was 4.2 ± 3.3 cm (range 0.7–15.0 cm). Tumors consisted of 42 (68.9%) invasive carcinoma, NST, 6 (9.8%) breast carcinomas with medullary features, 6 (9.8%) metaplastic carcinomas, 3 (4.9%) apocrine carcinomas, 2 (3.3%) invasive lobular carcinomas (pleomorphic variant), 1

Table 4. Correlation of microenvironment positivity of PD-L1 with clinicopathologic parameters

		Microenvironment positivity of PD-L1				p
		Positive (n=29)		Negative (n=32)		
		n	%	n	%	
Histologic type	Invasive carcinoma, NST	17	58.6	25	78.1	0.252
	Invasive carcinoma with medullary features	5	17.2	1	3.1	
	Metaplastic carcinoma	4	13.8	2	6.3	
	Invasive lobular carcinoma	1	3.4	1	3.1	
	Apocrine carcinoma	1	3.4	2	6.3	
	Mixed carcinoma	0	0.0	1	3.1	
	Secretory carcinoma	1	3.4	0	0.0	
Histologic grade	1	0	0.0	3	9.4	0.277
	2	5	17.2	3	9.4	
	3	24	82.8	26	81.3	
Nuclear grade	1	0	0.0	1	3.1	1.000
	2	5	17.2	6	18.8	
	3	24	82.8	25	78.1	
Pathologic stage	1	1	3.4	12	37.5	0.001
	2	23	79.3	10	31.3	
	3	3	10.3	6	18.8	
	4	2	6.9	4	12.5	
Lymph node metastasis	present	14	48.3	17	53.1	0.705
	absent	15	51.7	15	46.9	
Lymphovascular invasion	present	15	51.7	15	46.9	0.705
	absent	14	48.3	17	53.1	
DCIS	present	9	31.0	13	40.6	0.436
	absent	20	69.0	19	59.4	
Tumoral PD-L1 score	0	13	44.8	25	78.1	0.033
	1-5%	3	10.3	3	9.4	
	5-50%	9	31.0	2	6.3	
	>50%	4	13.8	2	6.3	
		Mean±SD (Median)		Mean±SD (Median)		p
Mean Ki-67 score (%)		44.5±25.9 (40)		33.3±20.7 (32.5)		0.066

SD: Standard deviation; NST: No special type; DCIS: Ductal carcinoma in-situ

(1.6%) secretory carcinoma, and 1 (1.6%) mixed carcinoma. Three cases (4.9%) were grade I, 8 cases (13.1%) were grade II, and 50 cases (82.0%) were grade III. According to the AJCC's 8th Edition of Cancer Staging Manual, 13 (21.3%) of the pathologically staged tumors were pT1, 33 (54.1%) were pT2, 9 were (14.8%) pT3 and 8 were pT4. At the time of diagnosis, 31 (50.8%) cases were positive and 30 (49.2%) cases were negative for lymph node metastasis (Table 1).

PD-L1 expression

Thirty six cases (59%) displayed PD-L1 expression in either the tumor or the tumor microenvironment. Twenty three cases (37.7%) showed tumoral positivity (score 1-3) with PD-L1. Six (9.8%) of these positive cases were score 1, 11 cases (18.0%) were score 2 and 6 cases (9.8%) were score 3. No tumoral staining (score 0) was observed in 38 cases (62.3%). Twenty nine cases (47.5%) showed PD-L1 positivity (>5%) in tumor microenvironment (Table 2).

Tumor PD-L1 positivity rate was relatively low in patients with invasive carcinoma, NST (23.8%) and high in patients with breast carcinomas with medullary features (83.3%) and metaplastic carcinoma (66.6%) (Table 3).

Programmed death ligand-1 positivity rate in the microenvironment was higher in cases where tumoral PD-L1 was also positive ($p=0.007$). Similarly, tumoral PD-L1 positivity of the cases with a positive microenvironment staining was statistically significantly high as well ($p=0.033$). Sixteen cases were PD-L1 positive in both the tumor and the microenvironment. There was no statistically significant relationship between tumoral or microenvironmental PD-L1 expression status and main clinicopathological and survival parameters such as tumor type, tumor grade, lymph node metastasis, lymphovascular invasion (LVI), the presence of ductal carcinoma in-situ (DCIS), recurrence and/or metastatic status (Table 3, 4).

Discussion and Conclusion

Triple negative breast cancers are generally aggressive tumors that occur in a younger population than other breast cancers. They constitute approximately 10-20% of all breast carcinomas (14, 15). Due to their rapid growth, they are usually encountered in advanced stage at the time of diagnosis (3). TNBCs do not benefit from neither hormone therapy nor trastuzumab, due to their lack of responsive receptors (3). Anthracycline, taxane, ixabepilone and platinum-based chemotherapeutic agents are the current treatment strategies; yet there is no single effective agent for these tumors (16). The presence of PD-L1 in TNBCs can justify a potential treatment option and prove to be a prognostic and predictive marker as was demonstrated in other types of tumors (5).

There are significant differences in the method and evaluation of PD-L1 immunohistochemistry assays in the literature. H scores, percentage thresholds (1%) and tiered scoring systems (0-3) are the most common approaches to evaluate tumoral PD-L1 expression (4, 10, 17, 18). Threshold values of 1% and 5% have been applied to assess PD-L1 positivity in the tumor microenvironment (10, 17). Three different clones of PD-L1 (E1L3N, SP142, 28-8) have been used in different studies (4, 6, 10, 17, 18). In one study that compares these three clones, the staining rates in each of the three clones were found to be different from each other but their superiority was not specified (19). Further studies are recommended in larger groups to determine the gold standard antibody and the optimal cutoff value (19). E1L3N was the preferred clone in our study. We evaluated the PD-L1 response both in the tumor and the tumor microenvironment as was done by

others (10, 20). We preferred a 0-3 scoring system for tumoral staining and a 5% cutoff for microenvironmental staining. The lack of validation among different PD-L1 clones limits our study. Besides, further analytic methods other than immunohistochemistry could enhance the value of our results.

Programmed death ligand-1 expression ranges between 8.3%-59% for the tumoral compartment and between 16.2%-93% for the microenvironment in the studies with different evaluation methods and clones (4, 6, 10, 17-21). We found a PD-L1 expression (score 1-3) rate of 37.7% (23 cases) in our 61 TNBC cases. Staining was negative (score 0) in 38 cases (62.3%). In detail, the numbers of cases with each score were 6 (9.8%), 11 (18.0%) and 6 (9.8%) for the score 1, 2 and 3 respectively. In two TNBC studies using the same clone, tumoral staining was reported as 21% and 33.2% (17, 21). Dill et al. (17) identified a subgroup of TNBC with high PD-L1 expression (>50%) which they named 'diffuse staining'; it constituted 5% of their cases. We named this pattern 'score 3' and 9.8% of our cases were in this subgroup. In our study, there was PD-L1 positivity in 36 cases (59%) in at least one compartment and there was a statistically significant positive correlation between the PD-L1 tumoral staining and the expression of the PD-L1 in tumor microenvironment ($p=0.007$).

The relationship between tumoral PD-L1 positivity and Ki-67 proliferation index was found to be statistically significant ($p=0.017$). This result should be supported by the data of further survival studies. There was no statistically significant relationship between PD-L1 expression in tumor or tumor microenvironment and parameters such as age, tumor size, tumor grade, lymph node metastasis, the presence of LVI or DCIS, recurrence and/or metastasis status. However, there are several studies in the literature that reported a significant relationship between some of these parameters and tumoral PD-L1 expression (4, 6, 10, 17, 18). There was a statistically significant difference in histopathological tumor types of the PD-L1 positive and negative cases in our study ($p=0.004$). Most of the 61 TNBC cases were invasive ductal carcinomas, NST and 84.2% of these showed no expression of PD-L1. However tumors with medullary-like features and metaplastic carcinomas showed high PD-L1 expression ratios; 83.3% and 66.6% respectively. Increased PD-L1 expression has been previously reported in breast carcinomas with medullary features, apocrine and metaplastic carcinoma subtypes of breast cancer (17).

Triple-negative breast cancers are tumors showing early and frequent recurrence and/or metastasis (22). The mean follow-up period in our study was 24.8 months (0-87 months) and recurrence and/or metastasis was seen in 31% of cases. The mean duration of disease-free follow-up was 22.6 months. However, the follow-up times of our cases were too short and the clinical data were mostly insufficient to build up a Kaplan-Meier plot. Several studies in the literature showed variable association between PD-L1 expression and overall or disease-free survival (10, 20, 21). Studies with larger series can clarify the relevance of PD-L1 with regards to survival.

In conclusion, PD-L1 expression rate was remarkable both in the tumor and the tumor microenvironment of TNBCs. There was a statistically significant association between the tumoral PD-L1 positivity and parameters such as histological type and Ki-67 index, but no relationship was found between PD-L1 expression and other prognostic factors. Data presented by other reports in the literature is highly variable on account of technical differences and use of several PD-L1 clones. Standardization should be provided with further studies.

Triple-negative breast cancers constitute a tumor category that has no specific targeted therapy and requires new therapeutic options. The expression of PD-L1 in and around these tumors may provide rationale for the use of anti-PD-L1 therapies (PD-L1 monoclonal antibodies) for these aggressive neoplasms. Larger cohorts of TNBC are required to further describe PD-L1 expression characteristics and help standardize PD-L1 immunohistochemistry use in these tumors.

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

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Determining Breast Cancer Treatment Costs Using the Top Down Cost Approach

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ABSTRACT

Objective: Breast cancer is the most common type of cancer among women in Turkey, with approximately 15,000 breast cancer diagnoses each year. In this study, our goal was to determine annual direct medical costs of all breast cancer patients in Turkey with top down cost approach.

Materials and Methods: Data regarding patients who have been diagnosed with breast cancer and received health services from any hospital in Turkey in 2014 were used for the purpose of the study. Data were obtained from the MEDULA System for a total of 126,664 patient. Treatment of costs of patients were calculated based on types of patient admissions (inpatient/outpatient/intensive care) and costs of drugs and medical equipment. Indirect costs and out of pocket costs were not included.

Results: Total medical costs of 126,664 patients was calculated as \$116,792,107.9, with an average treatment cost per patient of \$922.1. Based on types of patient admission, intensive care treatment had the highest average cost with \$2,916.5. In metastatic breast cancer patients, average annual treatment cost per patient is \$2,326.6, which is 2.8 times higher compared to non-metastatic breast cancer patients.

Conclusion: In order to ensure effective resource allocation at micro and macro level, healthcare administrators have to learn costs of diseases with high incidence such as breast cancer. Results obtained from studies on disease costs calculated using the top down cost approach provide data on actual health services use and therefore are seen as important tools for healthcare administrators in terms of effective resource allocation.

Keywords: Breast cancer, disease cost, treatment cost, top down cost approach

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Introduction

Increase in population and lifespan seen throughout the world during last years have resulted in a significant increase in new cancer cases. According to prediction based on current data; approximately 26.4 million annual new cancer cases and 17 million deaths caused by cancer is expected by the year 2030. In 2012, breast cancer was the most common type of cancer among women with more than 25% diagnosis rate among all types of cancer. 1.3 million women are diagnosed with breast cancer and 465,000 women lose their lives due to breast cancer annually. Breast cancer occurs due to many risk factors including early menstruation, late menopause, lactating, and obesity. Breast cancer incidence increases with age. Approximately 80% of breast cancer cases are women aged 50 and above. Breast cancer cases which occur at younger ages have a rather aggressive progression, with a lower survival rate compared to older patients. Similar to the global trend, the most prevalent type of cancer in women in Turkey is breast cancer which comprises 24.9% percent of all cancer cases. In Turkey, breast cancer incidence is 43.0/100,000, with approximately 15,000 women being diagnosed with breast cancer each year (1-5).

In parallel with increase in cancer cases, cancer spending has also significantly increased throughout the world. In majority of developed countries, cancer causes significant increase in national healthcare spending. Drug treatments and hospital admissions comprises the majority of such spending. In the USA, a large share of cancer-based spending is transferred to breast cancer treatment, also medical costs increase as the disease progresses. A study using Medicaid (fee-for-service program) data in the USA found that annual treatment cost of a patient with breast cancer diagnosis is around \$16,345. In the USA, another study using Medicare data found that lifelong treatment cost for patients diagnosed between the ages 65-69 was \$37,306, whereas such cost for patients diagnosed over the age of 85 was \$19,493.

In another study conducted in the USA, Blumen et al. (12) found that the total treatment cost for a patient 12 months after breast cancer diagnosis was approximately \$60,000. In a study conducted in Vietnam, Hoang Lan et al. (13) found that 5-year breast cancer treatment cost for a patient was \$975; breast cancer cases in Vietnam were seen in younger women compared to developed countries, and diseases were usually diagnosed during second stage (6-11).

Disease costs studies based on the principle of measuring the financial burden on the society caused by diseases are conducted for the purpose of determining the financial burden of a medical condition which has an impact on a certain society in terms of use of medical services and loss of production. Information obtained through such studies are used to determine the impact of diseases on the society, thereby assisting policy makers and decision makers in projecting future healthcare costs and making decisions regarding resource allocation. Top down medical costs is a method used frequently in disease costs studies on annual direct medical costs in which data on resource use related to the disease are obtained via the national healthcare system (14-19).

Total healthcare spending in 2017 in Turkey has been calculated as 38,551 million \$, total healthcare spending had a 4.5% share in Gross Domestic Product (GDP). In Turkey, there are no studies on the share of cancer treatments in total healthcare spending. Due to limited resources allocated to healthcare, conducting studies on costs of diseases such as breast cancer which have a significant disease burden on countries is crucial for many countries (20, 21).

In this study, our goal was to use the top down approach in order to determine treatment costs of breast cancer in Turkey from Social Security Institution's (SSI) perspective.

Materials and Methods

Study design and study sample

In order to determine treatment costs of breast cancer patients from SSI's perspective using the top down cost approach, we have used the MEDULA System, which has been created by SSI for the purpose of compiling invoice information obtained from healthcare services servers in electronic format and payment for services, in order to obtain data on outpatients and inpatients with breast cancer diagnosis who have been treated in hospitals contracted by SSI between January-December 2014. Based on data obtained from MEDULA, we were able to gather information on age, sex, outpatient/inpatient admission diagnosis, the procedure/operation/treatment for outpatient/inpatient, laboratory and radiology tests conducted for outpatient/inpatient, services provided to inpatients at intensive care, drugs used in and prescribed by the hospital, comorbidity diseases, and length of stay.

Evaluation of direct medical costs

Data obtained through MEDULA were used to obtain the information below regarding outpatients and inpatients who have applied to a hospital with breast cancer diagnosis in 2014:

- The procedure/operation/treatment at the polyclinic/clinic (along with the ICD-10 code)
 - Laboratory and radiology tests for outpatients/inpatients
 - Services provided to inpatients at intensive care (length of stay for intensive care, drugs used, treatments etc.)
- Drugs used in and prescribed by the hospital for outpatients/inpatients

- Complications occurred during or after the treatment/procedure/operation
- Comorbidities
- Length of stay

In Turkey, the principles of payments made by the SSI for all services offered in health institutions are regulated by Health Application Notification (SUT). SUT is a legislative announcement which provides guidance, guiding, pricing, and other implementation details of the state's health-related social policies.

Health Application Notification procedure scores of surgeries, laboratory and radiology examinations, clinical and intensive care administrations used in calculating medical costs have been calculated using SUT 2014 APP 2B-List of Procedure Scores per Service and APP 2C-List of Procedure Scores based on Diagnosis, with unit prices calculated from SSI's perspective. The list of drugs used were determined using the RX Media Program based on prices paid by the public in 2014 and deemed to units used in the hospital for calculations. At the same time, prices of drugs prescribed were determined by using the RX Media Program based on prices paid by the public in 2014, which was multiplied by the amount of drugs prescribed to determine the total drug costs.

