E-ISSN 2587-0831

eurjbreasthealth.com

Indexed in PubMed Central and Web of Science

European Journal of Breast Health

EUROPEAN JOURNAL OF BREAST HEALTH

VOLUME: 16 • ISSUE: 3 • JULY 2020

Société Internacionale de Sénologie
Senologic International Society

Global Federation of Breast Healthcare Societies

SIS is the official supporter of the European Journal of Breast Health

AVES

eurjbreasthealth.com

European Journal of Breast Health

Société Internacionale de Sénologie
Senologic International Society

Global Federation of Breast Healthcare Societies

SIS is the official supporter of the European Journal of Breast Health

TMHDF

European Journal of Breast Health is the official journal of the **TURKISH FEDERATION OF BREAST DISEASES SOCIETIES**

Contact
Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, C Service Çapa / İstanbul
Phone&Fax : + 90 212 534 02 10

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

AVES

Publisher
İbrahim KARA

Publication Director
Ali ŞAHİN

Editorial Development
Gizem KAYAN TEKAÜT

Finance and Administration
Zeynep YAKIŞIRER ÜREN

Deputy Publication Director
Gökhan ÇİMEN

Publication Coordinators
Betül ÇİMEN
İrem SOYSAL
Arzu YILDIRIM
Deniz KAYA
Gülnur MERCAN
Bahar ALBAYRAK

Project Coordinators
Sinem KOZ
Doğan ORUÇ

Graphics Department
Ünal ÖZER
Deniz DURAN
Beyzanur KARABULUT

Contact
Address : Büyükdere Cad. No: 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone : +90 212 217 17 00
Fax : +90 212 217 22 92
E-mail : info@avesyayincilik.com

European Journal of Breast Health

European Journal of Breast Health

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.

The journal publishes; original research articles, case reports, reviews, letters to the editor, brief correspondences, meeting reports, editorial summaries, observations, novel ideas, basic and translational research studies, clinical and epidemiological studies, treatment guidelines, expert opinions, commentaries, clinical trials and outcome studies on breast health, biology and all kinds of breast diseases that are prepared and presented according to the ethical guidelines.

TOPICS within the SCOPE of EJBH concerning the breast health, breast biology and all kinds of breast diseases:

Epidemiology, Risk Factors, Prevention, Early Detection, Diagnosis and Therapy, Psychological Evaluation, Quality of Life, Screening, Imaging Management, Image-guided Procedures, Immunotherapy, molecular Classification, Mechanism-based Therapies, Carcinogenesis, Hereditary Susceptibility, Survivorship, Treatment Toxicities, and Secondary Neoplasms, Biophysics, Mechanisms of Metastasis, Microenvironment, Basic and Translational Research, Integrated Treatment Strategies, Cellular Research and Biomarkers, Stem Cells, Drug Delivery Systems, Clinical Use of Anti-therapeutic Agents, Radiotherapy, Chemotherapy, Surgery, Surgical Procedures and Techniques, Palliative Care, Patient Adherence, Cosmesis, Satisfaction and Health Economic Evaluations.

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.

All expenses of the journal are covered by the Turkish Federation of Breast Diseases Societies. All expenses of the journal are covered by the Turkish Federation of Breast Diseases Societies. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Federation of Breast Diseases Societies, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All published content is available online, free of charge at www.eurjbreasthealth.com.

OPEN ACCESS

Editor-in-Chief: Prof. Vahit ÖZMEN
Address: Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, Çapa, İstanbul
Phone: +90 (212) 534 02 10
Fax: +90 (212) 534 02 10
E-mail: editor@eurjbreasthealth.com
Web: eurjbreasthealth.com

Publisher: AVES
Address: Büyükdere Cad., 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
Web page: avesyayincilik.com

European Journal of Breast Health

Instructions to Authors

European Journal of Breast Health (Eur J Breast Health) is an international, open access, online-only periodical published in accordance with the principles of independent, unbiased, and double-blinded peer-review.

The journal is owned by Turkish Federation of Breast Diseases Societies and it is published quarterly on January, April, July, and October. The publication language of the journal is English. 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 Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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.

Manuscripts submitted to the Journal of Breast Health will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Journal of Breast Health requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.eurjbreasthealth.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Journal of Breast Health requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to the Journal of Breast Health, authors accept to assign the copyright of their manuscript to Turkish Federation of Breast Diseases Societies. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. European Journal of Breast Health requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.eurjbreasthealth.com). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in the Journal of Breast Health reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2019 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies,

European Journal of Breast Health

Instructions to Authors

STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.eurjbreasthealth.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.eurjbreasthealth.com.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- 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).

Key Points: All submissions except letters to the editor should be accompanied by 3 to 5 "key points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Key Points" targeting the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Manuscript Types

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.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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.

Images in Clinical Practices: Our journal accepts original high quality images related to the cases that we come across during clinical practices, that cite the importance or infrequency of the topic, make the visual quality stand out and present important information that should be shared in academic platforms. Titles of the images should not exceed 10 words. Images can be signed by no more than 3 authors. Figure legends are limited to 200 words and the number of figures is limited to 3. Video submissions will not be considered.

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

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

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)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

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 paranthesis. The reference styles for different types of publications are presented in the following examples.

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

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett 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: Bengisson 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: McCracken Jenna Mae. Mechanisms and consequences of neutrophil apoptosis inhibition by Francisella tularensis. University of Iowa, PhD (Doctor of Philosophy) thesis, 2017.

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/ncidodlElD/cid.htm.

REVISIONS
When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Editor-in-Chief: Prof. Dr. Vahit ÖZMEN

Address: Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, Çapa, İstanbul
Phone: +90 (212) 534 02 10
Fax: +90 (212) 534 02 10
E-mail: editor@eurjbreasthealth.com
Web: eurjbreasthealth.com

Publisher: AVES

Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
avesyayincilik.com

European Journal of Breast Health

Contents

Editorial

Eur J Breast Health 2020; 16(3): 158-159
DOI: 10.5152/ejbh.2020.080620

Loco-Regional Treatment for Intact Primary Tumor in Patient with De Novo Metastatic Breast Cancer; Comments and Concerns of ECOG-ACRIN 2108 Trial

Atilla Soran, Serdar Özbaş, Lütfi Doğan, Efe Sezgin, Vahit Özmen, Sushil Beriwal, Adam Brufsky
On behalf of The Breast Disease Working Group

Cite this article as: Soran A, Özbaş S, Doğan L, Sezgin E, Özmen V, Beriwal S, Brufsky A. Loco-Regional Treatment for Intact Primary Tumor in Patient with De Novo Metastatic Breast Cancer; Comments and Concerns of ECOG-ACRIN 2108 Trial. Eur J Breast Health 2020; 16(3): 158-159.

Khan et al. (1) presented the results of the multicenter, phase 3, ECOG ACRIN 2108 study at the plenary session of ASCO 2020 virtual meeting earlier than expected. ECOG-ACRIN 2108 (Eastern Cooperative Oncology Group-American College of Radiology Imaging Network - NCT01242800) trial recruited 390 women with de novo metastatic breast cancer (MBC) from February 2011 through July 2015 to determine whether the addition of locoregional treatment improved overall survival (OS). While 134 of these cases were excluded from the study for different reasons, 256 eligible patients were assigned to systemic therapy based on patient and tumor characteristics. Those who did not progress during 4 to 8 months of treatment were then assigned to continue systemic therapy alone (ST - n=131) or ST plus locoregional treatment with surgery +/- radiation (LRT - n=125).

The primary endpoint of the study was overall survival, and secondary endpoints were the time for locoregional progression and health-related quality of life measurement (HRQoL). There was no significant difference between the groups in terms of patients' age, race, menopausal status, tumor burden, hormone receptor and HER2 status. The median patient age was approximately 56 years, and nearly two thirds of patients were postmenopausal. Surgery was done in 109 (86%) of 125 patients in the early LRT group. Only 87 (80%) of these patients had tumor free surgical margins and 74 patients (68%) received locoregional radiotherapy. On the other hand, 25 of the 131 patients in the ST group (19%) received palliative surgery during the study.

They found no statistical difference between the two groups in terms of 3-year OS (68.4% vs 67.9%) (HR, 1.09; 90% CI, 0.80-1.49; p=0.63). At an average of 53 months follow up; the average OS for the entire study population was 54 months.

In addition, no progression-free survival benefit was observed between the ST and early LRT groups (p=0.40). However, locoregional recurrence or progression was significantly higher in the ST arm alone (25.6% vs 10.2%; p=0.003).

When subgroup analyzes were performed; according to the tumor molecular subtypes (HER2-positive tumor, hormone receptor-positive and HER2-negative tumor) no significant difference was observed between ST and early LRT study groups in terms of OS.

Regarding HRQoL measurements, the percentages of patients who completed the FACT-B questionnaire at the 6., 18. and 30. months following randomization were 81%, 60% and 51%, respectively. Although there was no significant difference in HRQoL measurements between both groups at 6 and 30 month post randomization; it was worse in the early LRT arm at 18 month post randomization.

As conclusion, Dr. Khan et al. (1) stated that based on the available data, patients with de novo MBC should not be offered locoregional therapy for primary tumor with the expectation of survival benefit. First of all, because of some missing details in the presentation, it is important to wait for the publication of this study to make a better assessment and to reach some definite conclusions. However, we want to share our comments and concerns on this study under the following headings:

- While planning the study statistics, 3-year overall survival was predicted as 30% in the ST group and 49.3% in the early LRT group, but in the follow-up 3-year survival was 67.9% in the ST group and 68.4% in the early LRT group (HR, 1.09; 90% CI, 0.80-1.49;

Corresponding Author :
Atilla Soran; asoran@upmc.edu

Received: 01.06.2020
Accepted: 07.06.2020
Available Online Date: 08.06.2020

p=0.63). High survival rate in this control group results decreases power of the study significantly. Although 125 patients were randomized to the early LRT group; only 109 were treated surgically which further decreases power of the study to detect the difference in survival.

- Multivariate analysis is also missing.
- Although one of the inclusion criteria for randomization is "complete resection with tumor free surgical margins"; it was achieved in 87/109 patients and the surgical margin remained positive in approximately 20% of the early LRT group. Besides details about extent of surgery for axilla and radiation volumes are not available.
- The rate of patients with skin invasion, presence of satellite nodules and fascia invasion appears to be quite high in the study (44% of patients have skin involvement, skin nodules and fascia invasion; 48% of them have T4 and / or N2 / 3 diseases). The distribution of these patients with locally advanced disease is not specified.
- Subgroup analysis according to the metastatic site is missing. Although, 38% of patients had only bone metastases, a subgroup analysis for this group was not performed. Similarly, no organ-specific comparison was made between the groups.
- Although the initial and final evaluation comparisons of HRQoL measurements are similar; Considering significant locoregional progression in patients with metastasis, we think it would be important to evaluate the long-term or 3-year HRQoL score.
- The patients with 0 months follow-up were included in the analysis, and when the deaths within 6 months were examined, it was seen that the mortality rates in the early LRT arm were high. The importance of surgery for survival can be evaluated with an analysis to be made by subtracting early deaths from statistical evaluation, and then analysis of those living more than 3 years and more.

We will get answers to some of the questions mentioned above after the publication of the manuscript. It seems that the ECOG-ACRIN 2108 study may not powered to answer the question of whether primary surgery provides a survival advantage in de novo MBC. We will continue to look forward to the results of the JCOG 1017 trial and Stereotactic body radiation therapy studies.

However, ECOG-ACRIN 2108 study gives important data in terms of local control. It is important to achieve local control in oligometastatic cases, especially in patients with bone only metastases. In addition, surgical removal of the primary tumor is important to prevent local spread to the pleura and pericardium. In order to determine who will benefit from early surgery in de novo MBC patients, we need more studies and information in terms of tumor and patient characteristics including biomarkers.

Therefore, regarding the presented data concluding that early surgery has no place in de novo MBC patient's treatment is eliminating the possibility of long-term no evidence of disease or cure. Loco-regional treatment for intact primary tumor for de novo MBC need to be considered case by case with input and discussions from all stake holders.

Reference

1. Khan SA, Zhao F, Solin LJ, Goldstein LJ, Cella D, Basik M, Golshan M, Julian TB, Pockaj BA, Lee CA, Razaq W, Sparano JA, Babiera GV, Dy IA, Jain S, Silverman P, Fisher C, Tevaarwerk AJ, Wagner LI, Sledge GW. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: A trial of the ECOG-ACRIN Research Group (E2108). J Clin Oncol 2020; 38(Suppl): pp.LBA2. [Crossref]

Editorial

Eur J Breast Health 2020; 16(3): 160-161
DOI: 10.5152/ejbh.2020.200420

Breast Cancer Management during the COVID 19 Pandemic: French Guidelines

Emile Daraï[1], Carole Mathelin[2], Joseph Gligorov[3]

[1]Department of Gynaecology, Obstetrics and Human Reproductive Medicine, TENON Hospital, Paris, France
[2]Department of Surgery, Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France
[3]Executive Director of Institut Universitaire de Cancérologie AP-HP, Sorbonne Université, Paris, France

Cite this articles as: Daraï E, Mathelin C, Gligorov J. Breast Cancer Management during the COVID 19 Pandemic: French Guidelines. Eur J Breast Health 2020; 16(3): 160-161

At the beginning of 2020, the new coronavirus (SARS-CoV-2), responsible for severe acute respiratory syndrome, was identified as the viral agent causing pneumonia in several patients epidemiologically linked to a religious gathering in Mulhouse, a town located near Strasbourg (the town where SIS was created). Since then, the spread of this coronavirus disease (COVID-19) to many other French area was observed. In France, as of April 17th, 2020, there were more than 109 000 confirmed cases of COVID-19 and 18 681 related deaths (1).

Despite extraordinary containment measures implemented from 15th of March 2020 in France, the epidemic has spread, with clinical forms of varying severity, ranging from asymptomatic disease, minor flu-like symptoms to severe pneumopathies or multi-organ failure with a mortality rate of a few percent. Patients who are older and/or have co-morbidities (diabetes, cardiovascular disease, cancer, immunosuppression, obesity...) are the most likely to develop severe forms. The current pandemic is therefore of particular concern for cancer patients.

In France, the Nice-St Paul de Vence working group published on 9th of April 2020 (2) a series of recommendations concerning more specifically the medical care of people with breast cancer in the context of the COVID pandemic in partnership with the Collège National des Gynécologues et Obstétriciens Français, the Société d'Imagerie de la Femme, the Société Française d'Oncologie Gynécologique, the Société Française de Sénologie et Pathologie Mammaire et the French Breast Cancer Intergroup UNICANCER. The purpose of these recommendations was double. On the one hand, oncological management must be adequate, avoiding any potential loss of opportunity with regard to breast cancer (despite the pandemic, cancer patients must have care allowing the same level of curability or life expectancy). On the other hand, cancer patients must be protected from the risk of serious or lethal infection with CoV-2-SARS.

So, many changes concerning diagnosis and treatment have therefore been decided.

The main change concerns organized screening programs, completely suspended during the pandemic period. The only suspicious lesions requiring exploration are ACR5, ACR4 and ACR3 lesions in a context of high risk. If cancer is diagnosed and requires further local assessment, this should be carried out with the aim of limiting the number of visits to imaging departments. MRI should only be used in uninfected individuals (COVID-19 negative), due to the great difficulty of adequately disinfecting the equipment.

After diagnosis, multidisciplinary meetings must be maintained but modified according to new procedures recommended by our National Institute of Cancer. With regard to the choices made during these multidisciplinary meetings, whenever an option that reduces the number of hospital visits is as effective as a treatment that requires more trips to health care facilities, it should be preferred (home administration, 3-weekly vs. weekly regimen, oral vs. intraveinous administration, hypofraction of radiotherapy, etc.). Similarly, whenever possible, tele or phone consultations should be preferred.

Concerning breast surgery, all secondary reconstruction surgeries must be postponed after the pandemic. Surgeries concerning benign lesions (atypical hyperplasia, lobular carcinoma in situ, papillomas and other benign lesions) should be deferred for 3 months. When breast surgery is to be performed, special attention is requested for extemporaneous examination, which should be performed only if absolutely necessary. Surgeries should be ambulatory as often as possible. In the case of mastectomy, immediate breast reconstruction

Corresponding Author :
Carole Mathelin; C.Mathelin@icans.eu

Received: 15.04.2020
Accepted: 20.04.2020
Available Online Date: 21.04.2020

with a prosthesis/expander is possible if indicated, but other more extensive techniques requiring longer surgery and hospitalization should be avoided during the pandemic. For patients with significant co-morbidities making the risk of complications high in case of COVID-19 (elderly subjects, chronic respiratory or cardiac pathology, immunosuppression...), and having a slowly evolving and hormone-dependent invasive cancer, a first hormone therapy may be proposed in order to postpone the surgical procedure.

About radiotherapy, for intraductal carcinoma, a deferral of 3 to 6 months is possible. During the pandemic, a hypofractionated regimen should be preferred. For invasive cancers that are highly hormone-dependent in postmenopausal patients, stage I or II, or in patients with significant co-morbidities exposing them to the risk of severe complications in the case of COVID-19 (elderly subjects, chronic respiratory or cardiac pathology, immunosuppression, etc.), and with an indication for radiotherapy, a deferral of 3 to 6 months is possible and a hypofractionated regimen should also be preferred. An anti-estrogens treatment can be initiated before the radiotherapy. For other invasive cancers with an indication for radiotherapy, treatment must be carried out according to the usual indications.

These recommendations are also valid for men with breast cancer.

Indications for consultation for fertility preservation should be retained.

In the case of breast cancer occurring during pregnancy, the case must be discussed during a national multidisciplinary meeting (Cancer Associated with Pregnancy, CALG Network).

Indications for oncogenetic consultations must be maintained. However, in order to reduce the number of hospital visits, the procedures for requesting a test and reporting the results are simplified, with the possibility of teleconsultation in some cases.

Travel to attend supportive care should be limited to essential care, with tele or telephone consultations being preferred. The identification of distress and the offer of psychological support are imperative during this period. Hairdressers are closed in France and the only way to obtain a hair prosthesis is online on the websites or via patient associations. The online sites of the patient's associations are recommended to patients so that they can find the additional information and social support they need during this period.

Finally, regarding clinical trials for SARS-CoV-2 infection, a history of breast cancer or current management of breast cancer should not be considered in France as an exclusion criterion for these trials alone.

It is important during the pandemic period to establish data collection regarding breast cancer patient management and the impact of treatment changes on care pathways and caregivers in order to gain valuable experience in optimizing patient management.

References

1. Available from: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/articles/infection-au-nouveau-coronavirus-sars-cov-2-covid-19-france-et-monde.
2. Gligorov J, Bachelot T, Pierga JY, Antoine EC, Balleyguier C, Barranger E, et al. [COVID-19 and people followed for breast cancer: French guidelines for clinical practice of Nice-St Paul de Vence, in collaboration with the College Nationale des Gynecologues et Obstetriciens Francais (CNGOF), the Societe d'Imagerie de la FEMme (SIFEM), the Societe Francaise de Chirurgie Oncologique (SFCO), the Societe Francaise de Senologie et Pathologie Mammaire (SFSPM) and the French Breast Cancer Intergroup-UNICANCER (UCBG)]. Bull Cancer 2020: S0007-4551(20)30159-4. DOI: 10.1016/j.bulcan.2020.03.008. (PMID: 32278467) [Crossref]

Review

Eur J Breast Health 2020; 16(3): 162-166
DOI: 10.5152/ejbh.2020.5480

Breast Implant-Associated Anaplastic Large Cell Lymphoma Following Gender Reassignment Surgery: A Review of Presentation, Management, and Outcomes in the Transgender Patient Population

Shruti Zaveri[1], Alice Yao[2], Hank Schmidt[3]

[1]Department of Surgery, The Mount Sinai Hospital, New York, NY, USA
[2]Division of Plastic and Reconstructive Surgery, Department of Surgery, The Mount Sinai Hospital, New York, NY, USA
[3]Dubin Breast Center, Tisch Cancer Institute, The Mount Sinai Hospital, New York, NY, USA

ABSTRACT

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare peripheral T-cell lymphoma with approximately 650-700 reported cases worldwide. The incidence, however, is increasing as more practitioners become aware of the diagnosis, and recent studies show that early diagnosis and treatment is critical to improve prognosis. There have been four cases of BIA-ALCL in total reported in the transgender population in the literature. These reported cases were reviewed in detail to determine presentation and management of BIA-ALCL in transgender patients compared to the larger population of BIA-ALCL patients. This review highlights BIA-ALCL in transgender women, a population that is often excluded from breast screening and follow-up. Transgender women may not routinely go through the same post-operative follow-up protocols as patients with breast implants for breast cancer reconstruction and can thus be at risk for delayed recognition and diagnosis. BIA-ALCL is a rare complication of breast implantation, and it is important to counsel all patients undergoing implant placement, including transgender women, on its risk.

Keywords: BIA-ALCL, implant, lymphoma, transgender

Cite this article as: Zaveri S, Yao A, Schmidt H. Breast Implant-Associated Anaplastic Large Cell Lymphoma Following Gender Reassignment Surgery: A Review of Presentation, Management, and Outcomes in the Transgender Patient Population. Eur J Breast Health 2020; 16(3): 162-166.

Introduction

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare peripheral T-cell lymphoma discovered in recent years as a potential complication associated with breast implants. It was first described in 1997 (1), and has since been reported in approximately 650-700 cases worldwide (2). Only a fraction of these cases have been published in the literature (3). Some of these cases may be duplicates, thus the exact number of cases continues to be debated. While the precise incidence and prevalence is unknown, there is an estimated incidence of 2 per million per year and a lifetime prevalence of 33 per 1 million women with textured breast implants (4). Given the rarity of the disease, developing a protocol for diagnosis has been difficult and determining optimal treatment even more challenging. Recognition of BIA-ALCL is increasing as more practitioners become aware of the diagnosis, and it is important to identify the presentation of BIA-ALCL in all populations, including transgender women, that may be affected.

Gender-affirmation surgery is a critical component of the management of gender dysphoria. For male-to-female transgender women, breast implants are routinely used as a part of gender reassignment surgery (5). Transgender women typically initiate hormonal therapy for feminization of the chest, but response to hormonal therapy varies widely. Current evidence suggests that 60-70% of trans-women seek surgical breast augmentation in addition to cross-sex hormone therapy as a part of their feminization (6). The number of adolescents identified with gender dysphoria is increasing, and as such, the use of breast implants in this population is also on the rise (7). Given the increasing incidence of BIA-ALCL in all patients with breast implants, it is important to recognize BIA-ALCL in the transgender population. This review highlights the presentation, management, and outcomes of BIA-ALCL in transgender women, a population that is often excluded from breast screening and follow-up.