Treatment costs of patients were displayed according to types of patient admission (Outpatient/Inpatient/Intensive Care) and costs of prescribed drugs and medical equipment. At the same time, patients with comorbidity were classified according to Charlson's Comorbidity Index (CCI) and medical costs of breast cancer were calculated based on whether comorbidity is present. CCI has a score for each comorbidity and the scores of comorbidities in this study are as below:

- Diabetes Mellitus = 1 point
- Primary Hypertension = 1 point
- Hypertensive Heart Disease = 1 point
- Chronic Ischemic Heart Disease = 1 point
- Chronic Obstructive Lung Disease = 1 point
- Asthma = 1 point

In addition, metastatic diseases receive 6 points in this index. Based on the classification made according to total scores of patients, the intensity of comorbidities are mild for patients who scored 1-2, medium for patients who scored 3-4, and severe for patients who scored 5 and above; breast cancer medical costs were calculated using this classification.

We were not able to calculate medical costs of breast cancer based on stages due to the fact that the data did not include disease stages. We were able to determine stage IV breast cancer patients in accordance with The **Tumor-Node-Metastasis** (TNM) classification only; we have compared medical costs of stage I-II-III patients and that of stage IV patients.

The data obtained from the SSI MEDULA system did not include the first diagnosis dates of the patients. For this reason, it was not determined which patient was newly diagnosed and which patient was in the follow-up period. However, it is known that medical costs of newly diagnosed/active treatment and follow-up patients differ significantly. Expert opinions were consulted to determine newly diagnosed/active treatment patients and follow-up patients. According to expert opinions, patients who underwent breast cancer surgery in 2014 were identified as newly diagnosed patients and metastatic patients which determined according to TNM classification were accepted as active treatment patients. Breast cancer treatment costs were also determined based on data of these patients.

Statistical Analysis

Data from the MEDULA system were obtained in accordance with the International Classification of Diseases 10th Revision (ICD-10) code of the C50 – Breast Malign Neoplasm in excel file format 7 sepa-

Table 1. Summary Statistics for Breast Cancer Patients, 2014, Turkey

	n	%
Age groups	126,664	
18-39	10.994	8.7
40-64	85.554	67.5
65+	30.116	23.8
Sex		
Male	2.432	1.9
Female	124.232	98.1
CCI ¹		
Charlson score of zero	70.510	55.7
Charlson score of 1-2	45.790	36.2
Charlson score of 3-4	5.841	4.6
Charlson score of 5+	4.523	3.6
Comorbidities		
Yes	56.154	44.3
Primary Hypertension		45.8
Diabetes		22.3
Chronic Ischemic Heart Disease		13.2
Asthma		12.3
COPD ²		5.6
Hypertensive Heart Disease		0.8
Metastasis		
Yes	7.678	6.1
Malignant Neoplasm of Lung		52.4
Malignant Neoplasm of Brain		20.4
Malignant Neoplasm of Liver		16.0
Malignant Neoplasm of Bone		11.2

¹Charlson Comorbidity Index

²Chronic Obstructive Pulmonary Disease

rate folder. Data files were extracted into separate Microsoft Access (MS Access) (Microsoft; USA) files to create a database, modifications necessary for analysis were made by using MS Access and Microsoft Structured Query Language (MS SQL) (Microsoft; USA) program later on, after which data were transferred to Statistical Packages for the Social Sciences 18.0 (IBM Corp.; Armonk, NY, USA). Following such modifications, patient numbers from all files were matched with 126,664 patient data from the initial diagnosis file in order to extract data.

In the first stage, total cost of breast cancer treatment, average treatment cost per patient with standard deviation (SD) and the percentage of total treatment cost according to the type of patient admissions and prescribed drugs and medical equipment were displayed. In the further stage, parametric tests were applied to determine the relationship between cost of breast cancer treatment and independent variables (patient with and without comorbidity, metastatic/non-metastatic patient, patients' CCI score, patients with 1 or more than one metastasis, newly diagnosed and follow-up patients). Because the sample size was 126,664, distribution of the cost of treatment was assumed to be normal and parametric tests were applied. Independent Samples T-Test was analyzed for variables composed of two groups, One-Way ANOVA was applied for variables composed of more than two groups.

This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, ethical approval and informed consent were not required.

Results

Among 126,664 patients included in the study, 98.1% were women and 1.9% were men, 67.5% were between the ages of 40-64, and the average age was 55.7 years (SD: 12.3). 44.3% of breast cancer patients had a comorbidity. Among patients with comorbidities, 45.8% had primary hypertension, 22.3% had diabetes, 13.2% had chronic ischemic heart disease, 5.6% had chronic obstructive lung disease (COPD), 12.3% had asthma, and 13.2% had hypertensive heart disease. Metastasis was detected in 6.1% of patients. Among patients who have metastasis, 52.4% had malignant neoplasm of lung, 20.4% had malignant neoplasm of brain, 16.0% had malignant neoplasm of liver, and 11.2% had malignant neoplasm of bone (Table 1). %85.9 of patients were outpatients, whereas 12.8% were inpatients and 1.3% were admitted to intensive care (Figure 1).

Total medical costs of 126,664 patients with breast cancer diagnosis who have received services from hospital contracted with SSI throughout Turkey between January-December 2014 was calculated as \$116,792,107.9, with an average treatment cost per patient of \$922.1. Total medical cost of outpatients was \$73,534,475.5, total

Table 2. Distribution of Breast Cancer Treatment Cost by Patient Hospital Admission, 2014, Turkey

	n	Total (\$)	Mean (\$)	SD	%
Outpatient	124.308	73,534,475.5	591.6	1.560.3	63.0
Inpatient	18.479	23,159,274.9	1.253.3	2.243.6	19.8
Intensive care	1.815	5,293,348.4	2.916.5	3.874.8	4.5
Drugs and medical equipments	71.333	14,805,009.2	207.5	360.1	12.7
Total Cost	126,664	116,792,107.9	922.1	2.226.8	100.0

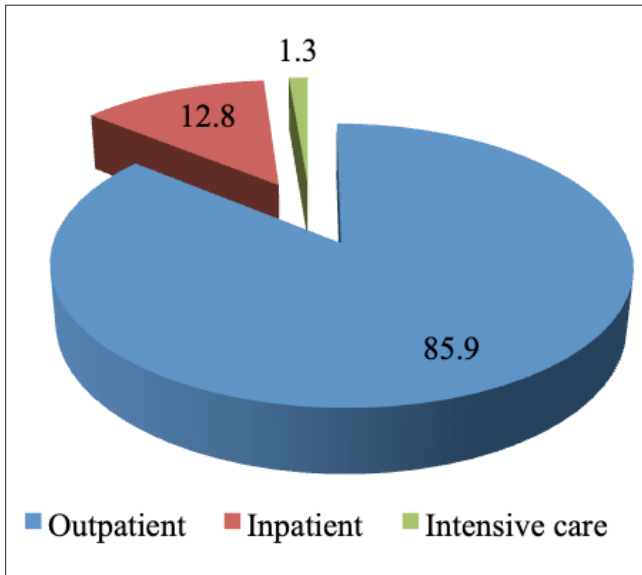


Figure 1. Distribution of Patients Hospital Admission Types, 2014, Turkey

medical cost of inpatients was \$23,159,274.9, total cost of patients admitted into intensive care was 5,293,348.4, and total cost of drugs and medical equipment \$14,805,009.2. 63.0% of total medical costs of breast cancer for 1 year were due to outpatients, whereas this ratio was 19.8% for inpatients, 12.7% for drugs and medical equipment and 4.5% for intensive care treatment (Table 2).

Average medical cost per breast cancer patient with comorbidity was found to be higher compared to average medical cost per patient without comorbidity ($p<0.05$). Average medical cost was 968.8\$ for breast cancer patients with comorbidity. Also, it was found that medical costs of metastatic patients were higher compared to non-metastatic patients ($p<0.05$). Average medical cost was found to be 2,326.6\$ for metastatic breast cancer patients, whereas average medical cost was found to be 831.4\$ for non-metastatic breast cancer patients. Among metastatic breast cancer patients, it was found that medical costs, particularly that of inpatients and outpatients, were significantly high compared to non-metastatic patients (Table 3).

According to the classification made based on CCI, average medical cost per breast cancer patient was significantly high in terms of severe

Table 3. Distribution of Breast Cancer Treatment Cost by Presence of Comorbidity and Metastasis, 2014, Turkey

	Yes			No			p value
	Total (\$)	Mean(\$)	SD	Total (\$)	Mean(\$)	SD	
<i>Comorbidity</i>							
Outpatient	33,411,643.1	608.0	1.546.5	40,122,832.4	578.5	1.548.7	p<0.05
Inpatient	11,046,563.8	1.238.3	951.8	12,112,711.1	1.267.3	974.2	
Intensive care	3,179,728.6	2.917.2	669.3	2,113,619.9	2.915.4	495.0	
Drugs and medical equipments	6,763,838.2	208.9	311.1	8,041,170.9	206.4	274.6	
Total Cost	54,401,773.6	968.8	1.396.8	62,390,334.3	884.9	1.132.8	
<i>Metastasis</i>							
Outpatient	9,300,064.5	1.254.9	2,246.2	64,234,411.0	549.5	1.482.3	p<0.05
Inpatient	4,361,820.2	1.860.9	3,726.9	18,797,454.7	1.165.0	1.866.5	
Intensive care	1,810,492.2	3.063.4	7,243.7	3,482,856.2	2.845.5	5.461.7	
Drugs and medical equipments	2,391,178.7	351.0	523.1	12,413,830.6	192.4	264.8	
Total Cost	17,863,555.5	2.326.6	3.798.8	98,928,552.4	831.4	2.010.7	

Table 4. Distribution of Breast Cancer Treatment Cost According to Charlson's Comorbidity Index Classification, 2014, Turkey

	Mild			Moderate			Severe			p
	Total (\$)	Mean (\$)	SD	Total (\$)	Mean (\$)	SD	Total (\$)	Mean (\$)	SD	
Outpatient	25,316,412.6	563.3	1.453.2	3,082,548.5	543.0	1.387.7	5,012,682.0	1.156.6	2.084.9	$p<0.05$
Inpatient	7,499,605.3	1.148.8	3.432.3	1,169,710.8	1.162.7	3.542.9	2,377,247.7	1.713.9	5.073.9	
Intensive care	1,618,631.0	2.911.2	4.312.6	396,675.3	2.333.4	5.418.9	1,164,422.2	3.198.9	6.890.5	
Drugs and medical equipments	4,885,674.6	229.3	398.7	554,424.1	202.1	792.3	1,323,739.5	455.0	891.9	
Total Cost	39,320,323.5	858.7	2.012.8	5,203,358.7	890.8	2.705.8	9,878,091.3	2.184.0	3.963.4	

comorbidity classification ($p < 0.05$). Average medical cost per patient was calculated as \$2,184.0 for breast cancer patients with severe comorbidity, of which 51.0% was due to outpatients. It was found that average medical cost per patient for breast cancer patients with comorbidities at mild or moderate level were similar (Table 4).

Average medical cost per patient was calculated for metastatic breast cancer patients based on whether they had one or more than one metastasis and it was found that average medical cost per patient was \$3,251.4 for patients with more than one metastasis, which was higher compared to those with one metastasis ($p < 0.05$) (Table 5).

In terms of average medical cost per breast cancer patients for patients who are newly diagnosed/active treatment and follow-up (remission), average medical cost per patient was \$5,112.6 for newly diagnosed/active treatment patients. This average cost was approximately 14 times higher than the average medical costs of follow-up patients ($p < 0.05$) (Table 6).

Discussion and Conclusion

The goal of this study was to determine annual direct medical cost of patients with previous or new breast cancer diagnosis who have received inpatient or outpatient care between January-December 2014 in a hospital in Turkey contracted by SSI. Interpretations were made by taking into consideration that the number of studies conducted on the issue in Turkey and throughout the world are few and medical costs predictions from various countries are heterogeneous in terms of demographics, culture, healthcare system structure, and current resources.

According to data obtained, total medical costs of 126,664 patients with breast cancer diagnosis was calculated as \$116,792,107.9, with an average treatment cost per patient of \$922.1. %85.9 of patients were outpatients, whereas 12.8% were inpatients and 1.3% were admitted to intensive care. Total medical cost of outpatients was \$73,534,475.5, total medical cost of inpatients was \$23,159,274.9, total cost of patients admitted into intensive care was \$5,293,348.4, and total cost of drugs and medical equipment were \$14,805,009.2. 63.0 % of total annual medical cost of breast cancer is due to outpatients. A majority of treatment services provided to breast cancer patients such as radiotherapy, adjuvant and non-adjuvant chemotherapy, and certain hormone treatments do not require in-patient admission (2). Therefore, outpatient medical costs are expected to have a higher share in total cost. Indeed, Allaire et al. (3) and Bonastre et al. (22) have similarly found that a majority of breast cancer medical costs is due to outpatient treatments and the cost of outpatient treatment is significantly higher compared to that of inpatient treatment. In another study, Ekwueme et al. (23) studied medical costs of breast cancer treatment for women between ages 19-44 who are subscribed to Medicaid at national level in the USA and calculated monthly average medical cost per patient to be \$5.711. In the same study, monthly average medical cost of outpatient patients with cancer diagnosis was found to be \$4.058, whereas monthly average medical cost of inpatient patients with cancer diagnosis was \$1.003 and average cost of prescribed drugs was \$539. In contrast, a study by Lindgren et al (24) conducted in Sweden in order to calculate breast cancer costs found that cost of inpatients are higher than that of outpatients. Again, a study by Ivanauskienė et al. (25) found that average cost of inpatients newly diagnosed with breast cancer was 1655€ in 2011, whereas the average cost for outpatients was 564€.

Table 5. Distribution of Metastatic Breast Cancer Treatment Cost According to 1 or More Metastasis, 2014, Turkey

	1 Metastasis			>1 Metastasis			p
	Total(\$)	Mean(\$)	SD	Total(\$)	Mean(\$)	SD	
Outpatient	7,991,349.4	1.221.0	2.176.3	1,308,715.2	1.511.2	2.567.8	p<0.05
Inpatient	3,435,734.1	1.742.3	3.761.9	926,086.1	2.489.5	5.807.6	
Intensive care	1,521,515.8	3.286.2	9.872.9	288,976.4	2.257.6	8.862.9	
Drugs and medical equipments	1,991,926.6	457.0	921.4	399,251.9	612.2	983.7	
Total Cost	14,940,526.0	2.203.9	3.879.0	2,923,029.5	3.251.4	5.613.3	

Table 6. Distribution of Metastatic Breast Cancer Treatment Cost According to Newly Diagnosed/Active Treatment or Follow-Up Patients, 2014, Turkey

	Newly Diagnosed/ Active Treatment Patients			Follow-Up Patients			p
	Total(\$)	Mean(\$)	SD	Total(\$)	Mean(\$)	SD	
Outpatient	44,929,024.1	3.225.4	3.772.9	28,605,451.3	259.2	374.4	p<0.05
Inpatient	20,299,880.9	1.924.5	3.122.8	2,859,394.1	360.5	1.231.8	
Intensive care	5,177,849.8	3.447.3	8.712.9	115,498.6	369.0	1.457.8	
Drugs and medical equipments	5,607,260.3	476.6	599.9	9,197,748.8	175.0	468.9	
Total cost	76,014,015.2	5.112.6	5.022.7	40,778,092.7	364.8	712.6	

In this study, it was determined that cost of breast cancer treatment has statistically significant difference according to all independent variables used in the study (patient with and without comorbidity, metastatic/non-metastatic patient, patients' CCI score, patients with 1 or more than one metastasis, newly diagnosed and follow-up patients).