Corresponding Author:
Hank Schmidt; hank.schmidt@mountsinai.org

Received: 29.01.2020
Accepted: 30.05.2020

Table 1. Presentation of BIA-ALCL in transgender patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age at presentation (years)	49	56	40	54
Age at implant placement (years)	42	36	33	37
Interval from placement to initial symptoms (years)	1	5	5	9
Interval from placement to presentation (years)	7	20	7	17
Interval from initial symptoms to diagnosis (years)	6	15	2	8
Type of implant	Textured	Textured	Textured	Textured
Hormonal therapy	1 year	0 years	6 years	11 years
Initial symptoms	Pain Discomfort Pruritus	Pain Fevers Capsular contracture	Pain Discomfort	Pain Pruritus Hyperpigmentation
Presenting symptoms	Cutaneous papules, seroma, palpable mass	Periprosthetic seroma, implant rupture, palpable mass	Palpable mass	Multiple palpable masses

BIA-ALCL: breast implant-associated anaplastic large cell lymphoma

Cases of BIA-ALCL in Transgender Patients

There are four cases of BIA-ALCL in total in the transgender population reported in the literature (8-11). These reported cases were reviewed in detail to determine whether there are any discrepancies in the presentation and management of BIA-ALCL in transgender patients compared to the population at large.

In the reported transgender cases, the mean age at implant placement was 37 years and mean age at presentation was 49.75 years (Table 1). Mean time from implant placement to initial symptoms was 5 years while the mean time to presentation was over 12 years. Each of the reported cases in the transgender population involved the use of textured implants, and initial symptoms were vague, including breast pain, discomfort, and pruritis. By the time of presentation, each of the patients a palpable breast lesion.

The breast imaging of choice-ultrasound, mammogram, or MRI-varied between the cases, however each patient underwent Positron Emission-Tomography (PET) for evaluation of metastatic spread (Table 2). Each patient underwent implant removal with capsulectomy and mass excision, however the extent of the resection varied by case. The pectoral muscle was resected in half of the cases. Evaluation of lymph nodes also varied by case-the first reported case included an axillary node dissection and was found to have negative nodes. Subsequent cases either did not check axillary nodes or utilized a sentinel lymph node (SLN) biopsy. The case in which a SLN biopsy was employed identified 1 positive lymph node. This patient underwent adjuvant radiation therapy with a total of 36 grays (Gy) delivered in 18 fractions to right axilla and 30Gy to right breast. Three out of four patients were treated with adjuvant chemotherapy consisting of 4 to 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy. All patients presented at a late stage with lymphoma infiltrates beyond the capsule, thus falling under the T4 tumor extent category of the American Joint Committee on Cancer TNM Staging of BIA-ALCL (Table 3). Each of the patients was tumor-free at 6 months post-surgical excision; 2 years was the longest follow-up time in the reported cases.

Discussion and Conclusion

Pathogenesis and presentation

Anaplastic large cell lymphoma (ALCL) is a type of non-Hodgkin T-cell lymphoma that is characterized by the presence of lymphoid cells that express cell-surface protein CD30. Approximately 60% of non-implant-associated ALCL cases are anaplastic lymphoma kinase (ALK) positive; however, BIA-ALCL is found to be ALK-negative, thus differentiating systemic ALCL from BIA-ALCL. ALCL arises predominantly from the implant capsule, and the vast majority of reported cases have thus far occurred with the use of textured implants (12). While the exact pathogenesis of Breast Implant-Associated ALCL is still unknown, overexpression of CD30 is often seen in states of chronic inflammation, and it is proposed that BIA-ALCL develops from chronic inflammation in the breast secondary to the implant. Theories include bacterial biofilm growth on the implant surface and abnormal immune responses to textured implants (13-16). Several studies have highlighted that a chronic biofilm infection on implants can cause capsular contracture. An animal study compared biofilm formation in textured versus smooth implants and showed significantly higher numbers of lymphocytes, particularly T-cells, in bacterial biofilm on textured implants compared to smooth implants, furthering the evidence to support the theory that a chronic biofilm infection on textured implants leads to T-cell hyperplasia and may potentiate BIA-ALCL (16).

There are several differences in the typical presentation of BIA-ALCL compared to the presentation of the disease in the transgender patient population. A recently published large systematic review of 115 BIA-ALCL articles and 95 patients found that 66% of patients presented with a late-onset seroma, 8% of patients presented with a new breast mass, and others presented with capsular con-

Table 2. Diagnosis and management of BIA-ALCL in transgender patients

	Patient 1	Patient 2	Patient 3	Patient 4
Imaging	CT, Breast MRI, PET	Ultrasound, Mammogram, PET	Breast MRI, PET	Ultrasound, Mammogram, PET
Surgery	Unilateral mastectomy (implant previously removed) with resection of pectoral muscle, and axillary node dissection	Bilateral implant removal with capsulectomy of affected side	Unilateral implant removal with capsulectomy, mass resection with part of pectoral muscle	Bilateral implant removal with capsulectomy of affected side and sentinel lymph node biopsy, excision of active lymph node
Implant status	Intact	Intact (previous rupture and exchange)	Ruptured	Intact
Margin status	Positive	Negative	Negative	Positive
Axillary status	Negative	Unchecked	Unchecked	Positive
Radiation	No radiation therapy	No radiation therapy	No radiation therapy	Total 36Gy in 18 fractions to R axilla and 30Gy to R breast
Chemotherapy	4 cycles of CHOP	No chemotherapy	6 cycles of CHOP	6 cycles of CHOP

BIA-ALCL: breast implant-associated anaplastic large cell lymphoma; CT: computer tomography; MRI: magnetic resonance imaging; PET: positron emission-tomography; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone

tracture, skin findings, or axillary lymphadenopathy (3). While all the transgender patient cases reviewed noted the presence of vague implant-related symptoms such as pain or pruritus and a seroma in the years prior to presentation, they did not present for evaluation until the development of a palpable mass. The mean time to presentation in the overall BIA-ALCL population is 8-10 years after implant placement (3, 17, 18) compared to 13 years in the transgender patients reviewed. Each of the transgender patients developed symptoms on average 5 years following implant placement, however all the patients did not present for evaluation until at least 2 years following initial symptoms.

Diagnosis and treatment

Recent guidelines recommend that all patients who present with a late-onset periprosthetic fluid collection should be evaluated for BIA-ALCL. Ultrasound can be used to identify the seroma and help determine the presence of masses surrounding the capsule (19). Seroma aspiration with seroma fluid cytology or ultrasound-guided core needle biopsy in cases presenting with a mass can be used to confirm the diagnosis. All reported cases of BIA-ALCL have been anaplastic lymphoma kinase (ALK)-negative and CD30-positive. Anaplastic large cell lymphomas are usually FDG avid; thus, once the diagnosis is confirmed, PET CT can be used to determine the extent of the disease (20-22).

The 2019 National Comprehensive Cancer Network (NCCN) guidelines outline both the traditional Ann Arbor staging system for non-Hodgkin lymphoma as well as a solid tumor staging system based on tumor, lymph node, and metastasis (TNM) status (23). The Ann Arbor staging system divides BIA-ALCL based on status of extranodal spread: stage IE (disease limited to a single extranodal site), stage IIE (extranodal disease with spread to local lymph nodes), or stage IV disease (spread to multiple extranodal sites). The TNM system provides a more detailed stage by taking into account tumor extent with invasion confined to or beyond the capsule. There are significant differences in the stage at diagnosis of BIA-ALCL in most patients compared to the reported transgender patients. 35-70% of typical BIA-ALCL cases are diagnosed at stage IA with tumor confined to the effusion or the luminal aspect of the capsule and no lymph node involvement (23). As seen in Table 3, all the transgender patients were diagnosed at a late stage, IIA and higher, with tumor infiltrates already spread beyond the capsule.

Given that our knowledge on the natural progression of the disease is still sparse, the optimal treatment protocol remains unclear. Complete surgical resection with removal of the implant, capsulectomy, and excision of any masses to clear margins has been shown to improve disease-free survival (23). The role for mastectomy and axillary staging with sentinel lymph node biopsy remains unclear. Per recent 2019 National Comprehensive Cancer Network (NCCN) guidelines in the United States, adjuvant radiation therapy is indicated for patients with local residual disease or unresectable disease with chest wall invasion, while adjuvant chemotherapy is indicated for patients with Stage II-IV disease (24).

The first case of BIA-ALCL in a transgender woman was reported in 2016, prior to these NCCN guidelines. This patient was found to have positive margins post-surgical resection but did not receive radiation therapy as would have been indicated per the new NCCN guidelines. In the last reported case, the patient received both chemotherapy and radiation following surgical resection given the finding of positive margins and multiple involved axillary lymph nodes. Excision of the contralateral implant may be considered given 2-4% of patients develop bilateral disease (24). Reconstruction following surgical treatment of BIA-ALCL is still highly debated with recent guidelines suggesting reconstruction may be pursued after a 6-month disease-free interval (3, 17, 25). Despite the recent NCCN guidelines, we lack a precise treatment protocol for BIA-ALCL and

Table 3. Outcomes of BIA-ALCL in transgender patients

	Patient 1	Patient 2	Patient 3	Patient 4
Year of report	2015	2017	2018	2019
Ann-Arbor stage	Stage IE	Stage IE	Stage IE	Stage IIE
TNM stage	T4N0M0 (Stage IIA)	T4N0M0 (Stage IIA)	T4N0M0 (Stage IIA)	T4N2M0 (Stage III)
Follow-up (years)	Tumor-free at 6 months	Tumor-free at 10 months	Tumor-free at 2-year follow-up	Tumor-free at 1-year follow-up
Follow-up imaging	Post-treatment PET with no evidence of disease	Unknown	Post-treatment PET with no evidence of disease	Post-treatment PET with no evidence of disease

BIA-ALCL: breast implant-associated anaplastic large cell lymphoma; TNM: tumor extent, Lymph node status, Metastasis

there is still limited evidence on the extent of breast and axillary surgery needed for effective locoregional control.

Of note, transgender patients often receive antiandrogen therapy and supplementation with exogenous estrogens for breast development in the months prior to breast augmentation (26). The World Professional Association for Transgender Health recommends estrogen supplementation for at least one year after considering breast augmentation (5). It is unknown whether antiandrogen therapy may have an impact on neoplastic potential in the breast and risk of ALCL associated with implants (27).

Outcomes and impact on clinical practice

Breast implants are accepted as standard of care for cosmetic breast augmentation, reconstruction following mastectomy, and as in the patients discussed above, gender reassignment surgery (28). Implants remain the most common method for breast augmentation and reconstruction with currently more than an estimated 10 million women with implants worldwide (29). Textured implants were introduced in the 1980s to combat capsular contracture, and since then, have been increasingly used for breast reconstruction in certain parts of the world, possibly leading to an increased risk of BIA-ALCL following implant placement. Textured implants previously represented approximately 10% of all breast implants and were recalled by one of their major manufacturers in 2019. Though a few other companies continue to produce textured implants legally, their use is now declining as patients and surgeons become more aware of BIA-ALCL and choose either smooth implants or autologous options instead.

Recent studies have shown that early diagnosis and surgical resection is critical to improved prognosis of BIA-ALCL (23, 24). For this reason, it is crucial that practitioners in plastic surgery, breast surgery, and primary care gain awareness of the disease and appropriate diagnosis and treatment pathways. Most of the discussion around BIA-ALCL has been in the plastic surgery literature (4, 17, 30, 31), and there is need for increased awareness of this entity amongst not only surgeons but also primary care providers who may often be the first to encounter these patients. Furthermore, unlike breast cancer patients who have routine follow-up and screening, patients who have breast implants secondary to either cosmetic breast augmentation or as a part of gender reassignment surgery sometimes do not routinely follow-up with their plastic surgeons, thus carrying a risk of delayed diagnosis. Although there is a very small number of reported cases of BIA-ALCL in transgender patients, comparison of these cases to other patients with BIA-ALCL does highlight significant delay in presentation and diagnosis for this subset of patients.

This review highlights the presentation of BIA-ALCL in a transgender woman after breast implant placement as a part of gender reassignment surgery. The transgender patients reviewed had a longer mean time to presentation than typically cited in BIA-ALCL series, and each of the transgender patients was not diagnosed until at least 2 years following initial symptoms. The transgender patients were thus diagnosed a significantly advanced stages compared to most BIA-ALCL patients. Transgender women may not routinely go through the same post-operative follow-up protocols as patients with breast implants secondary to breast cancer reconstruction and can thus be at risk for delayed recognition and diagnosis. BIA-ALCL is a rare but serious complication of breast implantation and it is important to counsel all patients undergoing implant placement, including transgender women, on its risk.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Z., H.S.; Design - S.Z., H.S.; Supervision - H.S., A.Y.; Data Collection and/or Processing - S.Z., A.Y.; Analysis and/or Interpretation - S.Z., H.S., A.Y.; Literature Search - S.Z., H.S., A.Y.; Writing Manuscript - S.Z., H.S., A.Y.; Critical Review - S.Z., H.S., A.Y.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Keech JA, Jr., Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. Plast Reconstr Surg 1997; 100: 554-555. (PMID: 9252643) [Crossref]
2. Maisel W. Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL) - Letter to Health Care Providers: U.S. Food and Drug Administration 2019 [Web Document]. Available from: https://www.fda.gov/medical-devices/letters-health-care-providers/breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl-letter-health-care-providers.
3. Leberfinger AN, Behar BJ, Williams NC, Rakszawski KL, Potochny JD, Mackay DR, Ravnic DJ. Breast Implant-Associated Anaplastic Large Cell Lymphoma: A Systematic Review. JAMA Surg 2017; 152: 1161-1168. (PMID: 29049466) [Crossref]

4. Doren EL, Miranda RN, Selber JC, Garvey PB, Liu J, Medeiros LJ, et al. U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg 2017; 139: 1042-1050. (PMID: 28157769) [Crossref]
5. Eli Coleman WB, Marsha Botzer. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People. 7 ed: World Professional Association for Transgender Health (WPATH); 2012.
6. Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. J Sex Med 2014; 11: 1240-1247. (PMID: 24618412) [Crossref]
7. Aitken M, Steensma TD, Blanchard R, VanderLaan DP, Wood H, Fuentes A, Spegg C, Wasserman L, Ames M, Fitzsimmons CL, Leef JH, Lishak V, Reim E, Takagi A, Vinik J, Wreford J, Cohen-Kettenis PT, de Vries ALC, Kreukels BPC, Zucker KJ. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. J Sex Med 2015; 12: 756-763. (PMID: 25612159) [Crossref]
8. Orofino N, Guidotti F, Cattaneo D, Sciume M, Gianelli U, Cortelezzi A, Iurlo A. Marked eosinophilia as initial presentation of breast implant-associated anaplastic large cell lymphoma. Leuk Lymphoma 2016; 57: 2712-2715. (PMID: 26984254) [Crossref]
9. de Boer M, van der Sluis WB, de Boer JP, Overbeek LIH, van Leeuwen FE, Rakhorst HA, van der Hulst RRWJ, Hijmering NJ, Bouman MB, de Jong D. Breast Implant-Associated Anaplastic Large-Cell Lymphoma in a Transgender Woman. Aesthet Surg J 2017; 37: NP83-NP7. (PMID: 29036941) [Crossref]
10. Patzelt M, Zarubova L, Klener P, Barta J, Benkova K, Brandejsova A, Trneny M, Gürlich R, Sukop A. Anaplastic Large-Cell Lymphoma Associated with Breast Implants: A Case Report of a Transgender Female. Aesthetic Plast Surg 2018; 42: 451-455. (PMID: 29101436) [Crossref]
11. Ali N, Sindhu K, Bakst RL. A Rare Case of a Transgender Female With Breast Implant-Associated Anaplastic Large Cell Lymphoma Treated With Radiotherapy and a Review of the Literature. J Investig Med High Impact Case Rep 2019; 7: 2324709619842192. (PMID: 31010324) [Crossref]
12. BIA-ALCL Physician Resources: American Society of Plastic Surgeons; 2019 [Web Document]. Available from: https://www.plasticsurgery.org/for-medical-professionals/health-policy/bia-alcl-physician-resources.
13. Story SK, Schowalter MK, Geskin LJ. Breast implant-associated ALCL: a unique entity in the spectrum of CD30+ lymphoproliferative disorders. Oncologist 2013; 18: 301-307. (PMID: 23429741) [Crossref]
14. Blombery P, Thompson ER, Jones K, Arnau GM, Lade S, Markham JF, Li J, Deva A, Johnstone RW, Khot A, Prince HM, Westerman D. Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast implant-associated anaplastic large cell lymphoma anaplastic large cell lymphoma. Haematologica 2016; 101: e387-90. (PMID: 27198716) [Crossref]
15. Kadin ME, Morgan J, Xu H, Epstein AL, Sieber D, Hubbard BA, Adams Jr WP, Bacchi CE, Goes JCS, Clemens MW, Medeiros LJ, Miranda RN. IL-13 is produced by tumor cells in breast implant-associated anaplastic large cell lymphoma: implications for pathogenesis. Hum Pathol 2018; 78: 54-62. (PMID: 29689246) [Crossref]
16. Hu H, Jacombs A, Vickery K, Merten SL, Pennington DG, Deva AK. Chronic biofilm infection in breast implants is associated with an increased T-cell lymphocytic infiltrate: implications for breast implant-associated lymphoma. Plast Reconstr Surg 2015; 135: 319-329. (PMID: 25383716) [Crossref]
17. Shine JJ, Boghossian E, Beauchemin G, Papanastasiou VW, Borsuk DE. Breast Implant-Associated Anaplastic Large Cell Lymphoma: Immediate or Delayed Implant Replacement? Aesthetic Plast Surg 2018; 42: 1492-1498. (PMID: 30094550) [Crossref]
18. Clemens MW, Brody GS, Mahabir RC, Miranda RN. How to Diagnose and Treat Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg 2018; 141: 586e-599e. (PMID: 29595739) [Crossref]
19. O'Neill AC, Zhong T, Hofer SOP. Implications of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) for Breast Cancer Reconstruction: An Update for Surgical Oncologists. Ann Surg Oncol 2017; 24: 3174-3179. (PMID: 28762113) [Crossref]
20. Kim B, Predmore ZS, Mattke S, van Busum K, Gidengil CA. Breast Implant-associated Anaplastic Large Cell Lymphoma: Updated Results from a Structured Expert Consultation Process. Plast Reconstr Surg Glob Open 2015; 3: e296. (PMID: 25674377) [Crossref]
21. Adrada BE, Miranda RN, Rauch GM, Arribas E, Kanagal-Shamanna R, Clemens MW, Fanale M, Haideri N, Mustafa E, Larrinaga J, Reisman NR, Jaso J, You MJ, Young KH, Medeiros LJ, Yang W. Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. Breast Cancer Res Treat 2014; 147: 1-14. (PMID: 25073777) [Crossref]
22. Cahu X, Bodet-Milin C, Brissot E, Maisonneuve H, Houot R, Morineau N, Solal-Celigny P, Godmer P, Gastinne T, Moreau P, Moreau A, Lamy T, Kraber-Bodere F, Le Gouill S. 18F-fluorodeoxyglucose-positron emission tomography before, during and after treatment in mature T/NK lymphomas: a study from the GOELAMS group. Ann Oncol 2011; 22: 705-711. (PMID: 20739714) [Crossref]
23. Clemens MW, Medeiros LJ, Butler CE, Hunt KK, Fanale MA, Horwitz S, Weisenburger DD, Liu J, Morgan EA, Kanagal-Shamanna R, Parkash V, Ning J, Sohani AR, Ferry JA, Mehta-Shah N, Dogan A, Liu H, Thormann N, Di Napoli A, Lade S, Piccolini J, Reyes R, Williams T, McCarthy CM, Hanson SE, Nastoupil LJ, Gaur R, Oki Y, Young KH, Miranda RN. Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma. J Clin Oncol 2016; 34: 160-168. (PMID: 26628470) [Crossref]
24. Clemens MW, Jacobsen ED, Horwitz SM. 2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Aesthet Surg J 2019; 39(Supplement 1): S3-S13. (PMID: 30715173) [Crossref]
25. Lamaris GA, Butler CE, Deva AK, Miranda RN, Hunt KK, Connell T, Lipa JE, Clemens MW. Breast Reconstruction Following Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg 2019; 143: 51S-8S. (PMID: 30817556) [Crossref]
26. Unger CA. Update on Gender-Affirming Treatment for the Transgender Woman. Semin Reprod Med 2017; 35: 442-447. (PMID: 29073683) [Crossref]
27. Moore E, Wisniewski A, Dobs A. Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. J Clin Endocrinol Metab 2003; 88: 3467-3473. (PMID: 12915619) [Crossref]
28. Chao AH, Garza R, 3rd, Povoski SP. A review of the use of silicone implants in breast surgery. Expert Rev Med Devices 2016; 13: 143-156. (PMID: 26690709) [Crossref]
29. Albornoz CR, Bach PB, Mehrara BJ, Disa JJ, Pusic AL, McCarthy CM, Cordeiro PG, Matros E. A paradigm shift in U.S. Breast reconstruction: increasing implant rates. Plast Reconstr Surg 2013; 131: 15-23. (PMID: 23271515) [Crossref]
30. Gidengil CA, Predmore Z, Mattke S, van Busum K, Kim B. Breast implant-associated anaplastic large cell lymphoma: a systematic review. Plast Reconstr Surg 2015; 135: 713-720. (PMID: 25490539) [Crossref]
31. Fleming D, Stone J, Tansley P. Spontaneous Regression and Resolution of Breast Implant-Associated Anaplastic Large Cell Lymphoma: Implications for Research, Diagnosis and Clinical Management. Aesthetic Plast Surg 2018; 42: 672-678. (PMID: 29445921) [Crossref]

Original Article

Eur J Breast Health 2020; 16(3): 167-170
DOI: 10.5152/ejbh.2020.5041

Dosimetric Comparison of Superflab and Specially Prepared Bolus Materials Used in Radiotherapy Practice

Serhat Aras[1], İhsan Oğuz Tanzer[2], Türkan İkizceli[3]

[1]Medical Imaging Programme, University of Health Sciences, İstanbul, Turkey
[2]Biomedical Technology Programme, University of Health Sciences, İstanbul, Turkey
[3]Department of Radiology, University of Health Sciences, Haseki Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: This study compares standard commercial bolus material (Superflab) to custom prepared silicone dental impression material (CDIM) and play dough material (PDM) with respect to dosimetric properties and applicability by using ion chamber measurement and calculated dose values.

Materials and Methods: The CDIM bolus was prepared by mixing dental impression silicone material with enough water to maintain a density of about 1.0 g/cm^3. The prepared bolus material is applied on an RW3 solid phantom by covering 10x10 cm^2 area with 0.5-1 cm thickness. Ion chamber measurements were performed separately with and without bolus material application. The setup was scanned in CT and the same procedure was repeated in the TPS using the scan data, in which the Pencil Beam Convolution dose calculation algorithm was used. To compare the effect of bolus material on tissue, the Superflab bolus and CDIM bolus were applied with 1 cm of thickness on postmastectomy scar and dose calculations on TPS were performed.