44.3% of breast cancer patients had a comorbidity. Average medical cost was \$968.8 for breast cancer patients with comorbidities. According to the classification made based on Charlson's Comorbidity Index, average medical cost per breast cancer patient was significantly high in terms of severe comorbidity classification with \$2,184.0. According to Radice and Redaelli (2003), medical costs during initial diagnosis phase of breast cancer was higher for patients with comorbidities compared to patients with no comorbidity and follow-up costs for breast cancer patients was particularly higher for patients with comorbidity. In another study conducted in Germany, Gruber et al. (27) found that 90% of all medical costs of breast cancer patients between ages 30-45 was due to breast cancer treatment, whereas only 50% of all medical costs of breast cancer patients between ages 80-90 was due to breast cancer treatment, which was explained as a result of increase in severity of comorbidities with age and consequent increase in medical costs (26).

In our study, we determined that 6.1% of breast cancer cases develop metastasis. In study, average medical cost for metastatic breast cancer patients was 2.8 higher compared to average medical cost for non-metastatic breast cancer patients. This conclusion is in parallel with conclusion of studies from the literature. In a study based on Medicare costs, Rao et al. (28) calculated the average medical cost for a metastatic breast cancer patient as \$35,164. In a study conducted in Lithuania, Ivanauskienė et al. (25) found the average medical cost for patients with newly diagnosed breast cancer was 2580€, whereas the average medical cost for patients with newly diagnosed "metastatic" breast cancer was 3687€. In the same study, the average medical cost was 2409€ for stage I breast cancer patients and 3688€ for stage IV patients. In another study, Blumen et al. (12) found that average medical cost for stage IV breast cancer patients was significantly high compared to that of stage I, II, or III patients. Similarly, in a study on the costs of different types of cancer in England, Laudicella et al. (29) found that, in terms of colorectal and breast cancers, the medical costs of patients at later stages (stage III-IV) were higher compared to the medical costs of stage I-II patients.

Average medical cost per patient for 1 year for newly diagnosed breast cancer patients was found to be quite high at \$5,112.6. These high costs can be attributed to the fact that this 1-year period is a process during which initial treatment such as surgical, chemotherapy and radiotherapy are administered and diagnosis studies of doctors are carried out. For example, in a study conducted in 2013 on medical cost of breast cancer in Vietnam, Hoang Lan et al. (13) found that initial medical costs, for example chemotherapy costs, have a large share (64.9%) in total cost. In a study conducted in Belgium, it was found that the average medical cost for female breast cancer patients was 10.071€ for the initial diagnosis year, which was down to 3.245€ for the second year. Similarly, Blumen et al. (12) studied breast cancer medical costs for the initial year and the following second year and found that the initial year' average cost of \$47.452 went down to \$5.636 for the second year (30).

Early diagnosis in breast cancer lowers medical costs whereas medical costs increase as the disease progresses, which was shown in this study using average medical costs of metastatic and non-metastatic breast cancer patients. Lack of palliative care centers, which can be seen throughout the world and are slowly being integrated into Turkey's healthcare system, can be considered as one of the main reasons. In Turkey, metastatic patients receive medical treatment towards pain relief at hospital services and intensive care rather than palliative care centers. Many studies from the literature point out to the fact that palliative care center are more cost-effective compared to hospital services and intensive care.

In addition, late-stage care in Turkey is usually administered at home. As a result, patients return to the hospital in case of a severe complication, which lowers life quality of patients and increases medical care costs. Considering the increase in prevalence of cancer in Turkey, increasing the number of palliative care centers to a required amount and preventing unnecessary treatments and procedures by administering proper care would both improve quality of life of patients at last stage while ensure more effective use of resources in terms of healthcare spending.

Optimizing and establishing cancer care, establishing and maintaining accompanying health policies is a difficult and complex issue. Healthcare administrators need such cost studies, which are used as evidence-based data in order to eliminate inequalities in terms of treatment and care of cancer patients and allocate resources effectively. We hope that this study, which is on breast cancer with high incidence and costs, serves as a solid evidence for healthcare administrators and political decision makers.

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Lymph Node Ratio (LNR): Predicting Prognosis after Neoadjuvant Chemotherapy (NAC) in Breast Cancer Patients

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ABSTRACT

Objective: Axillary lymph node status is an important prognostic factor in breast cancer (BC). Residual nodal disease burden after neoadjuvant chemotherapy (NAC) is one of the important prognostic factors to determine the prognosis and in the treatment of BC. Lymph node ratio (LNR) defined as the ratio of the number of positive lymph nodes to total excised axillary lymph nodes, may be a stronger determinant of prognosis than pN in axillary nodal staging, although there is very limited data evaluating its prognostic value in the setting of NAC. In this cohort of patients, we studied the utility of LNR in predicting recurrence and overall survival (OS) after NAC.

Materials and Methods: An Institutional cancer registry was queried from 2009 to 2014 for women with axillary node-positive BC with no evidence of distant metastasis, and who received NAC followed by surgery for loco-regional treatment (axillary dissection with breast conserving surgery or total mastectomy). Patients with axillary complete response were excluded. Locoregional recurrence (LRR), distant recurrence (DR) and overall survival (OS) rates were reviewed regarding pN and LNR.

Results: A total of 179 patients were analyzed. Median follow up time was 24 [25%, 75%: 13-42] months. Patients with pN1 in comparison to pN2 and pN3 had lower rate of LRR (9% vs. 15% and 14%, respectively; $p=0.41$), lower rate of DR (14% vs. 25% and 27%, respectively, $p=0.16$) and increased rate of OS (89% vs. 79% and 78%, respectively, $p=0.04$). In comparison to patients with LNR >20%, patients with LNR ≤20% had lower LRR (9% vs. 14%, $p=0.25$), lower DR (13% vs. 27%, $p=0.01$) and improved OS (89% vs. 79%, $p=0.02$) rates. In the pN1 group, patients who had a LNR >20% had higher DR (22% vs. 14%, $p=0.48$) rates in comparison to patients with LNR ≤20%. In ER/PR (+) patients who had LNR ≤20% DR was 6% compared with 23% in patient who had LNR >20% ($p=0.02$), and in triple negative patients' OS rate was significantly better compared the LNR less/equal or more than 20% (71% vs 33%, $p=0.001$).

Conclusion: Our study demonstrated that LNR adds valuable information for the prognosis after NAC and this additional information should be considered when deciding further treatment and follow-up for patients who had residual tumor burden on the axilla. This observation should be tested in a larger study.

Keywords: Breast cancer, lymph node, neoadjuvant chemotherapy, prognosis

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Introduction

Axillary lymph node status is one of the most important prognostic factors in patients with breast cancer (BC) (1-3). Advanced nodal disease is associated with increased locoregional recurrence (LRR) and poor overall survival (OS) (1, 4-6). The total count of involved lymph nodes has been the determinant of nodal staging (pN) in the current AJCC staging system (6, 7). However, excluding the total number of removed lymph nodes could possibly under stage the axilla, leading to inadequate treatment and an overall improper prediction of prognosis (3, 8). Lymph node ratio (LNR) of total number of positive nodes to the total number of removed lymph nodes has been introduced as an alternative prognostic factor by some studies (3, 9-12): authors have argued that LNR predicts OS and LRR more accurately than pN staging.

Neoadjuvant Chemotherapy (NAC) is a standard treatment modality in locally advanced BC, and is being increasingly used for triple negative and Her 2 neu (+) patients in early stage breast cancer (13-15). Residual nodal cancer burden after neoadjuvant chemotherapy (NAC) is one of the important prognostic factors for determining the prognosis (16). It is well known that NAC is as effective in downstaging the axilla

as treating the primary tumor (13, 17, 18). On the other hand, it has been reported that the total count of lymph nodes excised during axillary dissection is decreased in most cases following NAC as compared to patient with no NAC (13, 17, 18). As a result, traditional pN staging may underestimate true residual nodal disease in patients who have completed NAC. Alternatively, LNR may be a stronger determinant in axillary nodal staging and has only been evaluated by a few studies in the NAC setting (19). The aim of this study was to evaluate the importance of LNR in predicting LRR, distant recurrence (DR) and OS after NAC.

Materials and Methods

After obtaining Institutional Review Board approval, our institutional breast cancer registry was queried from 2009 to 2014 for women with a node positive axilla and no evidence of distant metastasis, who sequentially received NAC and local treatment (segmental or total mastectomy with axillary lymph node dissection [ALND]). Patients with a complete pathologic response in the axilla to NAC were excluded from the study. Also, patients who were lost to follow up, or died because of a non-breast cancer related reason, were excluded from the study. Electronic medical records were reviewed for age and menopausal status at time of diagnosis, histology, histological grade, TNM staging, type of surgery, total count of excised lymph nodes, adjuvant therapies, date of last follow up visit, local/distant recurrence and death.

Hematoxylin and eosin staining or immunohistochemical (IHC) staining were used, and microscopic or macroscopic diseases were accepted to be positive for nodal involvement. LNR was calculated by dividing the number of positive lymph nodes to total number of lymph nodes excised then multiplied by 100. In prior studies LNR was categorized as 1-20%, 21-60% and >61% (20). We categorized into two groups: patients with LNR $\leq$ 20% and patients with LNR >20% based on literature and considering LNR $\leq$ 20% is less tumor burden. LRR, DR and OS rates were assessed regarding pN and LNR.

Student's t-test was used for continuous variables, and chi-square test was used for categorical variables. Linear regression test was used for multivariate analysis. Overall survival (OS) was compared using Kaplan-Meier log-rank tests. Univariate and multivariate Cox models were used to estimate hazard ratios. Statistical package for social sciences (SPSS) software (version 20.0) was used for analysis. P values of less than 0.05 were considered as statistically significant.

Results

A total of 179 BC patients who underwent ALND after NAC were included in the study. Median follow up time was 24 [25%, 75%: 13-42] months. The mean age of the cohort was 53.7 $\pm$ 11.7 years with 65% (n=116) of the cohort being 50 years of age or older. 58% (n=103) of the patients were postmenopausal (Table 1).

At initial presentation, 47% (n=65) of the patients had a clinical stage 3 disease and 63% (n=110) underwent segmental mastectomy. Adjuvant radiation treatment was given to 75% (n=130) of the cohort (85% WBRT, 15% PMRT), (Table 1). The majority had a tumor histology of invasive ductal carcinoma (90%, n=160), while 7% (n=12) had invasive lobular carcinoma. ER /PR+ and Her2/neu (-), triple positive, Her2/neu + and triple negative tumors comprised 53% (n=94), 16% (n=29), 16% (n=9), and 22% (n=39), respectively.

The mean count of lymph nodes excised during ALND was 17.1 $\pm$ 5.4 [10-39]. Rates of pN1, pN2 and pN3 diseases were 59% (n=

105), 29% (n=52) and 12% (n=22), respectively. Fifty-seven percent (n=102) of the cohort has a LNR $\leq$ 20%. Lymphovascular invasion was seen in 45% (n=79) of the patients, and 44% (n=78) of the patients with axillary metastases had extracapsular invasion in the metastasized lymph node (Table 1).

Twenty patients (11%) had a LRR in the cohort. Patients with LNR $\leq$ 20% had lower LRR rate compared with LNR >20% (9% vs. 14%, p=0.25) (Table 2). Patients with pN1 disease had lower LRR rate (9%) in comparison to pN2 and pN3 disease (15% and 14%, respectively, p=0.41). Among patients with pN1 disease, patients with LNR $\leq$ 20% had lower LRR rate compared with LNR >20% (8% vs. 11%,

Table 1. Descriptive characteristics of the patient group (n=179)

Age (y)		53.7 $\pm$ 11.7
Median [%25, 75%]		54 [46.61]
Follow up (months) (median (25%, 75%))		24 [13.42]
Postmenopausal patients		103 (58)
Stage	1	13 (9)
	2	61 (44)
	3	65 (47)
Mastectomy	Segmental	110 (63)
	Total	65 (37)
Lymph nodes examined		17.3 $\pm$ 5.5
Median [%25, 75%]		16 [13-20]
Adjuvant radiotherapy		130 (75)
Tumor histology	Ductal	160 (90)
	Lobular	12 (7)
	Other	6 (3)
Tumor grade	1	100 (62)
	2	59 (37)
	3	2 (1)
Hormonal receptor status	ER and/or PR (+),	
	Her-2 (-)	94 (53)
	Triple positive	29 (16)
	HER 2 type	16 (9)
	Triple negative	39 (22)
pN stage	1	105 (59)
	2	52 (29)
	3	22 (12)
Lymph node ratio (%)	$\leq$ 20	102 (57)
	>20	77 (43)
Lymphovascular invasion (%)		79 (45)
Extracapsular invasion in the lymph node (%)		78 (44)

Categorical data were presented as n (%)

Continuous data were presented as (mean $\pm$ SD [range]) unless stated otherwise

Table 2. Comparison of pN staging and LNR with LRR

Locoregional Recurrence		No (%)	Yes (%)	p
Lymph node ratio	≤20%	93 (91)	9 (9)	0.25
	>20%	66 (86)	11 (14)	
pN	1	96 (91)	9 (9)	0.41
	2	44 (85)	8 (15)	
	3	19 (86)	3 (14)	
pN1	≤20%	88 (92)	8 (8)	0.78
	>20%	8 (89)	1 (11)	
Lymph node ratio ≤20%	pN1	88 (92)	8 (8)	0.49
	pN2	5 (80)	1 (20)	
	PN3	0 (0)	0 (0)	
ER/PR (-), ≤20%	20 (83)	4 (17)	0.23	0.38
Her 2 (-)	>20%	10 (67)	5 (33)	
ER/PR (-),	≤20%	11 (92)	1 (8)	
Her 2 (+)	>20%	3 (75)	1 (25)	0.40
ER/PR (+),	≤20%	45 (96)	2 (4)	
Her 2 (-)	>20%	43 (91)	4 (9)	
ER/PR (+),	≤20%	17 (89)	2 (11)	0.97
Her 2 (+)	>20%	9 (90)	1 (10)	

Categorical data were presented as n (%)
Continuous data were presented as (mean ±SD [range]) unless stated otherwise

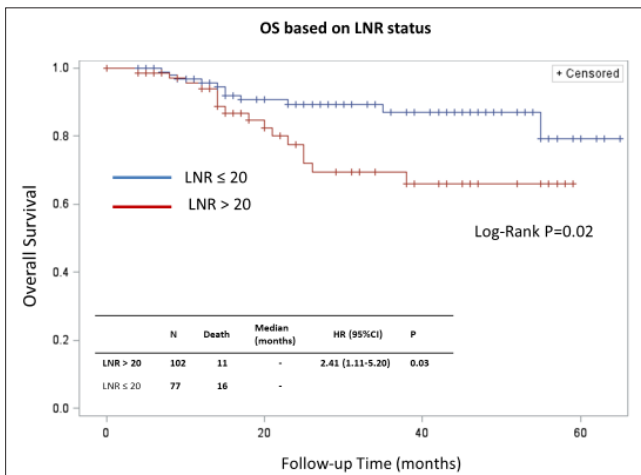


Figure 1. KM survival curve based on LNR

$p=0.78$). Among patients with $\text{LNR} \leq 20\%$, patients with pN1 disease had lower LRR rate (8%) in comparison to patients with pN2 disease (20%) ($p=0.49$).

We then evaluated the data for distant recurrence; 34 patients (19%) had a DR in entire cohort. Patients with a pN1 disease had a lower DR rate (14%) in comparison to patients with pN2 and pN3 diseases (25% and 27%, respectively, $p=0.16$) as projected. After we combined the pN2 and pN3 patients and compared it to the pN1 patients the p value for DR approached significance ($p=0.056$). In

our study, $\text{LNR} > 20\%$ increased DR rate by 2.57-fold (27% vs. 13%, $p=0.01$, OR 2.57 [1.19-5.54]). Among patients with pN1 disease, patients with $\text{LNR} \leq 20\%$ had lower DR rate compared with $\text{LNR} > 20\%$ (14% vs. 22%, $p=0.48$). Patients with pN2 disease and $\text{LNR} \leq 20\%$ had a DR rate of 0% while it is 25% ($n=13$) in all pN2 patient without considering the LNR; all pN2 patients with DR had $\text{LNR} > 20\%$ (Table 3). In ER/PR (+) and Her 2/neu (-) patients who had $\text{LNR} \leq 20\%$ DR was 6% compared with 23% in patient who had $\text{LNR} > 20\%$ ($p=0.02$).