Results: After comparison of the dosimetric values for Superflab, CDIM and PDM, we obtained statistically meaningful results between superflab and CDIM. For PDM, the results obtained with TPS and ion chamber measurements indicated that, it is not suitable to use in radiotherapy application due to its material properties. For the simulated skin dose values obtained at five random points on the scar tissue, the comparison of Superflab and CDIM TPS calculation results were not statistically significant.

Conclusion: The CDIM is easy to prepare and apply on irregular mastectomy scar tissue and it prevents formation of air gaps in the application surface. Especially for curved anatomical regions such as scar tissue, inclusion of the bolus material in treatment planning protocol will reduce dose uncertainty in application. It is safe to use CDIM as an alternative to Superflab in radiotherapy application, whereas PDM is not useful in clinical practice due to its material properties.

Keywords: Bolus material, superflab, dental impression material, play dough, radiotherapy

Cite this articles as: Aras S, Tanzer İO, İkizceli T. Dosimetric Comparison of Superflab and Specially Prepared Bolus Materials Used in Radiotherapy Practice. Eur J Breast Health 2020; 16(3): 167-170.

Introduction

The Bolus Material is defined as a tissue equivalent material that maximizes, reduces or adds radiation dose in an irradiated area according to the ICRU Report 24 (1). Bolus is used in radiotherapy (RT) to increase skin dose for photon beams (2-4).

Bolus materials are used in high-energy RT in order to overcome the skin-sparing effect of high energy radiation beams, which prevents delivery of sufficient dose to the skin. Several types of commercially available bolus materials are often used in RT units (5). It is important in clinical practice that the bolus material is sufficiently elastic and deformable in order to conform to the surface and not adversely affected by high dose levels, be durable, nontoxic, and cost effective (6). Bolus materials should be nearly tissue-equivalent and allow sufficient surface dose boost. Superflab is a commercial bolus material widely accepted in RT clinics worldwide. It is made of a proprietary synthetic gel, resulting in a mouldable material that does not suffer inelastic strain from normal stresses. Consequently, Superflab does not have to be bagged or wrapped in plastic film to maintain its shape during treatment. To optimally support dose build-up for varying surface contours and target volumes, several sizes are available. The material density of Superflab is 1.02 g/cm^3 which is similar to water in approximating tissue-equivalence and well accepted clinically (7). In practice though, Superflab is not effective in making sufficient contact with irregular anatomical surface on the patient's skin. This is the case particularly around the nose, ear, and scalp, resulting in

Corresponding Author :
Serhat Aras; serhat.aras@sbu.edu.tr

Received: 31.05.2019
Accepted: 18.11.2019
Avialible Online Deta: 31.03.2020

air gaps, thus creating the skin sparing effect which reduces both the maximum and surface dose (8). In literature, various bolus materials are used, such as; thermoplastic sheets, blue water phantoms, 3D customized bolus (9, 10).

The purpose of this study is to compare the ion chamber measurements and calculated dose values of a standard commercial bolus material (Superflab) with two other materials which are-custom prepared silicone dental impression material (CDIM) and play dough material (PDM). In addition, we also compare the treatment simulation of skin dose values between Superflab and CDIM on surgical scar using twenty 20 randomly selected and anonymous breast cancer patients who underwent modified radical mastectomy, using the treatment planning system (TPS).

Materials and Methods

Preparation of bolus materials

Superflab (Radiation Products Design Inc, Albertville, MN) bolus is widely used in clinical practice and commercially available. Since commercially available silicone dental impression material is not flexible enough for satisfactory application right out of the box, we prepared a CDIM; 900 mL of silicone dental impression material (Detax Exaplast) with a density of 0.95-1.02 g/cm^3 was mixed with water in such a way that the material density of the CDIM was close to 1.0 g/cm^3 and the resulting material was sufficiently flexible for application. The amount of water needed for the desired flexibility of the CDIM was determined to be 100 mL after several trial samples were chemically analysed.

The play dough material (PDM) used in this study is mainly a solid-liquid mixture and commercially available. PDM contains water, starch-based binder, salt, oil, preservative, hardener, moisturizer, perfume and food colouring and has a density around 1.0 g/cm^3.

Data acquisition on solid phantom

Bolus materials covering an area of 10x10 cm^2 with 0.5 cm and 1 cm thickness were prepared and applied on RW3 solid phantom for the ion chamber measurements. Using the linear accelerator (Siemens Primus, Germany) in our clinic, 6 MV photon energy is applied to give 100 monitor unit (MU) in order to measure the dose values at a depth of 5 cm of the solid phantom. Measurements were performed separately with and without bolus material application. Next, a computed tomography (CT) (Siemens Somatom Definition, Germany) scan with 3 mm slice thickness is performed on the measurement setting. Using the CT scan data, same procedure was repeated in the TPS (Eclipse $V_{8.9.08}$ Varian, USA) in which the Pencil Beam Convolution (PBC) dose calculation algorithm was used. The absorbed dose values at 5 cm depth of the solid phantom were calculated (1 Gy/fr and 6 MV).

Obtaining calculated data on skin

For the skin dose simulation on surgical scars, CT images for a group of 20 randomly selected anonymous breast cancer patients who underwent modified radical mastectomy operation in our clinic were selected for evaluation. Ethics committee approval was not required since this was not a clinical study performed on patients, but a dosimetric simulation study. Informed Consent was not required since the dosimetric simulation study was performed on anonymous patient data. In the TPS, Superflab bolus and CDIM bolus are applied with 1 cm of thickness on each of the post-mastectomy scars in order to increase the dose on the scar. This thickness was preferred because the 6 MV photon energy in the tangential field has a maximum dose depth of 1.5 cm. The effect of the bolus materials on the TPS dose calculation values are compared. PDM bolus was not used for the breast cancer patient simulation due to its dosimetric and material properties which were not suitable for practical clinical application.

Simulated radiotherapy procedure using different bolus materials

In the TPS, two different treatment plans were prepared for the cases where Superflab and CDIM is used. Parameters for the treatment simulation are Pencil Beam Convolution dose calculation algorithm, 6 MV photon energy, skin source distance of 100 cm, scar + 0.5 cm multi leaf collimator (MLC) margin and 2Gy dose, and 5 mm slice thickness in CT images. For the CT image set, absorbed dose at five randomly chosen points on the surgical scars were calculated in TPS. Since a virtual bolus [0-400 Hounsfield Unit (HU)] is used and dose calculations are performed on TPS, an ethics committee approval was not needed.

Statistical analysis

The treatment simulation data with bolus materials for the 20 patient CT image set was subject to statistical analysis with Statistical Package for Social Sciences Software version 18 (IBM SPSS Corp.; Armonk, NY, USA) using Student's t-test. The calculated $p<0.05$ and considered statistically significant.

Results

Both for the measurements made with the ion chamber system and for the results obtained in the TPS, with and without bolus material, the percent dose differences between the absorbed dose values (Gy) were calculated. Each measurement was repeated 3 times and the average was taken. For 0.5 cm thick Superflab bolus, the absorbed dose reduction was calculated as 1.28% in the ion chamber measurements and 2.41% in the TPS; for 1,0 cm thick bolus, the absorbed dose reduction was calculated as 2.80% in the ion chamber measurements and 5.80% in the TPS. For CDIM bolus of 0.5 cm the absorbed dose reduction was calculated as 3.15% in the ion chamber measurements and 4.24% in the TPS; for 1,0 cm thick bolus, the absorbed dose reduction was calculated as 3.42% in the ion chamber measurements and 3.88% in the TPS. Finally, for the play dough bolus of 0.5 cm the absorbed dose reduction was calculated as 2.04% in the ion chamber measurements and 3.21% in the TPS; for 1.0 cm thick bolus, the absorbed dose reduction was calculated as 5.13% in the ion chamber measurements and 6.88% in the TPS (Table 1).

For different bolus materials and simulated dose values calculated at 5 random points within 20 mastectomy patient CT dataset, it was observed that the difference in absorbed dose value between the Superflab and CDIM bolus had less than 1% difference in the TPS. The differences in dose values were not statistically significant (Table 2).

Discussion and Conclusion

In our study we have compared the dosimetric values for Superflab, CDIM and PDM. Commercially available dental impression material is inflexible out of the box to be of suitable use in the clinic. We created a special mixture with readily available dental impression material and water, creating a flexible material suitable for application as bolus and obtained statistically meaningful results ($p<0.05$) when compared with Superflab. In the literature, it was reported that resulting radiation doses were similar when Play-Dough and Superflab bolus were used and doses resulting from Play-Dough bolus approximated those of Superflab (11). However, in our study, when the PDM is applied

Table 1. Absorbed dose values and percentage differences, measured at a depth of 5 cm, when using Superflab and CDIM for bolus material thickness of 0.5 cm and 1.0 cm

	Absorbed Dose				Percent Difference (%)			
	Ion Chamber Measured Dose (Gy)		TPS Calculated Dose (Gy)		Ion Chamber		TPS	
	0.5 cm	1 cm	0.5 cm	1 cm	0.5 cm	1 cm	0.5 cm	1 cm
No bolus	0.8756	0.8756	0.8750	0.8750				
Superflab	0.8644	0.8510	0.8510	0.8240	1.28	2.80	2.41	5.80
CDIM	0.8480	0.8476	0.8450	0.8410	3.15	3.42	4.24	3.88
PDM	0.8577	0.8307	0.8440	0.8050	2.04	5.13	3.21	6.88

Gy: Gray; CDIM: silicone dental impression material; PDM: play dough material; TPS: treatment planning system

Table 2. Comparison of calculated TPS dose values for Superflab and CDIM at five random point locations on post-mastectomy scar area

Location	Material	Mean dose (Gy) ± sd	p
Point 1	Superflab	1.0159±2.22	0.271
	CDIM	1.0150±2.27	
Point 2	Superflab	1.0244±2.50	0.481
	CDIM	1.0235±2.49	
Point 3	Superflab	1.0254±2.62	0.669
	CDIM	1.0262±2.73	
Point 4	Superflab	1.0254±2.73	0.754
	CDIM	1.0260±2.77	
Point 5	Superflab	1.0182±3.12	0.476
	CDIM	1.0163±3.38	

Gy: Gray; CDIM: silicone dental impression material

and analysed with both TPS and ion chamber measurements, the results indicated that it is not appropriate to use PDM in RT application consequently it was not used clinically on our patients.

Radiotherapy related parameters such as dose application technique, area size, beam angle, and the algorithms in use to calculate the dose values between calculated and applied dose, cause, either a linear or non-linear dose increase in skin tissue between the bolus application sessions. Therefore, further dosimetric studies are required in order to assess the accuracy of a certain beam energy, bolus thickness and the algorithm used in the TPS technique for dose calculation. Although there are various suggestions in the literature for RT planning techniques, there are very few comments and suggestions regarding bolus use. The optimal thickness of the bolus material and appropriate remains uncertain and vary from one RT centre to another (12).

As noted in the literature, the dose taken by the skin is lower than the dose defined for the target due to difference in RT plans' usage of high-energy beams. Bolus materials are widely used to bring the absorbed skin dose to the desired level. According to the desired clinical outcome, dose absorption of the skin can be determined, and the bolus used in respective treatment fractions can be decided upon (13). During RT it is important to accurately detect chest wall and skin surface depth in order to limit early and late skin reaction and to prevent cancerous recurrence close to the skin surface. The dose contribution of bolus material to skin and subcutaneous tissue is especially important (14, 15).

For breast cancer patients, RT is an essential part of the treatment protocol. During post-mastectomy RT, tissue-equivalent bolus materials with enough thickness are often used in order to provide a build-up dose on the skin and chest wall. In our simulation study for the patients who had undergone mastectomy and RT, for the five randomly chosen points on the scar tissue the comparison of Superflab and CDIM TPS calculation results were not statistically significant ($p>0.05$). In the phantom study we have seen that both materials have similar properties. We observed that for the RT treatment of breast cancer patients who underwent modified radical breast mastectomy, the CDIM had the closest effect on the absorbed dose compared to the Superflab bolus.

It is important to evaluate the difference between calculated and measured skin dose and to compare patient plans. Parameters such as irradiation technique, area, beam angle, presence of air pockets and the use of bolus material affect the amount of skin dose (16, 17). Optimizing the use different bolus materials is also clinically useful. In the calculation of skin dose, while treatment planning systems do not fully account for all factors contributing to surface dose, new techniques such as Monte Carlo and 3D modelling algorithms are able to calculate the skin dose with higher accuracy (18, 19).

In clinical practice, bolus thickness required to increase the surface dose is optimized according to the skin type and build-up zone dosimetry (20, 21). The actual thickness of the bolus material for a patient is decided by the by radiation oncologist and medical physicist during dose planning in the Treatment Planning System (TPS). If a high amount of dose distribution is requested on the skin or near the skin, a bolus thickness of 1 cm is preferred. On the other hand, in certain cases, 0.5 cm bolus thickness is preferred in order to decrease radiation related complications

The CDIM is easy to prepare and apply on irregular mastectomy scar tissue and it prevents formation of air gaps in the application surface. Especially for curved anatomical regions such as scar tissue, inclusion of the bolus material in treatment planning protocol will reduce dose

uncertainty in application. PDM is not useful in clinical practice for two reasons, the dosimetry results for PDM shows that it absorbed more dose than required compared to Superflab bolus. Second, PDM is challenging to use routinely with daily fraction treatments as bolus material, as it hardens when in contact with air and this might create undesired air gaps in uneven skin applications. It is safe to use CDIM as an alternative to Superflab in radiotherapy application, whereas PDM is not useful in clinical practice.

Ethics Committee Approval: Ethics committee approval was not required since this was not a clinical study performed on patients, but a dosimetric simulation study.

Informed Consent: Informed Consent was not required since the dosimetric simulation study was performed on anonymous patient data.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.A., I.O.T., T.I.; Design - S.A., I.O.T.; Supervision - S.A., I.O.T., T.I.; Funding - S.A.; Materials - S.A.; Data Collection and/ or Processing - S.A.; Analysis and/or Interpretation - S.A., I.O.T., T.I.; Literature Review - S.A., I.O.T., T.I.; Writer - S.A., I.O.T., T.I.; Critical Review - S.A., I.O.T., T.I.

Acknowledgements: The authors would like to thank Dr. Özge Nurcan Tanzer for helpful comments.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Journal of the International Commission on Radiation Units and Measurements. Report 1976; 24: 13.
2. Babic S, Kerr A, Westerlan M, Gooding J, Schreiner J. Examination of Jeltrate Plus as a tissue equivalent bolus material. J Appl Clin Med Phys 2002; 3: 170-175. (PMID: 12132938) [CrossRef]
3. Vyas V, Palmer L, Mudge R, Jiang R, Fleck A, Schaly B, Osei E, et al. On bolus for megavoltage photon and electron radiation therapy. Med Dosim 2013; 38: 268-273. (PMID: 23582702) [CrossRef]
4. Banaee N, Nedaie H.A, Nosrati H, Nabavi M, Naderi M. Dose measurement of different bolus materials on surface dose. Journal of Radioprotection Research 2013; 1: 10-13. [CrossRef]
5. Khan FM. The physics of radiation therapy. 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2010.
6. Kong M, Holloway L. An investigation of central axis depth dose distribution perturbation due to an air gap between patient and bolus for electron beams. Australas Phys Eng Sci Med 2007; 30: 111-119. (PMID: 17682400) [CrossRef]
7. Solanki A, M A, A H, Kumar HS. Reduction of Dose to the Contralateral Breast by Superflab Use in Radiation Therapy for Mammary Carcinomas. Asian Pac J Cancer Prev 2017; 18: 1025-1029.
8. Khan Y, Villarreal-Barajas JE, Udowicz M, Sinha R, Muhammad W, Ahmed N. Abbasi et al. Clinical and dosimetric implications of air gaps between bolus and skin surface during radiation therapy. J Cancer Ther 2013; 4: 1251-1255. [CrossRef]
9. Visscher S, Barnett E. Comparison of bolus materials to highly absorbent polypropylene and rayon cloth. J Med Imaging Radiat Sci 2017; 48: 55-60. (PMID: 31047211) [CrossRef]
10. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann. ICRP 1991; 21: 4-11. [CrossRef]
11. Walker M, Cohen N, Menchaca D. Play-Doh and water-soaked gauze sponges as alternative bolus material for cobalt-60 teletherapy. Vet Radiol Ultrasound 2005; 46: 179-181. (PMID: 15869164) [CrossRef]
12. Yokoyama S, Roberson P, Litzenberg D, Moran J, Fraas B. Surface build up dose dependence on photon field delivery technique for IMRT. J Appl Clin Med Phys 2004; 5: 71-81. (PMID: 15738914) [CrossRef]
13. Andıç F, Ors Y, Davutoglu R, Çifci B, Ispir EB, Erturk E. Evaluation of skin dose associated with different frequencies of bolus applications in post-mastectomy three-dimensional conformal radiotherapy. J Exp Clin Cancer Res 2009; 28: 41. (PMID: 19317895) [CrossRef]
14. Hsu SH, Roberson PL, Chen Y, Marsh RB, Pierce LJ, Moran JM. Assesment of skin dose for breast chest wall radiotherapy as a function of bolus material. Phys Med Biol 2008; 53: 2593-2606. (PMID: 18441412) [CrossRef]
15. Mahdavi H, Jabbari K, Roayaei M. Evaluation of various boluses in dose distribution for electron therapy of the chest wall with an inward defect. J Med Phys 2016; 41: 38-44. (PMID: 27051169) [CrossRef]
16. Hennequin C, Barillot I, Azria D, Belkacémi Y, Bollet M, Chauvet B, et al. Radiotherapy of breast cancer. Cancer Radiother 2016; 20: 139-146. (PMID: 27522187) [CrossRef]
17. Fischbach M, Halg RA, Hartmann M, Besserer J, Gruber G, Schneider U. Measurement of skin and target dose in post-mastectomy radiotherapy using 4 and 6 MV photon beams. Radiat Oncol 2013; 8: 270. (PMID: 24238366) [CrossRef]
18. Sharma SC, Johnson MW. Surface dose perturbation due to air gap between patient and bolus for electron beams. Med Phys 1993; 20: 377-378. (PMID: 8497226) [CrossRef]
19. Butson MJ, Cheung T, Yu P, Metcalfe P. Effects on skin dose from unwanted air gaps under bolus in photon beam radiotherapy. Radiat Meas 2000; 32: 201-204. [CrossRef]
20. Malaescu I, Marin C.N, Spunei M. Comparative study on the surface dose of some bolus materials. Int J Med Phys Clin Eng Radiat Oncol 2015; 4: 348-352. [CrossRef]
21. Court LE, Tishler R, Xiang H, Allen AM, Makrigiorgos M, Chin L. Experimental evaluation of the accuracy of skin dose calculation for a commercial treatment planning system. J Appl Clin Med Phys 2008; 9: 29-35. (PMID: 18449168) [CrossRef]

Original Article

Eur J Breast Health 2020; 16(3): 171-176
DOI: 10.5152/ejbh.2020.5075

Ultrasound-Guided Core Biopsy of Breast Lesions in a Resource Limited Setting: Initial Experience of a Multidisciplinary Team

Chinedu Okoli[1], Uzoamaka Ebubedike[2], Stanley Anyanwu[1], Gabriel Chianakwana[1], Chinemelum Emegoakor[1], Cornelius Ukah[3], Eric Umeh[2], Micheal Onwukamuche[3], Ochonma Egwuonwu[1], Eric Ihekwoaba[1]

[1]Department of Surgery, Nnamdi Azikiwe University, Anambra, Nigeria
[2]Department of Radiology, Nnamdi Azikiwe University, Anambra, Nigeria
[3]Department of Pathology, Nnamdi Azikiwe University, Anambra, Nigeria

ABSTRACT

Objective: There is increasing tendency to multidisciplinary care of patients with of breast lesions. This study sought to evaluate the initial experience of the diagnostic arm of a new breast program in a resource limited setting.

Materials and Methods: In 2015, we commenced the pilot phase of an IRB-approved breast care protocol. As part of the protocol's diagnostic arm, an ultrasound-guided breast core biopsy training was implemented. Eligible patients were clinically evaluated and underwent CNB using 16G needle under US guidance. The procedure was rated by the participants and histopathological results compared with surgical specimens.

Results: Eighty six participants (18.22%) with 113 palpable breast lesions completed the study. The diagnostic accuracy, sensitivity, and specificity were 94.44%, 92.86%, and 95.83% respectively. Unweighted kappa- coefficient (k) agreement between histopathology of core biopsy and surgically excised specimens, were 0.798 (95% CI of 0.69 - 0.90) and 0.801 (95% CI of 0.71-0.92) for benign and malignant breast lumps respectively. The procedure was well accepted and all the patients were willing to accept a repeat CNB and would recommend it.

Conclusion: Despite the prevailing challenges, co-ordinated team diagnosis is feasible and may result in the modest improvement in the diagnostic accuracy of breast lesions and patient satisfaction.

Keywords: Ultrasound-guided, core biopsy, palpable, breast

Cite this articles as: Okoli C, Ebubedike U, Anyanwu S, Chianakwana G, Emegoakor C, Ukah C, et al. Ultrasound-Guided Core Biopsy of Breast Lesions in A Resource Limited Setting: Initial Experience of A Multidisciplinary Team. Eur J Breast Health 2020; 16(3): 171-176.

Introduction

Globally, the multidisciplinary breast care team is responsible for breast cancer detection, diagnosis, as well as treatment and, are generally regarded as mandatory for the gold standard of care of breast diseases (1, 2). These multidisciplinary teams comprise specialists involved in all aspects of care of patients with breast diseases including medical, nursing, allied professionals, and diagnostic experts. This coordinated team approach to breast diseases diagnosis and management were formed after observational evidence showed better outcomes among patients treated by a team of different specialists for various common cancers (3).

This multidisciplinary model has usurped the surgeon-directed practice model prevalent in most resource-limited settings like Nigeria. Expert opinions suggest that collaborative efforts among these professionals during various phases of the diagnostic process and patient evaluation help to improve optimal patient care and eliminate system inefficiencies that may result in delayed breast cancer diagnoses. Hence, this approach is central to the delivery of a high-quality service.

Until recently, a tertiary healthcare provider in South-eastern Nigeria, offered full-time surgical oncology and breast care services using the surgeon-directed practice model. In this model, patients with breast lesions were directed to the surgeons who diagnose as well as perform either open or close biopsy. Prior implementation of freehand guided CNB (Core needle biopsy) was met by low diagnostic accuracy and several repeat open biopsy (4). This resulted in continual accrual of patients who neither had breast cancer nor required a breast operation in the operating list. Thus, worsening the waiting list of patients, decreased patient compliance, and further delayed the diagnosis of already late cases. These systemic delays are not only likely to impact negatively on the survival but also have a profound effect on the qual-

Corresponding Author :
Okoli Chinedu; eduokoli@yahoo.com

Received: 23.07.2019
Accepted: 16.11.2019
Avialible Online Deta: 31.03.2020

ity of life of these patients. Breast cancer patients living in developing countries already have high case fatality rate (5) and severely impaired quality of life (6). With the increasing awareness of breast cancer, we believe that the number of biopsies will likely increase which will further compound the matter.