Overall survival rate was 85% in our cohort and 27 patients (15%) died because of BC during follow up. OS rate was higher among patients with $\text{LNR} \leq 20\%$ compared with $\text{LNR} > 20\%$ (89% vs. 79%, $p=0.02$) (Table 4). Hazard of death was significantly higher in the $\text{LNR} > 20\%$ compared with $\text{LNR} \leq 20\%$ with a HR of 2.41 (95%CI: 1.11-5.20; $p=0.03$) (Figure 1). OS rate was higher among pN1 patients (89%) in comparison to pN2 (79%) and pN3 patients (78%) ($p=0.04$). After we combined the pN2 and pN3 and compared with pN1 for OS p value was statistically significant; mortality rate was 10.4% in the pN1 group vs 21.6%, in the pN2/3 patients; $p=0.04$). Among patients with pN1 disease, OS rate was similar between patients with $\text{LNR} \leq 20\%$ and $\text{LNR} > 20\%$ (90% vs. 89%, respectively, $p=0.89$). In triple negative patients, OS rate was significantly better among patients with a $\text{LNR} \leq 20\%$ compared with $\text{LNR} > 20\%$ (71% vs 33%, $p=0.001$). Crude and adjusted for age, ER, PR and Her2/neu status multivariate Cox regression analysis showed that hazard of death was significantly high in $> 20\%$ LNR and pN2-3 patients (Table 5).

Table 3. Comparison of pN staging and LNR with DR

Distant Recurrence (DR)		No (%)	Yes (%)	p
Lymph node ratio	≤20%	89 (87)	13 (13)	0.01
	>20%	56 (73)	21 (27)	
pN	1	90 (86)	15 (14)	0.16
	2	39 (75)	13 (25)	
	3	16 (73)	6 (27)	
pN1	≤20%	83 (86)	13 (14)	0.48
	>20%	7 (78)	2 (22)	
Lymph node ratio ≤20%	pN1	83 (86)	13 (14)	0.33
	pN2	6 (100)	0 (0)	
	PN3	0 (0)	0 (0)	
Lymph node ratio >20%	pN1	7 (78)	2 (22)	0.93
	pN2	33 (72)	13 (28)	
	PN3	16 (73)	6 (27)	
ER/PR (-),	≤20%	16 (67)	8 (33)	0.41
Her 2 (-)	>20%	8 (53)	7 (47)	
ER/PR (-),	≤20%	12 (100)	0 (0)	0.07
Her 2 (+)	>20%	3 (75)	1 (25)	
ER/PR (+),	≤20%	44 (94)	3 (6)	0.02
Her 2 (-)	>20%	36 (77)	11 (23)	
ER/PR (+),	≤20%	17 (89)	2 (11)	0.48
Her 2 (+)	>20%	8 (80)	2 (20)	

Categorical data were presented as n (%)

Continuous data were presented as (mean ±SD [range]) unless stated otherwise

Discussion and Conclusion

It is well documented that axillary lymph node metastasis and the extent of axillary disease is one of the most important prognostic factors in the care of the BC patient (3). The number of lymph nodes obtained during ALND can however be affected by several factors. These may include inadequate surgical experience, increased patient age, patient's co-morbidities and improper handling of the specimen. The latter can therefore lead to under-staging of the disease, improper prediction of prognosis and inadequate treatment (4, 8, 9). LNR has been suggested as an alternative or complementary method to AJCC staging (1, 11-14, 21-25). It aims to improve the prognostication of BC by reducing the effect of heterogeneity of axillary procedures on staging the axilla. Recently, there has been increasing evidence demonstrating the superiority of LNR to traditional pN staging as an indicator of axillary tumor burden. In addition, a ratio based staging system, which confers additional information on the total number of lymph nodes dissected, can be a powerful predictor of prognosis in patients with axillary disease (25-30). In our study DR rate was significantly higher in patient who had LNR>20 compared with LNR ≤20%, but pN was not a discriminator for DR. On the other hand, patients who had ER/PR + and Her2/neu (-) phenotype tumor DR was almost 4 times higher when LNR was greater than 20%.

Vinh-Hugh et al. (25) and Kuru et al. (27) have emphasized the improvement in survival as the numbers of total lymph nodes and negative lymph nodes increased and reported the LNR as a significant independent predictor for survival in patients with axillary involvement. In our study, LNR and pN were both good discriminators to predict the OS rate, but LNR was a better predictor for DR than pN. Patients with a diagnosis of triple negative phenotype and LNR >20% had more than 2 times risk of death compared with the same phenotype with LNR ≤20% (p=0.001).

Studies have shown that quantity of lymph nodes retrieved during ALND in patients who have received NAC is significantly lower than the patient, who did not receive NAC (6-9). This can lead to under-staging the disease and predicting the prognosis incorrectly. Although LNR has been repeatedly studied in patients undergoing upfront surgery, very few studies examined its efficacy in NAC setting (10, 19, 31). Tsai et al. (19) studied on 165 node positive patients and found that lymph node categories were inversely associated with disease free survival. They picked a LNR single value of 15% and found that LNR<15% was significantly associated with disease free survival in ER/PR+ (p=0.04) and triple negative patients (p=0.001). In another study Kim et al. (10) studied LNR in patients with 1-3 positive LNS and found in the multivariate analysis that >18% of LNR had HR=1.81 (95%CI, 1.34-2.45, p=0.0001), and the estimated survival

Table 4. Survival rate regarding pN staging and LNR

		Alive (%)	Dead (%)	LogRank P
Lymph node ratio	≤20%	91 (89)	11 (11)	0.02
	>20%	61 (79)	16 (21)	
pN	1	94 (89)	11 (11)	0.04
	2	41 (79)	11 (21)	
	3	17 (77)	5 (23)	
pN1	≤20%	86 (90)	10 (10)	0.89
	>20%	8 (89)	1 (11)	
Lymph node ratio ≤20%	pN1	86 (90)	10 (10)	0.84
	pN2	5 (83)	1 (17)	
	PN3	0 (0)	0 (0)	
ER/PR (-),	≤20%	17 (71)	7(29)	0.001
Her 2 (-)	>20%	5 (33)	10 (67)	
ER/PR (-),	≤20%	12 (100)	0 (0)	0.01
Her 2 (+)	>20%	3 (75)	1 (25)	
ER/PR (+),	≤20%	44 (94)	3 (6)	0.48
Her 2 (-)	>20%	43 (91)	4 (9)	
ER/PR (+),	≤20%	18 (95)	1 (5)	0.73
Her 2 (+)	>20%	9 (90)	1 (10)	

Categorical data were presented as n (%)
Continuous data were presented as (mean ±SD [range]) unless stated otherwise

Table 5. Crude and adjusted Cox models for overall survival

	Univariate		Multivariate ^a	
	HR (95%CI)	P	HR (95%CI)	p
Lymph node ratio				
≤20%	Reference		Reference	
>20	2.41 (1.12-5.20)	0.02	4.22 (1.85-9.63)	0.0006
pN				
pN1	Reference		Reference	
pN2	2.53 (1.09-5.85)	0.03	4.07 (1.68-9.84)	0.002
pN3	2.85 (1.00-8.21)	0.05	5.89 (1.84-18.88)	0.003

^aAdjusted For Age
Estrogen receptor, progesterone receptor, and Her2 status

was 76.7% in the LNR<18% and it was 61.4% in the LNR>18%. In addition to the overall survival they found that postmastectomy radiation therapy increased the estimated survival rate at 10 years around 30% in the group that had LNR>18% compared with low LNR.

The number of required LNs for ALND is also controversial and there is a potential possibility of down staging the axilla by examining low number of LNs (10, 21, 28, 32). While the AJCC recommends removing and examining a minimum of 6 LNs, Fisher et al. (33) has demonstrated that nodal involvement can most reliably be evaluated

if at least 10 LNs are evaluated. The predictability of the prognoses by LNR and pN has also been shown to depend on evaluation of at least 10 or more LNs (34). In this study, we utilized the previously validated cutoffs (≤20%; 20-65%; ≥65%) for LNR categories, however we simplified the cutoffs to ≤20% vs >20%. These were tested via bootstrap resampling of a population-based cohort of women with lymph-node positive BC (8).

pN staging classification tends to accept all axillary dissections as homogenous. It is therefore, important to keep in mind that when

heterogeneity in the number of excised and examined lymph nodes is encountered (i.e. patients, who received NAC), LNR-based classification as defined by $\leq 20\%$ vs $>20\%$ can give additional information in predicting prognoses of the disease and this knowledge should be considered when deciding further treatment and follow-up patients who had residual tumor burden on the axilla.

This study has a limited number of NAC patients, but the accumulation of data from large prospective studies with longer follow up periods, will solidify the LNR-based classification system.

In conclusion residual nodal tumor burden after NAC is a sign of poor prognosis, however, how much residual tumor is left is important to predict the prognosis and it also affects the decision of the further treatment. Notwithstanding, LNR-based classification is not widely used it is a useful additional tool that can be implemented in the clinic practice to better predicting prognosis and planning the further treatment after NAC inpatient with BC.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Magee Womens Hospital of University of Pittsburgh Medical Center.

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

Peer-review: Externally peer-reviewed.

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

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Prognostic Importance of Ki-67 in Breast Cancer and Its Relationship with Other Prognostic Factors

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ABSTRACT

Objective: The clinical feature of breast cancer is very heterogeneous because of the variable prognostic factors impact its behaviour. The aim of study is to find the prognostic importance of Ki-67 and to analyse the correlation between Ki-67 index and the other conventional prognostic factors in breast cancer patients.

Materials and Methods: Between 2010 and 2017, patients with invasive ductal carcinoma who received radiotherapy after surgery were included in study. A single pathologist re-defined of all cases retrospectively. Ki-67 were established three categories based on Ki-67 levels: low (<10%), intermediate (10-25%) and high (>25%).

Results: A total of 258 patients were included. 46 of 258 (18%) patients were in low, 82 of 258 (32%) patients were in intermediate and 130 of 258 (50%) patients were in high Ki-67 group. There were no correlations between menopausal status, age, and Ki-67 level. Low-pT stages tended to have low Ki-67 expression ($p=0.07$). Low-pN stages correlated with low Ki-67 values ($p=0.007$). Patients with ECE (+) were prone to have higher Ki-67 values ($p=0.02$). The significant correlation was seen between Ki-67 and tumour grading ($p<0.0001$). Patients with LVI (+) had higher Ki-67 expression ($p=0.007$). Luminal A tumours were correlated with low Ki-67 group ($p<0.0001$). Ki-67 values had significant effect on DFS ($p=0.03$) but not OS ($p=0.09$).

Conclusion: This study showed that high Ki-67 expression is associated with higher pT-stage, higher pN-stage, higher grade, ER/PR negativity, HER2/neu positivity, ECE and LVI positivity. The prognostic impact of Ki-67 was only demonstrated for DFS.

Keywords: Breast cancer, Ki-67, prognostic factors, radiotherapy, survival

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Introduction

The most common cancer type in women is breast cancer and the lifetime risk for breast cancer is 12% (1). The clinical feature of breast cancer is very heterogeneous because of the variable prognostic factors impact its behaviour (2). To know prognostic factors may help to estimate the prognosis and to choose the most appropriate treatment modality. Age, histopathologic subtypes, tumour size, tumour grade, lymph node involvement, extracapsular extension (ECE), lymphovascular invasion (LVI), and hormonal receptor status are the most important conventional prognostic factors (3).

In addition to these factors, to know proliferation pattern of tumour is important for the treatment decision. In routine clinical practice, immunohistochemical evaluation of Ki-67 is frequently utilised to assess proliferative features of tumour cells. Except resting phase (G₀), Ki-67 is detected in all proliferative phases of the cell cycle (G₁, S, G₂, and M). Ki-67 existing cells can be immunochemically marked, imaged, counted and showed as a percentage of total cells (4). It has been used for many years for breast cancer; it is currently utilised to distinguish between Luminal A-like and Luminal B-like subtypes in ER+/HER2- breast cancer and physicians frequently use Ki-67 index for making a decision on adjuvant treatment (5-7).

In spite of consistent data about Ki-67 index, the relationship between Ki-67 index and the other prognostic factors remains uncertain. The results of studies evaluating the association between Ki-67 and tumour grade in breast cancer have been varied. Some of the research-

ers claimed that high grade tumours were correlated with high expression of Ki-67, whereas the others did not find any association (8-11). The relationship between Ki-67 index and steroid hormone receptors (oestrogen hormone receptor (ER) and progesterone hormone receptor (PR)) were investigated in previous studies. Most of the studies showed a negative correlation between steroid hormone receptors and Ki-67 levels (8-10). In regard to human epidermal growth factor receptor 2 (HER2) status, the results are controversial, as some of the researchers have found a positive correlation but the others have not (8, 12, 13). The results of studies which investigated the association between tumour stage and Ki-67 index conflicted with each other. The relationship between nodal status and Ki-67 index is not clear yet (8). The effect of Ki-67 values on survival outcome is also uncertain.

The primary aim of this study was to find the prognostic importance of Ki-67 and to analyse the correlation between Ki-67 index and the other conventional prognostic factors in breast cancer patients who received curative radiotherapy. The secondary end point of this study was to evaluate the other possible prognostic factors that affect overall survival (OS) and progression free survival (PFS).

Materials and Methods

Patient population

Between 2010 and 2017, patients with invasive ductal carcinoma who received radiotherapy after surgery were included in this study. Totally, the data of 590 women with breast cancer were retrospectively evaluated. Patients age <18, Karnofsky Performance Status <70, had another concurrent cancer, had an incomplete lymph node dissection, received neoadjuvant chemotherapy, had bilateral tumours, had initially distant metastases, and follow-up period <12 months were excluded. Finally, 258 patients with breast cancer were evaluated.

This research was confirmed by the board of Necmettin Erbakan University Meram School of Medicine and complied with the Declaration of Helsinki. Because of the retrospective nature of study, informed consent was not taken from the patients.

Treatment and follow-up

After surgery, all patients received their radiotherapy, chemotherapy and/or hormone therapy according to routine treatment procedures. Patients were examined for tumour status in 3-month intervals for two years and in a 6-month interval for three to five years, and annually thereafter.

Histopathological evaluation

A single pathologist (E.S.) re-defined the histologic examples of all cases retrospectively, based on the guideline recommendations of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP protocols) without information of the patient outcomes (14). The histologic type, tumour grade, tumour dimension, number of metastatic axillary lymph nodes, the existence of ECE and the existence of LVI were re-evaluated using haematoxylin- and eosin-stained, formalin-fixed and paraffin wax-embedded tumour slides. Pathological staging was performed using the 7th American Joint Committee on Cancer (AJCC) TNM staging system. ER and PR were judged as a positive when the nuclei were stained in more than 1% of the cancer cells. HER2 was judged as a positive when strong complete staining in >10% of cancer cells (ie, 3+). Fluorescent in situ hybridization (FISH) or silver-enhanced in-situ hybridization (SISH) was carried out when moderate complete staining in >10 % of cancer cells (i.e., 2+). HER2 was accepted positive when the HER2/CEP17 ratio >2 and gene copy number >4 signal/cell (15).

Immunohistochemically stained sections were used for the assessment of Ki-67. MIB-1 staining for Ki-67 was examined with 4x and 10x object lenses to identify the area of most intense staining ("hot spot"). Scoring Ki-67 was performed by counting at least 500 tumour cells in high-power fields with a 40x object lens. All brown-stained nuclei, regardless of staining intensity, were counted as positive. We did not specify any cut-off value because of there is still no absolute cut-off value was defined for the Ki-67 proliferation index. We established three categories based on Ki-67 level: low (<10%), intermediate (10-25%) and high (>25%) as some authors specified 'low proliferative activity' as Ki-67 values <10%, and 'high proliferation activity' as Ki-67 values >25%. Ki-67 levels between 10% and 25% were defined as a grey zone interval (16).

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences software version 22.0 (IBM Corp.; Armonk, NY, USA). Patient, treatment and disease characteristics were evaluated using descriptive statistics. The correlation between Ki-67 groups and other clinicopathologic parameters were evaluated using Pearson's Chi-square test, and Fisher exact test or Spearman test. The relationship between absolute Ki-67 values and other clinicopathologic parameters were assessed using an ANOVA test. Different groups of continuous variables were compared by Kruskal-Wallis test. The overall survival (OS) was identified as the time from the surgery to the date of the death or last follow-up. The disease-free survival (DFS) was identified as the time from the surgery to the date of demonstrated recurrence/progression or death. Survival analyses were evaluated using Kaplan-Meier test and two-sided log-rank test was performed to make a comparison between subgroups. Hazard ratios and 95% confidence intervals (CIs) were measured using Cox regression analysis. The variables which had statistical significance in univariate analysis ($p < 0.05$) were added in multivariate analysis as covariates. A p value less than 0.05 was accepted statistically significant.

Results

Patients, tumour and treatment characteristics

A total of 258 patients were included in the current study with a median follow of 35 (range; 12-133) months from 2010 to 2017. One hundred of 258 patients (39%) were premenopausal, 24 of 258 patients (9%) were perimenopausal and 134 of 258 patients (52%) were postmenopausal. The median age was 52 (range; 27-83) years. The detailed patients, tumour, and treatment features are displayed in Table 1.

Relationship of Ki-67 status with patient and tumour characteristics

The median Ki-67 value was 27.5% (range: 0 to 95%; mean: 30%). Forty-six of 258 (18%) patients were in low, 82 of 258 (32%) patients were in intermediate and 130 of 258 (50%) patients were in high Ki-67 expression group. There were no correlations between menopausal status, age and Ki-67 groups ($p=0.3$ and $p=0.6$, respectively). Concerning the dimension of tumour, low-pT stages tended to have low Ki-67 expression ($p=0.07$). Ninety-two percent of low expression group had pT1-2 disease, whereas only 8% of the low expression group had pT3-4 disease. Similarly, 87% of the intermediate Ki-67 group had pT1-2 disease, whereas 13% of the intermediate Ki-67 group had pT3-4 disease. Because of low number of pT3-4 cases (32 of 258 patients), to make a conclusion about the high expression group is difficult but 53% of patients with pT3-4 disease were in high expression group. Regarding the

Table 1. Patients, tumour and treatment characteristics

Variables	No. of patients (total: 258)	%
Age (years)		
Median (range)	52 (27-83)	
Menopausal status		
Premenopausal	100	39
Perimenopausal	24	9
Postmenopausal	134	52
Surgery type		
Modified radical mastectomy	148	57
Breast conserving surgery	110	43
Tumour grade		
Grade 1	27	11
Grade 2	168	65
Grade 3	63	24
Tumour stages		
pT1	77	30
pT2	149	58
pT3	22	8
pT4	104	
Lymph node stages		
pN0	94	36
pN1	93	36
pN2	44	17
pN3	27	11
Hormonal status		
ER (+) PR (+) HER2 (-)	159	62
ER (+) PR (+) HER2 (+)	53	20
ER (-) PR (-) HER2 (+)	23	9
Triple (-)	23	9
ECE		
Yes	97	38
No	128	50
Unknown	33	12
LVI		
Yes	116	45
No	125	48
Unknown	17	7
Ki-67 values		
Low (0-9%)	46	18
Intermediate (10-25%)	82	32
High (>25%)	130	50

ER: oestrogen hormone receptor; PR: progesterone hormone receptor; HER2: human epidermal growth factor receptor 2; ECE: extracapsular extension; LVI: lymphovascular invasion

Table 2. The relationship between absolute Ki-67 values and clinicopathologic variables

Variables (n=258)	Absolute Ki-67 value (mean)	p
Menopausal status		
Premenopausal	30.50	0.1
Perimenopausal	31.50	
Postmenopausal	29.93	
Total	30.29	
Tumour grade		
Grade 1	11.96	<0.0001*
Grade 2	29.05	
Grade 3	41.46	
Total	30.29	
Tumour stages		
pT1-2	29.95	0.5
pT3-4	32.72	
Total	30.29	
Lymph node stages		
pN0-1	27.23	0.001*
pN2-3	38.07	
Total	30.29	
Hormonal status		
ER (+) PR (+) HER2 (-)	24.71	<0.0001*
ER (+) PR (+) HER2 (+)	31.04	
ER (-) PR (-) HER2 (+)	48.13	
Triple (-)	49.35	
Total	30.29	
ECE		
Yes	27.08	0.02*
No	34.07	
Total	30.09	
LVI		
Yes	26.93	0.02*
No	33.70	
Total	30.19	
Ki-67 values		
Low (0-9%)	4.09	<0.0001*
Intermediate (10-25%)	15.29	
High (>25%)	49.03	
Total	30.29	

ER: oestrogen hormone receptor; PR: progesterone hormone receptor; HER2: human epidermal growth factor receptor 2; ECE: extracapsular extension; LVI: lymphovascular invasion

nodal status, low-pN stages were correlated with low Ki-67 expression ($p=0.007$). Eighty-seven percent of low Ki-67 group had pN0-1 disease while 65% of pN2-3 patients had high expression of Ki-67. Patients with ECE (+) were prone to have high Ki-67 values, whereas patients with ECE (-) prone to have low Ki-67 values ($p=0.02$). Seventy-one percent of patients with ECE (-) were in low expression group, whereas 60% of patients with ECE (+) were in high expression group. The significant association was seen between Ki-67 levels and tumour grading ($p<0.0001$). Low-grade tumours were correlated with low Ki-67 expression whereas high-grade tumours were correlated with high Ki-67 expression. Forty-eight percent, 37% and 15% of grade 1 tumours were in low, intermediate and high Ki-67 expression group, respectively. Nine percent, 24% and 67% of grade 3 tumours were in low, intermediate and high Ki-67 expression group, respectively. Patients with LVI (+) had higher expression of Ki-67 than patients with LVI (-) ($p=0.007$). Eighty percent of patients with LVI (-) were in low expression group. ER/PR (+) tumours were correlated with low Ki-67 expression ($p<0.0001$). Ninety-eight percent of patient in low Ki-67 expression group had ER/PR (+) disease whereas 28% of patients with ER/PR (+) were in high Ki-67 group. Regarding HER2 status, HER2 (+) tumours were correlated with high expression of Ki-67 ($p<0.0001$). In a low Ki-67 group, 80% of patients were HER2 (-) while 68% of HER2 (+) patients were in high Ki-67 group. Parallely, hormonal receptor status was associated with Ki-67 values ($p<0.0001$). Luminal A (ER/PR (+), HER2 (-)) tumours were correlated with the low Ki-67 group. In low expression group, 81% of patients had ER/PR (+), HER2 (-) (Luminal A-like subtype), 17% of patients had ER/PR (+), HER2 (+) (Luminal B-like subtype), 2% of patients had ER/PR (-), HER2/neu (+) and none of the patient had ER/PR (-), HER2 (-) (triple (-)). Correlatively, 83%, 17% and 0% of patients with triple (-) disease were in high, intermediate and low Ki-67 expression group, respectively. The relationship between absolute Ki-67 values and clinicopathologic variables were also evaluated and the results were shown in Table 2.

Survival Analysis

During a median follow-up of 35 months, 250 of 258 patients (97%) were alive and 16 of 258 patients (4%) had distant metastases. The mean OS and DFS were 127 (range; 123 to 131) and 121 (range; 115 to 126) months, respectively. 5-year OS and DFS rates were 95% and 87%, respectively. The tumour grade ($p=0.01$), hormonal status ($p=0.006$), nodal stage ($p=0.01$), and LVI ($p=0.03$) were significant prognostic factors for OS in univariate analysis. Regarding Ki-67 values, 6 of 8 died patients

(75%) were in high expression group and 2 of 8 died patients 25% were in intermediate expression group while there was no died patient in low expression group. However, these differences did not reach **significance** (Figure 1; $p=0.09$). In terms of DFS, the tumour grade ($p=0.001$), hormonal status ($p=0.003$) and Ki-67 values ($p=0.03$) were independent prognostic factors for DFS. Twelve of 16 patients (75%) with metastases were in high expression group, 3 of 16 patients with metastases were in intermediate expression group and only 1 patient had metastasis in the low expression group. The disease-free survival outcomes based on Ki-67 values were shown in Figure 2 ($p=0.03$). According to multivariate analysis, only the hormonal status was independent prognostic factor for both OS ($p=0.02$; HR=9.98 [1.40-15.41]) and DFS ($p=0.03$; HR=4.20 [1.14-15.41]).

Discussion and Conclusion

The primary aim of this study was to find the prognostic importance of Ki-67 index and to analyse the correlation between Ki-67 index and other conventional prognostic factors in breast cancer patients who received curative radiotherapy.

Despite the variability in the cut-off points (5% to 34% or more) and the lack of standardized procedure for Ki-67 assessment, to find its predictive and prognostic value has been frequently attractive for researchers. The 2009 St. Gallen consensus divided three subgroups according to Ki-67 levels: low ($\leq 15\%$), intermediate (16% to 30%), and high ($\geq 30\%$); the 2011 St. Gallen recommended a Ki-67 cut-off point of 14% for distinguishing between Luminal A-like and Luminal B-like tumours; the 2013 St. Gallen changed the cut-off point to 20%, the 2015 St. Gallen advised the Ki-67 values between 20% and 29% was used to distinguish luminal B-like disease (5, 6, 16).

In the PACS01 study, the authors showed that, with using a cut-off point as 14%, the risk of misclassification was 37% when Ki-67 value was between 10-25%, and it was 11% when Ki-67 value was $<10\%$ or $\geq 25\%$ (17). In this study, there was not any cut-off point defined and Ki-67 was established as three categories based on levels: low ($<10\%$), intermediate (10-25%) and high ($>25\%$).

In the current study, we did not show any correlation between patient age, menopausal status, and Ki-67 index but most of well-known conventional prognostic factors significantly associated with Ki-67 values. Our data indicated that low-pT stages tended to have low expression of Ki-67. These findings were in accordance with the outcomes of

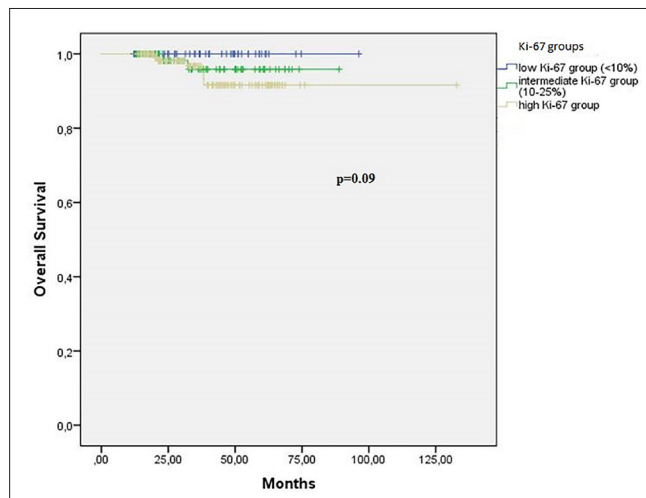


Figure 1. Overall survival based on Ki-67 values

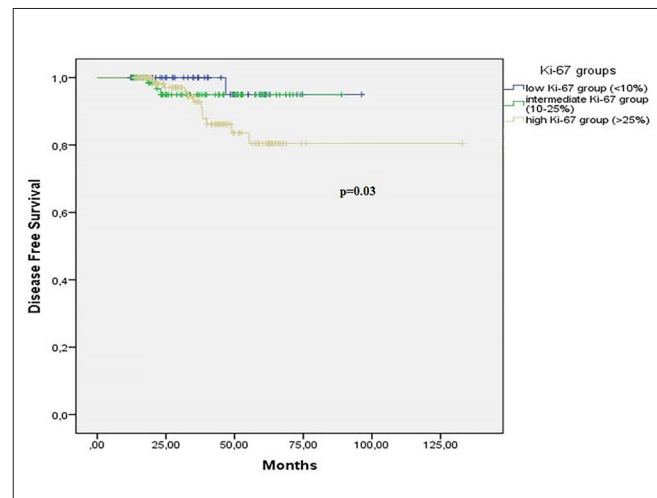


Figure 2. Disease free survival based on Ki-67 values

Fausto et al. (18) and Inwald et al. (19). In accordance with the current research, Alco et al. (20) reported the results of largest study from Turkey in 2015 and revealed that the Ki-67 index was positively correlated with an increasing tumour size. Low-pN stages were also correlated with low Ki-67 expression. Our findings were consistent with the results of previous studies (19-21). In the current study, the significant association was seen between Ki-67 levels and tumour grading. Low-grade tumours were correlated with low Ki-67 expression whereas high-grade tumours were correlated with high Ki-67 expression. This correlation was demonstrated in many previous studies (8-10, 19-22). The other powerful correlation was shown in steroid hormone receptor status and expression of Ki-67 in former research (8-10, 19-22). These studies showed a remarkable association between higher Ki-67 expression and ER/PR negativity. Our results were consistent with the literature. Regarding HER2 status, the results were inconsistent. Some of the studies showed a positive association between higher Ki-67 expression and HER2 negativity, but most of the studies displayed a positive correlation between higher Ki-67 expression and HER2 positivity (8, 12, 13, 19-22). In the current study, high Ki-67 expression was correlated with HER2 positivity. In addition, with these results, we found that Luminal A (ER/PR(+), HER2(-)) tumours tended to have low Ki-67 expression and triple (-) tumours tended to have high Ki-67 expression. In accordance with our results, Alco et al. (20) showed that the Ki-67 index was negatively correlated with HR positivity, and positively correlated with HER2 positivity.

We did not get any data which investigate the correlation between ECE and Ki-67 index in literature but according to our results, patients with ECE (+) prone to had higher Ki-67 values. There are very limited data analysing the correlation between LVI and Ki-67. In the present study, patients with LVI had high expression levels of Ki-67 similar to the results of Alco et al. (20).

The results of the studies investigating the effect of Ki-67 on survival outcomes were conflicting with each other. Although some of the researchers showed prognostic effects of Ki-67 expression on survival outcomes, the others did not demonstrate any correlation (8, 19, 21, 23). We found a significant relationship between high expression of Ki-67 and poor DFS. In spite of most of deaths (75%) were in high expression group we did not find any correlation between Ki-67 expression and OS. This may be because of a relatively small number of patients and short follow-up time.

Currently, Ki-67 assessment is used for prediction of prognosis, to distinguish between Luminal A-like and Luminal B-like subtypes in ER+/HER2- and to help with decision making on adjuvant chemotherapy (5-7, 16). Although, its routine use in clinical practice is still not recommended due to the lack of a standardized procedure of Ki-67 evaluation, interpretation, scoring, and definition of cut-off value; it has been suggested that each pathology department should specify their own assessment methodology of Ki-67 (24).

We are aware of that there are some limitations of the study, including limited sample size, relatively short follow-up time, and its retrospective nature. The retrospective design of the study did not negatively affect the association of the Ki-67 index with the other patient and tumour characteristics, but the survival outcomes might be affected by this situation.

In conclusion, this single institution study showed that high expression of Ki-67 is associated with higher pT-stage, higher pN-stage, higher

grade, ER/PR negativity, HER2/neu positivity, ECE and LVI positivity. The prognostic impact of Ki-67 was only demonstrated for DFS and longer follow-up time may be required to see its effect on OS.

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

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

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Diffusion-Weighted Imaging of Breast Cancer: Correlation of the Apparent Diffusion Coefficient Value with Pathologic Prognostic Factors

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ABSTRACT

Objective: The aim was to evaluate relationship between apparent diffusion coefficient (ADC) values with pathologic prognostic factors in breast carcinoma (BC).