To mitigate these scheduling issues and to provide more rapid and a reliable alternative to the open surgical biopsy, the diagnostic arm of the breast program, commenced the use of ultrasound-guided core needle breast biopsy in a point-of-care setting run by a team of specialists. Though image guidance could be provided using mammographic, stereotactic and sonographic guidance, the latter modality was chosen because of the inherent advantages. These include low cost, absence of ionising radiation, full control of needle position in real-time, affordability, speed, availability, access to difficult places such as axilla or near the nipple as well as the possibility of sampling multiple lesions in one session (7). Furthermore, local anaesthesia and hematoma do not hide the lesion (non-calcified masses can obscure stereotactic equipment) (8).

To our knowledge, there is a paucity of studies reporting their experience of ultrasound (US)-guided biopsy of breast lesions in Nigeria by a multidisciplinary team. In this article, we aimed to analyse our initial results as well as discussing some of the initial challenges we encountered in the early phase of the procedure. The results of this study will help to underscore the benefits and feasibility of setting up multidisciplinary management of breast cancer patients in resource-limited settings.

Materials and Methods

This study was a prospective study that involved 86 patients managed for breast diseases from January 2015 to October 2016 in the breast clinic of a university hospital. As part of the diagnostic arm of the protocol, the tumour board developed an ultrasound-guided percutaneous core-biopsy training programme for participating physicians. The surgeon performed biopsies with the sonographers assisting with image guidance and optimization.

Subjects

The patients were selected by purposive sampling from outpatient clinic attendees who fulfilled the study's inclusion criteria. The inclusion criteria included: i) presence of ultrasound-visible breast lesion; ii) subsequent surgery to remove the lesion or a minimum follow up of 1 year for patients with benign breast diagnosis on CNB who opted for no excision; and iii) a complete dataset. Exclusion criteria were: i) previous surgery of the target lesion; ii) Patients with non-palpable breast lesions. iii) Patients with a history of blood dyscrasia. iv) Patients with breast implants. v) Those who refused to give consent. vi) patients with benign breast lesions on CNB who were lost to follow up. This study was approved by the Ethics committee. It was carried out at no extra expense to the eligible patients who gave their informed consent. There was strict observation of the patients' confidentialities by using codes for reference, analysis and presentation of the results of this study. It also adhered to the tenets of the declaration of Helsinki for medical research in humans. Written consent was gotten from all the patients. Of the 181 patients with breast diseases that were assessed for eligibility, only 86 patients with 100 palpable breast lumps who completed the study were analysed. The clinical evaluation of both breasts was done by the attending consultant surgeon in the breast clinic while the sonographic evaluation was performed by the consultant radiologists. The dimensions of breast lumps were measured with a skin calliper and ultrasound Variables collected included age, clinical and Breast Imaging Reporting and Data System (BI-RADS®) diagnosis. The primary clinical diagnosis was classified as malignant or benign. The variables were documented in a pre-structured proforma.

Details of procedure

Before each procedure, in the absence of pre-existing biopsy pack, the materials for biopsy were assembled consistently in a biopsy tray to ensure easy identification of all the materials needed for the procedure. This helped to minimise the risk of accidental needle stick injury and/or contamination. Each biopsy tray comprised the following disposables: surgical glove to cover the ultrasound probe, tissue sample container, latex gloves, the semi-automated size 16- French gauge needle with 22 mm excursion (Egemen AC16150), lidocaine, 25 gauge needles, adhesive bandage, and size 11scalpel blade; while the multi-use and bulk supplies included the following: formalin, iodine, ultrasound gel, sterile gauze, sterile drapes, and an autoclave drum.

Before each procedure, the biopsy needle was tested to ensure proper functioning before use. The patient was made to lie supine on a couch after exposure of the upper half of the body, with the side of the breast being evaluated elevated with a pillow whilst the ipsilateral shoulder was abducted with the hand placed palm up next to the head which will be turned away from the examiner. The breast skin was prepared initially using povidone-iodine and then isolated with a sterile drape and lubrication with a gel to facilitate ultrasound transmission. The radiologist then gently applied the transducer of Aloka prosound SSD-350SX TM (Japan) ultrasound machine with a linear transducer (frequency of 7.5MHz) and colour Doppler capability after covering with a sterile surgical glove, on the breast for the initial evaluation of breast lesion. The location of the lump was noted by the radiologist and this is confirmed by the surgeon. The Breast Imaging Reporting and Data System (BI-RADS®) category of the mass was then assessed using both longitudinal and transverse scans. To minimise inter-observer variability, the ultrasound classification of the breast lesion was done by two Consultant Radiologists using the BI-RADS® guidelines. Lidocaine 2% (Jawa Lidocaine, Jawa group, Lagos, Nigeria) was injected superficially with a 25-gauge needle, creating a subcutaneous wheal where the skin was to be entered. A small vertical skin incision was made with No 11 scalpel to aid in re-approximation of the defect during healing. The needle was then introduced into the lesion through the skin incision. The needle's position was confirmed by direct visualisation of the needle tip in the lesion on the ultrasound screen. The automated biopsy gun was then fired and the needle tip before and after biopsy firing was determined by longitudinal and orthogonal images to ensure that the needle was within the lesion.

Three to five cores of tissue were usually taken through the shortest route from the skin to the lesion. The core tissue sampling was done by the surgeon. Patients were monitored for complications including residual pain, breast hematoma, and pneumothorax. The samples were immersed in 10% formalin and transferred to the pathology laboratory where they were processed and paraffin-embedded. The appearance and behaviour of the formalin-fixed core samples were examined during the procedure to confirm that the targeted lesion was adequately sampled. The punctures were compressed for 5–10 min to control bleeding.

After the procedure, each patient was asked to assess the procedure using a 5 point Likert scale to rate the procedure. Patients were moni-

tored for complications. The samples were then transferred to the pathology laboratory where they were processed and paraffin-embedded. The patients were followed up until the histopathological results of the CNB samples became available. The histopathological examinations were performed by 2 dedicated breast pathologists, and the results were categorized as malignant, high-risk, benign and indeterminate cases. Malignant results included invasive carcinoma and ductal carcinoma in-situ (DCIS). High-risk results included atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), papillary lesions (intraductal papilloma and papilloma with atypia), phyllodes tumours and indeterminate cases. All other lesions were classified as benign findings. The radio-pathological concordance was performed between CNB results and imaging findings for each case. If the CNB result yielded malignant lesion, the patient underwent the respective surgery including mastectomy or wide local excision. In high-risk cases on CNB, indeterminate cases, or radio-pathological discordance, open surgical excision was performed. If the CNB yielded benign results concordant with sonographic imaging, patients were given the choice of excision biopsy or follow-up with imaging. All the patients who had concordant benign lesions and did not have surgery were followed up for a minimum of 3 years. The histopathologists analysing the open surgical specimens were blinded to the initial CNB histopathological results.

Statistical analysis

Statistical analysis used was the Statistical Package for Social Sciences version 21 (IBM SPSS Corp; Armonk, NY, USA). Results of categorical variables were expressed using Tables and Charts where appropriate. The mean age of the patients and sizes of the lumps were measured clinically and using ultrasound, were reported as the mean ± standard deviation. The significance of the mean difference was determined using independent t-tests. The agreement between histopathological diagnosis of CNB and the histopathological result of surgically excised lumps was determined using unweighted kappa agreement tests with 95% confidence interval. A kappa score of 0 showed no agreement while a score of 1 showed perfect agreement. Statistical significance was inferred at a $p<0.05$. The sensitivity, specificity, false-positive rate, false-negative rate, positive predictive value, negative predictive value and overall diagnostic accuracy were determined for ultrasound-guided CNB. The false-negative rate (FNR) and false-positive rate were calculated using the formulae (False negative) / (True Positive + False negative) and (False Positive) / (False Positive +True Negative) respectively.

Results

All the patients that had the ultrasound-guided CNB in this study were females. The age of the patients studied ranged from 12-78 years (mean= 40.12±SD 13.81) with a median age of 39.0 years. The BI-RADS categories of the breast lumps in this study ranged from 2-5 with categories 2 and 4 as the most common category while category 3 was the least frequent assessment (Table 1). The sizes of the breast lumps were estimated clinically and sonographically. The mean of the widest diameter (SD) measured clinically and with ultrasound were 65.2 mm±0.6 and 46.57mm±6.46 respectively. Using a paired T-test, the difference in mean was found to be statistically significant ($p<0.001$). Pathological examination of the CNB revealed that malignant lesions accounted for 40% (n=40) of CNB diagnosis, high-risk lesions accounted for 6.0% (n=6), and benign lesions accounted for 45 (n=45). Indeterminate cases were seen in 9.0% of CNB diagnosis as shown in Table 1 and characterized in Table 2.

The final surgical histological results were determined and shown in Table 1. When the indeterminate cases were excluded, the sensitivity of CNB increased from 84.78% to 92.86%, while the specificity decreased from 96.23% to 95.83%. Other parameters are shown in Table 3. The agreement between the histopathological sub-classification of breast masses into definite histological entities using ultrasound-guided CNB specimens and open surgical specimens was analysed using unweighted kappa- coefficient and at a 95% confidence interval. The k- coefficient values were 0.798 (95% confidence interval of 0.69 to 0.90) and 0.801(95% confidence interval of 0.71 to 0.92) with $p<0.05$ for benign and malignant breast lumps respectively. This k value of >0.7 shows substantial agreement between the two pathological results and this was significantly greater than zero in this study (0=no agreement). Comparisons of the results in this study with other series are shown in Table 4 (9-15).

The degree of acceptance of the procedure ranged from fair to excellent. Most of the patients without complications had rated the procedure as excellent while 2 patients with complications rated the procedure as fair. No patient rated the procedure poorly, however, all the patients said they would recommend the procedure to friends and relatives and would undergo the procedure in the presence of other breast diseases. Details are shown in Table 5.