Materials and Methods: 83 patients were enrolled in this study. Prognostic factors included age, tumor size, expression of estrogen receptor (ER) and progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), nuclear grade (NG), lymph node involvement and histologic type. The relationship between ADC and prognostic factors was determined using Independent sample t-test, ANOVA, Pearson correlation and relative operating characteristics (ROC) analysis.

Results: There was no significant difference between ADC and prognostic factors, including age, tumor size, ER, HER2 and histologic type. The PR-positive tumors ($p=0.03$) and axillary lymph node involvement ($p=0.000$) showed a significant association with lower ADC values. The ADC values were significantly lower in high-grade tumors than low-grade tumors ($p=0.000$). ROC analysis showed an optimal ADC threshold of $0.66 (\times 10^{-3} \text{ mm}^2/\text{s})$ for differentiating low-grade tumors from high-grade tumors (sensitivity, 85.5%; specificity, 81%; area under curve, 0.90).

Conclusion: The lower ADC values of BC were significantly associated with positive expression of PR, LN positivity and high-grade tumor. Especially, ADC values were valuable in predicting NG subgroups.

Keywords: Breast cancer, diffusion-weighted imaging, apparent diffusion coefficient, prognostic factors

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Introduction

Prognostic factors including axillary lymph node (LN) involvement, tumor size, nuclear grade (NG), Ki-67, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) have been used to determine the prognosis and appropriate treatment options before or following surgery in breast cancer (1, 2). Magnetic resonance imaging (MRI) is widely used for the evaluation of morphologic characteristics and contrast enhancement patterns of BC. The diffusion-weighted image (DWI) is a technique which analyze random Brownian motion of water molecules in tissues. DWI also yields quantitative information by using apparent diffusion coefficient (ADC) maps which shows the tumor cellularity. Several studies have shown an inverse correlation between tumor cellularity and ADC values (2-6). As a result of this, ADC value has been used for differentiation of malignant tumors from benign lesions and determination of aggressiveness of a tumor. The possible relationship between pathologic prognostic factors and ADC values may be helpful in evaluating the treatment response by ADC values. The majority of the studies performed up to the present evaluated the association between ADC values and pathological prognostic factors in patients with BC (1, 7-11). However, the results which have been reported by previous studies were inconclusive and controversial. The purpose of this study was to evaluate the ADC values of invasive BC and investigate whether the use of DWI for ADC values could provide information about the prognostic factors in BC including age, tumor size, LN, NG, histologic type, ER, PR and HER2.

Material and Methods

Patient selection

The Institutional Review Board of Baskent University Hospital approved this retrospective study. Informed consent was not received due to the retrospective nature of the study. We enrolled 111 consecutive patients, who underwent MR imaging of the breast including DWI at our institute between April 2011 to December 2016, who were subsequently proven histopathologically to have BC. We excluded 28 patients, including 9 who received neoadjuvant chemotherapy and 19 with ductal carcinoma in situ or invasive foci of less than 1 cm (because of difficulty in drawing region of interest and poor reliability of signal intensity of the ADC map). Ultimately, 83 patients with a total of 83 breast cancers including 69 with invasive ductal carcinoma not otherwise specified (IDC NOS), 7 with invasive lobular carcinoma (ILC), 5 with invasive micropapillary carcinoma (IMPC) and 2 with invasive papillary carcinoma (IPC) were enrolled in this study.

The MRI protocol

All patients were examined using dynamic contrast-enhanced MRI (DCE-MRI) and DWI. MRI was performed with 1.5 Tesla MR (Siemens Magnetom Avanto, Erlangen, Germany) by using a dedicated breast coil while the patient was in prone position. Standard protocols for breast imaging, such as axial scout images, precontrast axial T1-weighted (TR/TE, 450/9.6; matrix, 257x384; NEX, 2; slice thickness, 4 mm; acquisition time, 2.17 s) and T2-weighted (TR/TE, 5600/59; matrix, 314x320; NEX, 2; slice thickness, 4 mm; acquisition time, 2.55 s) were performed. Both before and after intravenous contrast material injection, 6 sequential fat-suppressed 3D T1-weighted images were obtained, and subtraction was performed. A bolus dose of gadoversetamide was injected intravenously at a dose of 0.1 mmol/kg of body weight. The scanning parameters for dynamic contrast-enhanced MRI were TR/TE, 4.43/1.73; matrix, 336x448; NEX, 1; slice thickness, 1.2 mm; flip angle, 10°; FOV, 3.4x3.4 cm; acquisition time, 60 s, respectively. Prior to the dynamic analysis, echo-planar images were obtained with diffusion gradients in the x, y and z planes at b values of 0 and 500 s/mm². The DWI sequences were obtained with the following parameters: TR/TE, 8700/109; matrix, 96x192; NEX, 2; slice thickness, 4 mm; acquisition time, 3.38 s. (Grappa). The ADC maps were created automatically. Calculations were made based on mean ADC maps of the circular sampling region of interest (ROI), with care taken to perform measurements in solid areas rather than necrotic/cystic areas and visual artifacts. We placed three circular ROIs of 20±2 mm² within the tumor after referring to DCE-MRI for verification of

the lesion boundaries on the ADC map. We calculated the average of the ADC values for all three ROIs within the tumor. All MRI studies were examined by the same experienced radiologist. Figure 1 shows symbolic images.

Prognostic Factors

The histological grade of BC was assessed by using the modified criteria of Bloom and Richardson grading system which classifies tumors due to the amount of gland formation, pleomorphism and mitotic activity. The grades ranged from 1 to 3 points with a total score of 3-5 representative of grade 1 (NG1), a total score of 6 or 7 representative of grade 2 (NG2) and a total score of 8 or 9 representative of grade 3 (NG3). NG was also divided into two groups which were low-grade tumors (NG1 and NG2) and high-grade tumors (NG3). Tumor size, defined as the largest diameter of the primary breast tumor was obtained from the DCE-MRI. In this study tumor size was classified under three categories (≤20 mm, 21-50 mm and >50 mm). Immunohistochemistry was used to evaluate the expression of the molecular markers including ER, PR and HER2. The status ER and PR was considered as positive if expression was 10% or more. The intensity of HER2 was scored as 0 to 3+. Scores of 0 and 1+ were classified as HER2-negative, and scores of 3+ were defined as HER2-positive by immunohistochemistry. The lesions with a HER2 expression of 2+ were studied by fluorescent in situ hybridization to determine the HER2 gene amplification. Axillary lymph node specimens, obtained from lymph node dissection, were analyzed by the pathologist with more than 10 years' experience. The histologic types of BCs, were classified according to the WHO classification, were obtained from our database.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA). The Kolmogorov-Smirnov test was used to analyze the normal distribution of data. The ADC values were compared according to the ER (positive vs. negative), PR (positive vs. negative), HER2 status (positive vs. negative), NG (low-grade vs. high-grade) and LN (positive vs. negative) using the Independent sample *t*-test. We compared the ADC values with tumor size, NG subgroups and histologic types using the one-way analysis of variance (ANOVA, post-hoc). The Pearson correlation coefficient test was used to investigate the correlation between ADC values and patients' ages. In addition, we used relative operating characteristics (ROC) analysis to evaluate the association between ADC values and NG subgroups. The "p" value less than 0.05 was considered to show a significant difference.



Figure 1. a-c. A 51-year-old woman with left breast cancer diagnosed as progesterone receptor (PR)-positive, estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative. Dynamic contrast-enhanced MR shows heterogeneous, enhanced mass in outer quadrant of left breast (open arrow) (a). A nodule with high signal intensity was detected in the left breast on diffusion-weighted imaging (DWI) (open arrow) (b). Axial apparent diffusion coefficient (ADC) map shows low signal intensity (open arrow) in tumor (b-value: 500 s/mm²) (c).

Results

The patients' ages ranged from 27 to 82 years (mean age: 48.3 ± 11.3 years), and all patients were female. There was no significant correlation between the ADC and patients' ages (p value, 0.97; Pearson's correlation). The histopathological features and comparisons of mean ADC values in subgroups of prognostic factors are shown in Table 1. The size of the breast carcinomas ranged from 10 mm to 85 mm (mean size: 32.8 ± 19.6 mm). The majority of the lesions were ER-positive (77.1%) and PR-positive (74.7%). A total of 45 (54.2%) lesions were HER2-positive, and 38 (45.8%) were HER2-negative. Most of the tumors were IDC NOS (83.1%). There was no significant difference be-

Table 1. ADC values and Prognostic Factors in 83 Patients with Breast Cancer

Prognostic Factors	Number of Subjects (%) ^a	ADC Values	p
ER ^b			0.43
Positive	64 (77.1)	0.71 ± 0.11	
Negative	19 (22.9)	0.74 ± 0.1	
PR ^b			0.03
Positive	62 (74.7)	0.70 ± 0.11	
Negative	21 (25.3)	0.76 ± 0.09	
HER2 ^b			0.71
Positive	45 (54.2)	0.71 ± 0.1	
Negative	38 (45.8)	0.72 ± 0.12	
Lymph Node ^b			0.000
Positive	40 (48.2)	0.65 ± 0.08	
Negative	43 (51.8)	0.78 ± 0.09	
Histological type			0.28
IDC NOS	69 (83.1)	0.73 ± 0.1	
ILC	7 (8.4)	0.69 ± 0.15	
IMPC	5 (6)	0.63 ± 0.14	
IPC	2 (2.4)	0.69 ± 0.06	
Tumor size (mm) ^c			0.49
≤20	29 (35)	0.74 ± 0.13	
21-50	40 (48.2)	0.71 ± 0.09	
>50	14 (16.8)	0.7 ± 0.12	
Nuclear Grade ^c			0.000
1	15 (18)	0.87 ± 0.08	
2	47 (56.6)	0.72 ± 0.07	
3	21 (25.3)	0.6 ± 0.07	

ADC: apparent diffusion coefficient; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IDC NOS: invasive ductal carcinoma not otherwise specified; ILC: invasive lobular carcinoma; IMPC: invasive micropapillary carcinoma; IPC: invasive papillary carcinoma

^aBecause of rounding-up, the sum of percentages does not always equal 100

^bIndependent sample t-test

^cOne-way analysis of variance

tween mean ADC values and prognostic factors, including ER, HER2, tumor size and histologic type. The PR-positive tumors showed significant lower ADC values than PR-negative tumors ($p=0.03$). Lymph node status was positive in 40 (48.2%) and negative in 43 (51.8%) of the subjects. The LN positivity showed significant association with lower ADC values ($p=0.000$, Figure 2). There was a significant relationship between NG subgroups and ADC values ($p=0.000$). Histologic grades were classified as low-grade tumors (NG1 and NG2) in 62 (74.6%) and high-grade tumors (NG3) in 21 (25.3%) patients. The mean ADC values were significantly lower in high-grade tumors (NG3) as compared to low-grade tumors (NG1 and NG2) ($p=0.000$, Figure 2). In addition, ROC analysis was performed to determine threshold ADC value for prediction of nuclear grade of tumors. ROC analysis revealed an optimal ADC threshold of $0.66 (\times 10^{-3} \text{ mm}^2/\text{s})$ for differentiating low-grade tumors (NG1 and NG2) from high grade tumors (NG3) (Figure 3A). This cut-off showed a sensitivity of 85.5% and specificity of 81% with the area under curve (AUC) of 0.90 ($p=0.000$) (Table 2, Figure 3A).

We also compared the ADC values of NG1 ($n=15$) tumors with NG2 and NG3 tumors ($n=68$) and found significant difference between

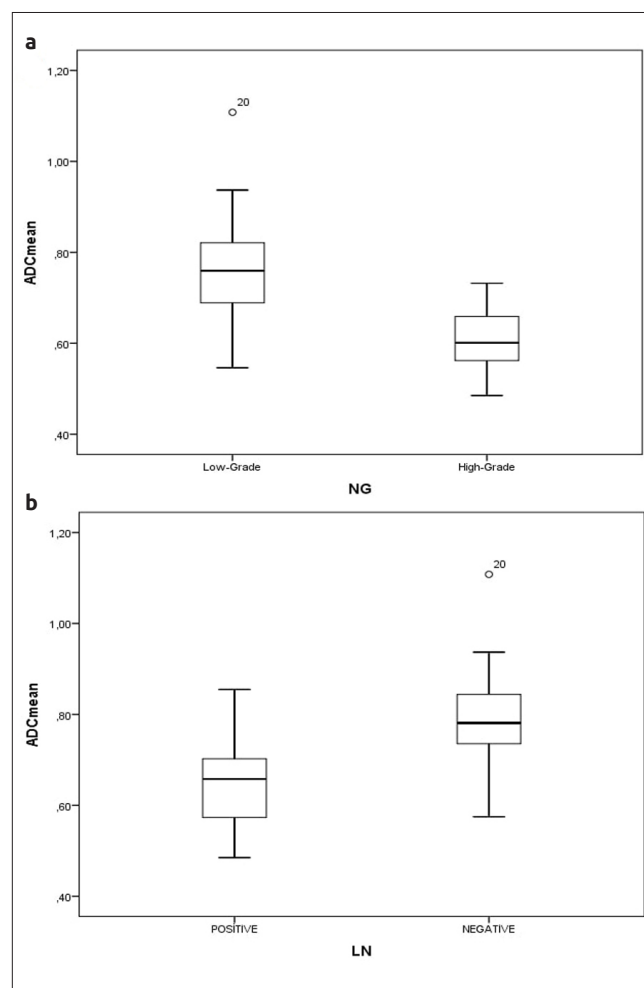


Figure 2. a, b. Boxplot showing the distribution of apparent diffusion coefficient (ADC) values of breast carcinoma according to nuclear grade (NG) (a) and axillary lymph node (LN) involvement (b). As shown, the ADC value of high-grade tumors is significantly lower than low-grade tumors (a). ADC value of the lesions with axillary lymph node involvement is significantly lower than that of the lesions without lymph node involvement (b)

NG1 and the other NG subgroups ($p=0.000$). ROC analysis showed an optimal ADC threshold of $0.769 (\times 10^{-3} \text{ mm}^2/\text{s})$ for differentiating NG1 from the other subgroups (Figure 3B). This cut-off showed a sensitivity of 100 % and specificity of 80.9 % with the AUC of 0.95 ($p=0.000$) (Table 3).

Discussion and Conclusion

Diffusion-weighted image is an inexpensive, noninvasive and easy method evaluating the random motion of water molecules in breast tissue. DWI has been applied for differentiating malignancy from benign tumor and evaluating treatment response in BC. Previous studies showed an inverse correlation between cellular density and ADC values, with malignancies having higher cellularity and lower ADC

values than benign lesions (6, 12). Pathological prognostic factors such as tumor size, ER, PR, HER2, NG, LN status and histologic type have been used to determine the aggressiveness of tumors. Although some previous studies evaluated the relationship between the ADC values and the pathological prognostic factors, the results were controversial (1, 2, 6-9, 11-18).

Axillary lymph node involvement is one of the major prognostic factors, which affect the prognosis and survival of the patients. Previous studies revealed various controversial results in the relationship between LN status and ADC values. Because of existence of metastatic LN was associated with the aggressiveness of tumor, we hypothesized the lower ADC values would be in a significant relationship with metastatic LN. By contrast, several studies showed no association between LN metastasis and ADC values (10-12, 18, 19). However, some studies, similar to our results, showed a significant relationship between LN status and ADC values with LN-positive tumors having lower ADC values than LN-negative tumors (2, 3). Interestingly, Kamitani et al. (16) reported that LN-positive tumors had significant higher ADC values and they considered that this might be related to the existence of micronecrosis in the LN.

Nuclear grade is a representative prognostic factor for determining tumor aggressiveness by evaluating the pleomorphism, gland maturation and mitosis which is reflective of tumor cellularity. As aforementioned

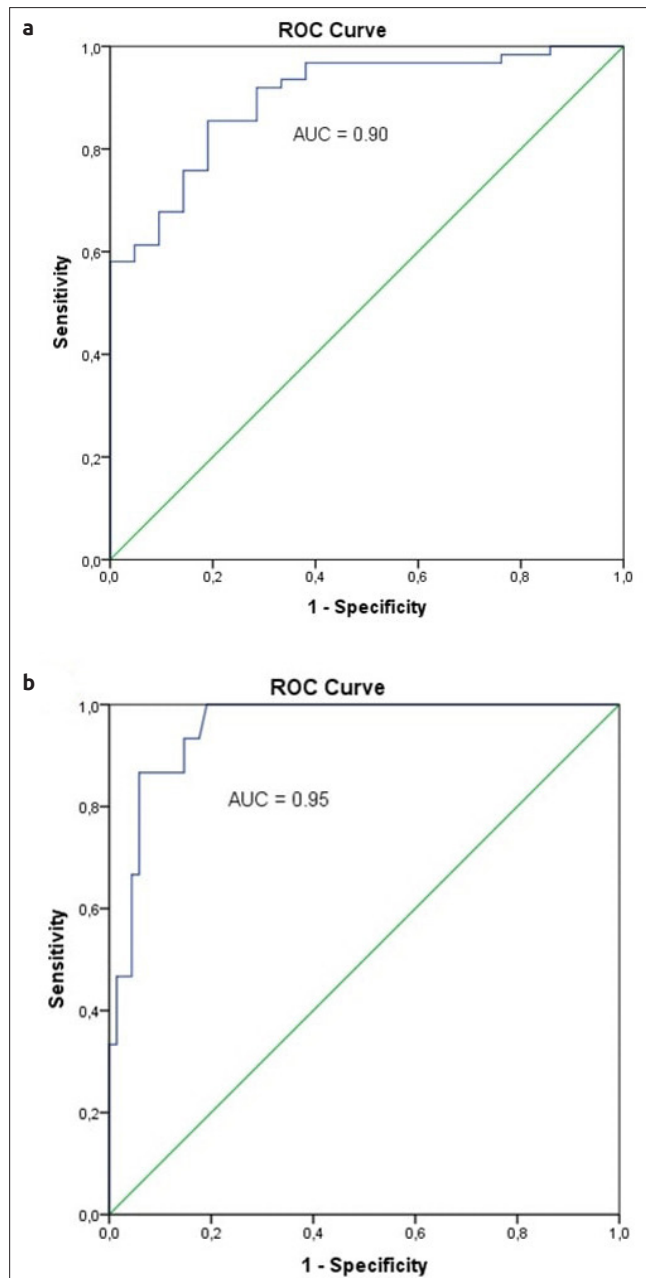


Figure 3. a, b. Relative operating characteristic curves (ROC). ROC curve in which low grade tumors (NG1 and NG2) were compared with high-grade tumors (NG3) (a). ROC curve in which NG1 was compared with NG2 and NG3 (b)

Table 2. ADC cut-off values in differentiation of low-grade (NG1 and NG2) and high-grade tumors (NG3), sensitivity and specificity values in different threshold values in the ROC analysis

Threshold Value*	Sensitivity	Specificity
0.647	93.5	66.7
0.653	91.9	71.4
0.660	85.5	76.2
0.664	85.5	81
0.681	79	81
0.688	75.8	85.7
0.701	71	85.7

ADC: apparent diffusion coefficient; NG: nuclear grade; ROC: relative operating characteristics
*($\times 10^{-3} \text{ mm}^2/\text{s}$)

Table 3. ADC cut-off values in differentiation of NG1 tumors and the other NG subgroups (NG2 and NG3), sensitivity and specificity values in different threshold values in the ROC analysis

Threshold Value*	Sensitivity	Specificity
0.769	100	80.9
0.784	93.3	85.3
0.811	86.7	94.1

ADC: apparent diffusion coefficient; NG: nuclear grade; ROC: relative operating characteristics
*($\times 10^{-3} \text{ mm}^2/\text{s}$)

before, the high cellularity is associated with lower ADC values in the tumor. However, some of the previous studies reported no significant association between the NG and ADC values in the BC (2, 10, 12, 16, 18, 20). We found significant difference between low-grade tumors (NG1 and NG2) and high-grade (NG3) tumors similar to the study by Martincich et al. (9). According to our results, the optimal cut-off value of $0.66 \times 10^{-3} \text{ mm}^2/\text{s}$ in the differentiation of low-grade tumors (NG1 and NG2) from high-grade tumors (NG3) with high sensitivity and specificity has been identified (Table 2). In this study, a significant difference was also observed in ADC values between NG1 tumors and the other subgroups (NG2 and NG3), which was consistent with two previous studies (8, 19). Yırgın et al. (19) revealed a cut-off ADC value of $1.05 (\times 10^{-3} \text{ mm}^2/\text{s})$ with the sensitivity of 75% and specificity 28 % to differentiate NG1 tumors from the others. We found three optimal threshold values with the higher sensitivity and specificity which were demonstrated in Table 3 to differentiate NG1 tumors from other subgroups than the previous studies (19). We consider that ADC cut off values can be used for predicting NG subgroups.

A previous study demonstrated that the five-year BC survival rates have been found to be longer in the tumors <2 cm than the tumors >5 cm (21). Our study indicated that larger tumors (>5 cm) had higher mean ADC values than the smaller tumors (<5 cm); however, the difference was not statistically significant. Nevertheless, there are some studies reporting significant association between the tumor size and ADC values with larger tumors having lower ADC values than smaller tumors (15, 22). However, in consistency with our study, some researches revealed that the ADC values and tumor size were not correlated (2, 10, 12, 17). This may be related to the variable amount of histologic contents such as fibrosis, necrosis, cellularity, angiogenesis or hemorrhage in the tumors.

Estrogen receptor-positive tumors are well differentiated and generally presents effective response to hormonal therapy (23, 24). The relationship between the ADC values and the ER status has been reported in several studies (1, 2, 9-11, 15-18). Some studies revealed that ER status was associated with high tumor cellularity which was related to the lower ADC values (25, 26). However, in our study we found no association between the ADC values and ER which is inconsistent with some previous studies (3, 9, 11, 12, 16, 17). We also observed significantly lower ADC values for PR-positive carcinomas as compared to PR-negative cancers ($p=0.03$). Similar to our results, some previous studies found a significant relationship between ADC values and PR expression (1, 16, 17). Nevertheless, several studies reported no association between ADC values and PR which forms a contrast to our study (2, 10, 11, 18, 19).

The overexpression of HER2 receptor was associated with epithelial cell growth and angiogenesis which may be related to the increased risk of recurrence and poor prognosis (27, 28). As a result of this, we hypothesized that lower ADC values may be associated with positive expression of HER2. However, we found no significant correlation between the ADC values and HER2 status in our study. Moreover, we observed that higher ADC values were more likely in HER2-positive tumors than in HER2-negative tumors. Nevertheless, this correlation was not significant. The majority of the previous studies revealed no significant relationship between ADC values and HER2 status which is consistent with our study (9, 15-17). However, some studies reported significantly lower ADC values for HER2-negative tumors as compared to HER2-positive tumors (10-12).

We also investigated the correlation of the ADC values with age and histologic type in this study. In breast cancer, both young and advanced age may be associated with poor prognosis (29). The influence of age on prognosis is more prominent in sub-types of breast cancer. Age has a more significant impact on prognosis in luminal cancer types as compared to other sub-types of BC (30). Similar to our study, previous studies did not report a significant correlation between ADC values and patients' age (12, 19).

Invasive ductal carcinoma NOS is the most common type of invasive breast cancer followed by ILC, the second most common tumor. The majority of the tumors were IDC NOS (83 %) in this study. No significant difference was observed between histologic types and ADC values in this study similar to some of the previous studies (2, 9). However, Kitajima et al. (15) found a significant association between the histologic type and the ADC values and stated that the ADC values of ILCs were lower as compared to IDCs.

This study has some limitations which have to be pointed out. First, it was designed as a retrospective study. Second, imaging was performed at 1.5 Tesla for evaluation of ADC values and therefore, we had to exclude the tumors <1 cm to accurately measure ADC values on 1.5 Tesla MRI. Third, Ki-67 which is an important prognostic factor of BC could not have been evaluated due to the inadequate data of the subjects.

The lower ADC values of BC were related to the positive expression of PR, LN positivity and high-grade tumor. Especially, ADC values were valuable in predicting both NG1 and NG3 tumors from the other subtypes. In addition, further studies are necessary to assess the additional role of ADC values in improving the detection of pathologic prognostic factors in a larger and more generalized population with prospective design.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Institutional Review Board of Baskent University Hospital (Approval Date: 09.05.2017, Approval No: KA17/143)

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

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Not Otherwise Specified-Type Sarcoma of Breast with CD10 Expression: Case Report

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ABSTRACT

Primary breast sarcomas are very rare and account less than 1% of invasive breast carcinomas. Primary sarcomas of breast are leiomyosarcoma, angiosarcoma, liposarcoma, fibrosarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor and pleomorphic sarcoma. Recently, a new CD10 positive group of sarcoma was identified. These tumors cannot be classified as a soft tissue sarcoma and show diffuse strong positive staining pattern with CD10 (NSCD10). Herein we report clinical and morphological characteristics of two cases diagnosed with not otherwise specified-type sarcoma with CD10 expression by histologically and immunohistochemical findings with the literature. NSCD10 shows similarity with leiomyosarcoma and sarcomatoid-type metaplastic carcinoma histomorphologically among specific sarcomas of breast. CD10 expression should be taken into consideration in the presence of not diagnosed and not specified tumors and CD10 should be added to the immunohistochemical panel.

Keywords: Breast, sarcoma, CD10 positive sarcoma

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Introduction

Primary breast sarcomas are very rare and account less than 1% of invasive breast carcinomas (1). Primary sarcomas of breast are a heterogeneous group of tumors including angiosarcoma, liposarcoma, leiomyosarcoma and pleomorphic sarcoma as the most common types (2). Primary breast sarcomas differ from the primary breast carcinomas with behavior pattern such as the soft tissue sarcomas of the other parts of body. They show distant metastatic spread pattern rather than nodal involvement.

They present as painless, mobile, circumscribed and hard masses. They are more frequently seen among women between the ages of 45-55 years (2).

In the diagnosis of primary breast sarcoma, there are two important features. Distant metastasis from another site should be eliminated and spindle cell metaplastic carcinoma (MC) and also malignant phylloides tumors (MPT) are important in the differential diagnosis.

The treatment modality of the primary breast sarcoma is surgery. Recently, wide local excision providing tumor free borders is sufficient for the treatment. Axillary lymph node dissection is unnecessary. It is recommended if there is a palpable lymph node is present.

CD10 (CALLA) neutral endopeptidase is a surface cell receptor and is expressed by lymphoid precursor cells and myoepithelial cells of breast (3-4)

Recently published studies suggest that CD10 could be a good indicator of stem cells in breast carcinoma, particularly precursors of metaplastic carcinomas (5). CD10 is positive in phylloides tumors that showing aggressive pattern in breast (3). Recently, a not otherwise specified-type sarcoma with CD10 expression is identified (1, 6-8). In this case report we aimed to discuss two cases diagnosed with not otherwise specified-type sarcoma with CD10 expression at our department with the literature data.

Case Presentations

Case 1

A 70-year-old female was admitted to the oncology department with a history of surgically excised lesion with a diagnosis of leiomyosarcoma one year ago. Her tumor was an ulcerated, hemorrhagic and discharging lesion. The paraffin blocs were referred to our department to re-evaluation.

Histological examination of outer center preparations; A tumoral lesion with hyperchromatic nuclei, apparent nucleoli and large eosinophilic cytoplasm in diffuse infiltrative pattern was seen under the stratified squamous epithelium and stroma of the breast. The tumor was also containing spindle shaped bundles with apparent nucleoli in some areas (Figure 1).

Perineural invasion was positive with in the tumor. In immunohistochemically evaluation, the tumor was strongly positively stained by smooth muscle actin (SMA), Calponin (Clone CALP, Code M3556, Dako, Denmark) and CD10 (Figure 2, Clone 56C6, Neomarkers, USA) however CD68 (MS-397-PCS, Thermo Scientific, USA) was focal positively stained.

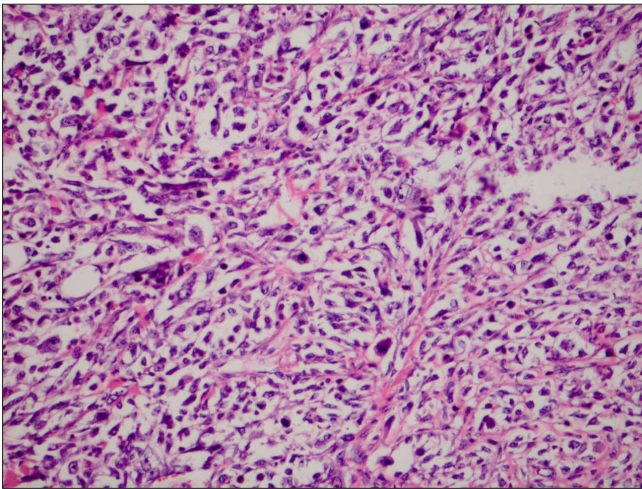


Figure 1. Tumor showed hyperchromatic nuclei, apparent nucleoli and large eosinophilic cytoplasm in diffuse infiltrative pattern (HE x200)

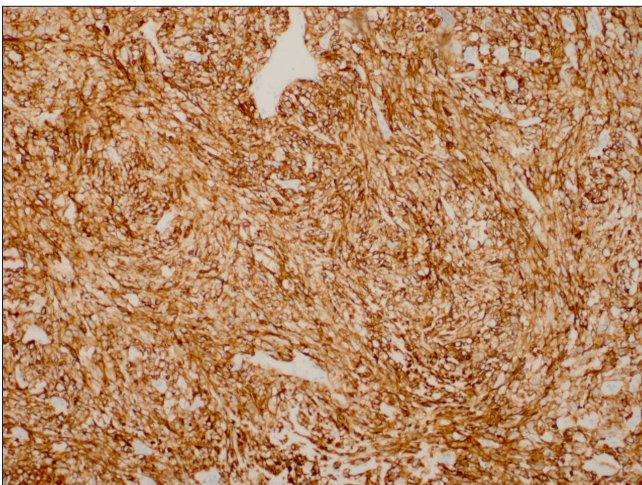


Figure 2. Immunohistochemically CD10-positive in tumor cells (x200)

Pan-cytokeratin (Clone AE1/AE3, Genemed, Germany), Desmin (Clone D33, Dako, Denmark), H-Caldesmon (Clone h-CD, Code IR054, Dako, Denmark), S-100 protein (Code ZO311, Dako, Denmark), p63, HMB45, CD34 (Clone QBEnd-10, Dako, Denmark), ER (Clone EP1, Code M3643, Dako, Denmark), PR (Clone Y85, 60-0056-7, Genemed, Germany), Cerb-2 (Code A0485, Dako, Denmark) were negative. The case was diagnosed with not otherwise specified-type sarcoma with CD10 expression with these morphological and immunohistochemical findings. Then the patient was followed-up at another center.

Case 2

A 38-year-old female was admitted to the department of general surgery at our hospital with a history of rapidly growing mass in the upper outer quadrant of right breast within the two months. The patient gave birth eight months ago. The mass has been first identified three months ago. At that time the longest diameter of the lesion was 6 mm at ultrasonography reports. At the second control the mass was within 35 mm diameter sonographically. The patient went to core-needle biopsy and the tumor was reported as a malignant tumor.

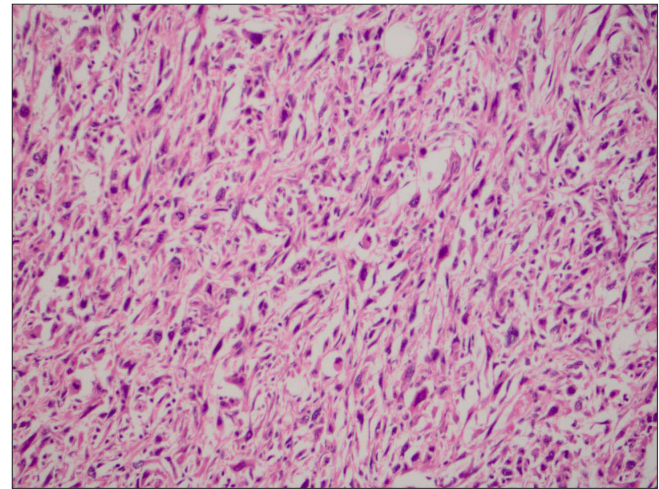


Figure 3. Tumor showed hyperchromatic-pleomorphic nuclei, apparent nucleoli and eosinophilic cytoplasm within the tumor fascicles (HE x200)

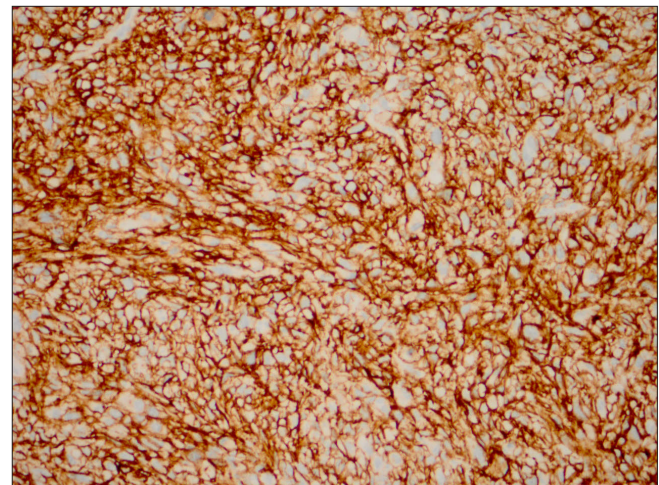


Figure 4. Immunohistochemically CD10-positive in tumor cells (x200)

The paraffin blocs were referred to our department for re-evaluation. These blocs showed a tumoral lesion composed of fasciculated spindle cells with hyperchromatic, pleomorphic nuclei, apparent nucleoli and eosinophilic cytoplasm in the breast stroma.

Immunohistochemically the tumor was positive for SMA (Clone 1A4, Code M0851, Dako, Denmark). Pan-cytokeratin, H-Caldesmon, S-100 protein, Bcl-2 (Clone 124, Code IR614, Dako USA), CD34, ER, PR and Cerb-B2 were negative.

The patient was diagnosed with malignant spindle cell tumor with the morphologic and immunohistochemical findings. Metaplastic carcinoma, breast sarcomas and malignant phyllodes tumor were considered within the differential diagnosis.

Magnetic Resonance Imaging (MRI) of the breast showed a subcutaneously located malignant lesion within a 5x6 cm diameters in the upper outer quadrant of the right breast. The tumor showed restricted diffusion. There were axillary lymph nodes with asymmetric cortical thickening.

The patient went mastectomy. Macroscopic evaluation showed a hard and solid mass measured at 6x5.5x4.5 cm diameters in the upper outer quadrant of the mastectomy specimen. The mastectomy specimen was weighted at 495 gr with 22x14 cm diameters.

The histologic evaluation of the tumor showed hyperchromatic- pleomorphic nuclei, apparent nucleoli and eosinophilic cytoplasm within the tumor fascicles and necrotic areas (Figure 3). 10 High-power fields presented 19-20 mitotic activity.

Immunohistochemically, CD10 (Figure 4), SMA and Calponin was positive, whereas pan-cytokeratin, CK5/6, HMWCK (Clone 34bE12, Genemed, Germany), P63 (Clone DAK, Code IR662, Dako, Denmark), Desmin, H-Caldesmon, bcl-2, CD34, ER, PR and cerb-b2 were negative with in the tumor.

The case was diagnosed with not otherwise specified-type sarcoma with CD10 expression with these morphological and immunohistochemical findings. The patient received chemotherapy and radiotherapy. The patient was alive and healthy at 18th month following surgery. Patients gave orally informed consent.

Discussion and Conclusion

Primary breast sarcomas are very rare and the most common types are angiosarcoma and liposarcoma (1, 2). Fibrosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma and osteosarcoma can be seen less frequently (2, 9).

Recently, not otherwise specified undifferentiated breast sarcoma (NOS) characterized by myoepithelial markers was identified among some of the CD10 expressing cases (1, 6-8). Patients are commonly presented with painless hard masses. They are common among 45-55 years.

Radiologically breast sarcomas can be seen as irregular or oval shaped masses at both mammography and MRI. Breast sarcomas are originating from the interlobular mesenchymal elements supporting the breast stroma.

For instance, angiosarcoma is originated from endovascular cells; however, clarifying the origins of bone and cartilage containing tumors

is hard. This is because the breast does not contain these tissues (8). Recently published studies showed that sarcomas are originating from the primitive cells with the totipotential differentiation capacity. Some studies suggested that CD10 is a good marker to monitor the stem cells in breast carcinoma particularly precursors of metaplastic carcinomas (5).

Metaplastic carcinomas that originating from the stem cells show two types of differentiation from epithelium and myoepithelium. However, NOSCD10 sarcomas are believed to be differentiated to mesenchyme and myoepithelium (5, 8). Because the immunophenotype of NOS type sarcoma with CD10 expression suggests that these neoplasms represent a mammary sarcoma variant with myoepithelial features (8).

If a spindle cell malignant lesion is identified in a breast, MC and/or MPT should be first come to mind in the differential diagnosis rather than a sarcoma. Undifferentiated mammary sarcoma or not otherwise specified sarcoma with CD10 expression is an exceedingly rare and diagnosis is made after exclusion of all other malignant cell tumors (for example: Metaplastic carcinoma, malignant phylloides tumors, spindle cell sarcoma, leiomyosarcoma, fibrosarcoma) in the breast (6).

Axillary lymph node dissection should be added in the treatment of particularly the MC due to the tendency of MC to lymphatic dissemination. Thus, NOS CD10 positive sarcomas and other breast sarcomas should be differentiated from MC (1).

Studies showed that axillary lymph node dissection is unnecessary in the treatment of breast sarcomas (9). Invasive breast carcinomas and/or in-situ carcinoma areas should be searched with multiple samplings to show the presence of spindle cell lesion that is made of pure spindle cells or mixed with epithelial components (squamous or glandular) or not. A large cytokeratin panel should be performed in tumors containing pure spindle cells.

Malignant phyllodes tumors should be differentiated from breast sarcomas. The presence of benign epithelial component or leaf like structure supports the diagnosis of phyllodes tumors. A lot of sampling should be needed. However, patient history should be questioned carefully because apparent stromal growth occurs in high grade or recurrent phyllodes tumors.

Particularly, MPT's can show the positivity of CD10, SMA and Vimentin. For this reason, differential diagnosis should be made with CD34 and BCL-2 positivity with immunohistochemical staining (1, 3, 10). In our cases CD34 and BCL-2 were negative and epithelial component cannot be seen in multiple samples.

Not otherwise specified-type sarcoma with CD10 expression shows similarity with leiomyosarcoma and sarcomatoid type metaplastic carcinoma histomorphologically among specific sarcomas of breast.

Immunohistochemically, CD10 was negative in leiomyosarcoma or it can show positivity in focal areas and at least one of SMA as well as also desmin or h-Caldesmon is positive. However, CD10 is strongly positive, desmin and h-Caldesmon is negative in 'not otherwise specified-type' sarcoma (1, 8). In both of our cases, CD10 was positive, while desmin and h-Caldesmon were negative.

In metaplastic carcinomas, multiple sampling as well as a large cytokeratin immunohistochemical panel should be performed. In both of our cases, p63, CK7, CK5/6 and HMWCK are negative.

The primary treatment of breast sarcomas is surgery. The role of radiotherapy and chemotherapy is not clear in the treatment strategies (9). The treatment protocol of the CD10 positive sarcomas will be clarified in the future with the increased number of defined cases. Thus, it should be kept in mind in the differential diagnosis.

The molecular studies to clarify the origins of NSCD10 tumors should be performed together due to the closed relationship between MC, PT and NSCD10.

Although, NOSCD10 sarcomas are proposed to be originating from the primitive stem cells and showing mesenchymal and myoepithelial differentiation, histopathogenesis is still unclear.

As a result, not otherwise specified-type sarcoma with CD10 expression should be taken into consideration in the presence of not diagnosed and not specified tumors and CD10 should be added to the immunohistochemical panel.

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

Peer-review: Externally peer-reviewed.

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

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Tuberculosis Mastitis: Fever of Unknown Origin in a Kidney Transplant Recipient

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ABSTRACT

Tuberculous mastitis is a rare presentation of tuberculosis, which is a major health problem in kidney transplant recipients due to its high incidence and prevalence, and difficulty in diagnosis as well as high risk of morbidity and mortality. In daily practice, physicians may frequently be led to a misdiagnosis such as breast carcinoma or abscess. We believe it is crucial for clinicians to recognize this important presentation of the disease. Therefore, we present a case of tuberculous mastitis in a kidney transplant recipient who was admitted with fever of unknown origin and successfully treated using standard anti-tuberculosis therapy without any complications.

Keywords: Tuberculosis mastitis, fever of unknown origin, kidney transplantation, anti-tuberculosis treatment

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Introduction

Tuberculosis (TB) is a major health issue in kidney transplant recipients due to its high incidence and prevalence and difficulty in diagnosis as well as high risk of morbidity and mortality, especially in developing countries. The incidence of tuberculosis is estimated to be 20-74 times higher in kidney transplant recipients than the general population. Beyond the high incidence, atypical presentations and organ involvements are also frequent in these patients (1, 2).

Tuberculous mastitis is one of those rare presentations of TB accounting for less than 1% of all breast diseases in developed countries, however, its incidence is higher in developing and undeveloped nations where TB is endemic (3-5). It usually occurs as a lump on the central or upper outer quadrant of the breast. Owing to this location and scarce nature of the disease, clinicians may frequently be led to a misdiagnosis such as a breast carcinoma or abscess (6). Here, we present a case with the fever of unknown origin in a kidney transplant recipient due to tuberculous mastitis.

Case Presentation

A 59-year-old female kidney transplant recipient was admitted with a high fever, loss of appetite and weight loss which had been present for 3 months. The renal transplantation was performed from a living related donor 8 years ago and renal functions remained well on a triple immunosuppressive regimen including tacrolimus, azathioprine and prednisolone. On admission, her body temperature was 38.5 °C. Remaining of the examination did not point to a source of infection: No lymphadenopathy was noted, lungs were clear to auscultation, heart sounds were regular without, and her abdomen was not tender.

A laboratory workup revealed a C-reactive protein level of 86 mg/L and an erythrocyte sedimentation rate of 56 mm/h. Blood and urine cultures were drawn and broad-spectrum antibiotics were initiated. Computed tomography of the thorax and abdomen revealed no abnormalities. However, during the examination of the left breast, a tender mass with a 1-cm diameter was noticed. Magnetic resonance imaging (MRI) of the breast demonstrated that this lesion was consistent with an abscess (Figure 1). Acid-fast bacilli were present in the sample obtained from the lesion. The patient was started on an empirical anti-tuberculosis treatment regimen with

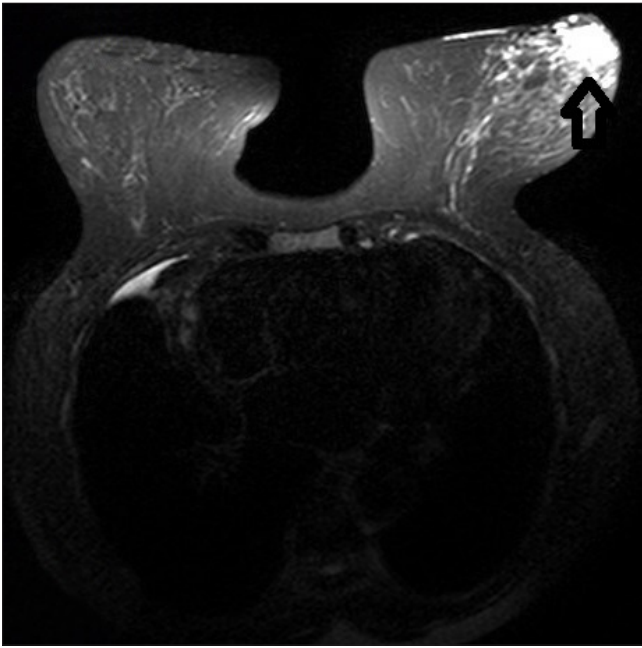


Figure 1. T2-weighted axial MRI image demonstrates a high signal-intensity area in the lower outer left breast at anterior depth

isoniazid, rifampicin, pyrazinamide, and ethambutol with the diagnosis of tuberculous mastitis (7-10). Tissue cultures were positive for *Mycobacterium tuberculosis*.

The treatment was well tolerated, and her fever dissolved after 10 days of treatment. At the end of the 12-month treatment period, the lesion completely disappeared.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent may be requested for review from the corresponding author.

Discussion and Conclusion

Tuberculosis is one of the most important opportunistic infections in kidney transplant recipients (2). It is more common in patients with kidney transplants when compared to other solid organ transplant recipients who have milder immunosuppressive treatment regimens and longer average lifespan (2).

It is even harder to diagnose tuberculosis in solid organ transplant recipients because of atypical presentations in this group of patients, and increase in negative results of tuberculin skin tests, interferon-gamma release assays, and examinations with Ziehl-Neelsen stain (2). In this particular instance, it should be kept in mind that tuberculous mastitis can mimic breast cancer and other causes of non-tuberculosis granulomatous mastitis (5). Tissue culture and Ziehl-Neelsen staining still remain as gold standards of diagnosis in tuberculous mastitis (6). However, tuberculosis bacilli are isolated in 25% of the cases with tuberculous mastitis, and acid-fast bacilli are seen in only 12% of the cases (7, 8). Thus, in the absence of microbiologic verification, the presence of a caseous granuloma may be helpful for diagnosis (7, 8).

Tuberculous mastitis should be treated using guidelines for pulmonary tuberculosis given the absence of specific guidelines for breast tubercu-

losis (10-12). European kidney transplantation guidelines recommend an initial treatment for 2 months using a regimen containing isoniazid, rifampicin, and pyrazinamide (with the addition of ethambutol when dealing with strains showing resistance to isoniazid), which will be followed with isoniazid and rifampicin for an additional 4 months (10-12). Treatment duration is recommended to be extended to 12, even 18 months in immunosuppressed patients based on the studies which showed no recurrence in patients treated for 12 months (10-12). Also, a 9-month therapy was reported with greater mortality (12). Considering these findings and immunocompromised status of our patient, anti-TB treatment was given for 12 months to prevent further relapses.

Maintenance of therapeutic drug levels is an important aspect of tuberculosis treatment. Rifampicin reduces blood levels of tacrolimus, cyclosporine, sirolimus, and everolimus (13, 14). Even with proper monitoring, combining rifampicin and tacrolimus increases the frequency of graft rejection and graft loss, and overall TB related mortality (13, 14). We increased tacrolimus doses 3 times throughout the treatment period monitoring drug trough level twice a week, and no complications were observed in terms of maintaining an adequate immunosuppressive state thereby preserving graft function.

In conclusion, we have presented a case of tuberculous mastitis in a kidney transplant recipient who was admitted with fever of unknown origin and successfully treated using standard anti-TB therapy without any complications.

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

Peer-review: Externally peer-reviewed.

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

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

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Corrigendum

Following the publication of the article by Özmen et al., entitled “Breast Cancer in Turkey; An Analysis of 20.000 Patients with Breast Cancer” (Eur J Breast Health 2019; 15: 141-146. DOI: 10.5152/ejbh.2019.4890) that was published in the July 2019 issue of the European Journal of Breast Health, authors noticed that the data presented in Table 1 was incorrect. These errors were corrected in the online version of the article.

The aforementioned article can be accessed via the following link:

<https://www.eurjbreasthealth.com/sayilar/60/buyuk/141-1461.pdf>