Table 1. Ultrasound grading/CNB histopathological diagnosis/ Open histological diagnosis

Category	Frequency (%)
BI-RADS®	
2	41 (41)
3	5 (5)
4	36 (36)
5	18 (18)
CNB histopathological diagnosis	
Indeterminate lesions	9 (9)
Benign	45 (45)
High risk	6 (6)
Malignant	40 (40)
Open histopathological diagnosis*	
Fibroadenoma	25 (25.3)
Fibrocystic diseases	14 (14.1)
Phyllodes tumour	4 (4.0)
Lactational Mastitis	8 (8.1)
Intraductal papilloma	2 (2.0)
DCIS	1 (1.0)
Invasive ductal carcinoma	43 (43.4)
Invasive lobular carcinoma	2 (2.0)

*One patient with benign breast lesion (mastitis) on CNB did not have surgical excision
BI-RADS®: Breast Imaging Reporting and Data System; DCIS: Ductal carcinoma in-situ

Table 2. Profile of indeterminate lesions

CNB diagnosis	BIRADS grade	Open surgical diagnosis	Mean size (SD) in cm*	Minimum (cm)*	Maximum (cm)*	Median (cm)*
N	2	FCD	5.35 (3.19)	2.01	11.4	3.9
N	2	FCD				
N	4	IDC				
N	5	IDC				
I	3	Chronic mastitis				
I	3	FCD				
I	2	Fibroadenoma				
I	2	IDC				
I	4	IDC				

Sonographic size. N: normal breast tissue; I: inadequate specimen; CNB: core needle biopsy; IDC: invasive ductal carcinoma; FCD: fibrocystic diseases; SD: standard deviation

Table 3. Diagnostic validities of clinical examination and US guided CNB for detection of malignant breast lumps

	CE	US	CNB*	CNB**	TA
Sensitivity	93.33	95.8	84.78	92.86	100.0
Specificity	79.63	80.39	96.23	95.83	61.11
FPR	20.4	17.85	3.77	4.17	
FNR	6.5	4.65	15.22	7.14	-
PPV	79.25	82.14	95.12	95.12	68.18
NPV	93.48	95.34	87.93	93.88	100.0
ODA	85.86	87.88	90.90	94.44	

CE: Clinical examination; US: Ultrasound; CNB: Core needle biopsy; TA: triple assessment; FPR: False positive rate; FNR: False negative Rate; PPV: Positive predicted value; NPV: Negative predicted value; US: Ultrasound; ODA: overall diagnostic accuracy.
*indeterminate lesions were assumed to be negative for malignancy
**indeterminate lesions excluded

Table 4. Published series of CNB

			Values in percentage						
Author	Year*	N	TPR	TNR	FPR	FNR	PPV	NPV	ODA
Present study		100	92.86	95.83	4.17	7.14	95.12	93.88	94.44
Zhou et al. (9)	2014	955	92.4/92.8+	-	-	1.4	-	-	-
Nagar et al. (10)	2012	162	100	90	-	-	93	-	-
Brancato et al. (11)	2012	1283	93.8	88.3	-	1.7	-	-	84.5
Lacambra et al. (12)	2012	464	96	99	-	-	99	94	-
Wei et al. (13)	2011	1431	88	98	-	-	-	-	89
Schueller et al. (14)	2008	698	95.8	-	-	1.6	-	-	-
Luechakiettisak et al. (15).	2008	92	92	100		7.6	100	46	92

FPR: False positive rate; FNR: False negative rate; PPV: Positive predicted value; NPV: Negative predicted value; TA: Triple assessment; TPR: True positive rate; TNR: True negative rate; N: Number of breast lesions
+ Two different needles were used 16G (92.4%) & 18G (92.8%)

Table 5. Acceptance and complications rates of CNB

Degree of acceptance		No complications N=73	Complications N=13	Total N=86	p
Fair		-	3 (23.08)	3 (3.49)	0.831
Good		15 (20.55)	8 (61.54)	23 (26.74)	
Very good		2 (2.74)	2 (15.38)	4 (4.65)	
Excellent		56 (76.71)	-	56 (65.11)	
		Benign	Malignant		
Recommend to friends and relatives	Yes	46 (100)	40 (100)	86 (100)	1.000
	No	-	-	-	
Will accept a repeat procedure	Yes	46 (100)	40 (100)	86 (100)	
	No	-	-	-	

Discussion

These findings suggest that our team met its expectations of high overall diagnostic accuracy, specificity, sensitivity and low false-negative rates of ultrasound-guided CNB. These findings are comparable with other previously published series in the literature as shown in Table 4.

In this study, 9 breast lumps were diagnosed as indeterminate lesions, thus giving a non-diagnostic rate of 9.0% and a false negative rate of 7.14%. Both are within the rate recommended by NHS Breast Cancer Screening Programmes (NHSBSP) (16). Some of the suggested reasons that may account for unsatisfactory sampling include the nature of the lesion such as a radial scar or complex sclerosing adenosis and error in sampling technique (17). In the present study, we noticed that all the indeterminate cases were recorded at the initial part of the study, suggesting that the accuracy improves as the volume of procedures increase.

The recorded false-positive rates in this study (FPR) of 4.17% was higher than the recommended rate by the NHSBSP16. NHSBSP recommends that the minimum value for FPR is 0.5%. The high value of FPR recorded in this study was undesirable. This may have been accounted for by initial interpretation errors by the pathologist suggesting the need for independent diagnosis by at least two breast pathologists. This will help to maximise the detection of malignancy and achieve a high level of accuracy and consistency in reporting breast lesions.

With the exclusion of the indeterminate lesions, ultrasound-guided CNB showed sensitivity and specificity of 92.8% and 95.83% respectively with an overall diagnostic accuracy of 94.44%. The sensitivity, specificity and diagnostic accuracy recorded in this study were comparable with findings in similar studies (9-15). The overall success rate recorded in this study further underscores the importance of a team approach in the evaluation of breast lesions.

The agreement between the histopathological subclassification of breast masses into definite histological entities using ultrasound-guided CNB specimens and open surgical specimens was analysed using unweighted kappa- coefficient and at a 95% confidence interval. The k- coefficient values were 0.798 (95% confidence interval of 0.69 to 0.90) and 0.801 (95% confidence interval of 0.71 to 0.92) with $p<0.05$ for benign and malignant breast lumps respectively. This k value of >0.7 shows substantial agreement (18) between the two pathological results and this was significantly greater than zero in this study (0=no agreement). Zhou et al. (9) also recorded similar high kappa value. Nevertheless, this kappa value is still less than 1(perfect agreement). This finding is within the acceptable range recommended by NHSBSP (16). Achieving a perfect agreement has been elusive despite advances in biopsy devices and techniques. Factors that may limit the accuracy of CNB in identifying the specific histology include certain conditions like Fibroepithelial lesions with cellular stroma and phyllodes tumours, papillary lesions, mucinous lesions, radial scars and atypical proliferative lesions. In this study, two cases of ductal carcinoma in-situ recorded on ultrasound-guided CNB sample histology were later found to be invasive on histopathological examination of the surgical specimen. This agrees with other reports in literature (19). Knowledge of this is important particularly for women contemplating whether or not to undergo surgery for DCIS. Though, in our study, we observed that the majority of the women opted for surgical excision of breast lumps even when they are benign. Only one patient with chronic mastitis diagnosed after CNB accepted to be followed up.

Ultrasound-guided CNB is generally regarded as a safe procedure and associated with few insignificant complications. The recorded few complications in this study included pain at the site of procedure which was relieved by the intake of oral analgesics (paracetamol) and breast hematoma. This concurs with findings in the literature (20). All the patients that had breast hematoma had malignant breast lumps. This is most likely due to increased vascularity associated with malignant conditions. In our standard practice, patients do not routinely undergo ultrasound post-biopsy so the results in this study may likely underestimate the true incidence of hematoma formation. It is reasonable, however, to conclude that no clinically significant complication occurred. For patients who are on anticoagulants or antiplatelet medications, FNAC (fine needle aspiration cytology) has been found to have reduced risk of bleeding than CNB though, Melotti et al. (21) did not record any significant bleeding when they carried out CNB in patients on anticoagulants and antiplatelets.

Finally, ultrasound-guided CNB was found to be acceptable among the patients that underwent the procedure even among patients with complication. All the patients in the current study said they would recommend the procedure to relatives and friends that have a similar condition. They were all willing for a repeat procedure in case of recurrence or

new case of a breast lump. This suggests that CNB is well accepted by the patients as reported in the literature (22). This high level of acceptance among the patients in this study may be due to absence of major complications during the procedure, or because the procedure was done at no extra cost to the patients care. Probably the response may be different if there were additional costs due to the ultrasound investigations.

There are certain limitations in the present study. First, this study was the preliminary experience in a breast clinic run by the multidisciplinary team. Technique errors and wrong interpretations experienced in the early phase of the work affected the various diagnostic parameters assessed particularly the high false-negative rates and false-positive rates compared with previous studies shown in Table 3. Further evaluation is necessary to report the actual sensitivity and specificity after the initial learning curve. Secondly, our team relied on a surgeon with prior experience on freehand guided breast biopsy which may have lowered the effectiveness of the initial procedures. In spite of these limitations, our study showed high concordance between CNB and open surgical specimens and reduced our waiting time for diagnosis

In conclusion, we have demonstrated that 16G ultrasound-guided CNB can be used as a reliable diagnostic alternative to surgical biopsy even in the absence of formal training to facilitate diagnostic evaluations of palpable breast lesions. The multidisciplinary breast care team that has successfully met its objectives of prompt accurate diagnosis also showed the need for further training of the members. We believed that competence in this procedure requires at minimum 40 samplings and there is a need for two pathologists to view the CNB specimens in the initial part of this procedure until competence is acquired. Team approach to breast diseases diagnosis is possible even in a resource-limited country like Nigeria. CNB is a relatively safe procedure, and well tolerated by patients with minimal complications with a high acceptance rate.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Nnamdi Azikiwe University Teaching Hospital Nnewi (24.06.2014/ NAUTH/CS/66/VOL.6/4)

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

Peer-review: Externally peer-reviewed.

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

Acknowledgements: We would like to thank the staff of Department of Radiology, Pathology, Surgery and Nnamdi Azikiwe University Tumour Board.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Rajan S, Foreman J, Wallis MG, Caldas C, Britton P. Multidisciplinary Decisions in Breast Cancer: Does the Patient Receive What the Team Has Recommended? Br J Cancer 2013; 108: 2442. (PMID:23736032) [CrossRef]
2. Association of Breast Surgery at Baso 2009. Surgical Guidelines for the Management of Breast Cancer. Eur J Surg Oncol. 2009; 35: 1-22. (PMID:19299100) [CrossRef]
3. Selby P, Gillis C, Haward R. Benefits from Specialised Cancer Care. Lancet 1996; 348: 313-318. (PMID: 8709693) [CrossRef]
4. Nzeako HC. Evaluation of Core Needle Biopsy in the Diagnosis of Palpable Breast Masses in Nnamdi Azikiwe University Teaching Hospital, Nnewi Dissertation for Fellowship of the Medical College in Surgery. Lagos: National Postgraduate Medical College of Nigeria. 2014.
5. Shulman LN, Willett W, Sievers A, Knaul FM. Breast Cancer in Developing Countries: Opportunities for İmproved Survival. J Oncol 2010 Dec 29. doi: 10.1155/2010/595167. [Epub ahead of print] (PMID: 21253541) [CrossRef]
6. Okoli C, Anyanwu SN, Ochomma AO, Emegoakor CD, Chianakwana GU, Nzeako H, et al. Assessing the Quality of Life of Patients with Breast Cancer Treated in a Tertiary Hospital in a Resource-Poor Country. World J Surg 2018; 27: 1-8. (PMID:30151677) [CrossRef]
7. Apesteguía L, Pina LJ. Ultrasound-guided Core-needle Biopsy of Breast Lesions. Insights Imaging 2011; 2: 493-500 (PMID: 22347970) [CrossRef]
8. Van Breest Smallenburg V, Nederend J, Voogd AC, Coebergh JW, Van Beek M, Jansen FH, et al. Trends in Breast Biopsies for Abnormalities Detected at Screening Mammography: A Population-based Study in the Netherlands. Br J Cancer 2013; 109: 242. (PMID: 23695018) [CrossRef]
9. Zhou JY, Tang J, Wang ZL, Lv FQ, Luo YK, Qin HZ, et al. Accuracy of 16/18G Core Needle Biopsy for Ultrasound-visible Breast Lesions. World J Surg Oncol 2014; 12: 1-7. (PMID: 24400744) [CrossRef]
10. Nagar S, Iacco A, Riggs T, Kestenberg W, Keidan R. An Analysis of Fine-needle Aspiration Versus Core Needle Biopsy in Clinically Palpable Breast Lesions: A Report on the Predictive Values and a Cost Comparison. Am J Surg 2012; 204: 193-198. (PMID: 22464444) [CrossRef]
11. Brancato B, Crocetti E, Bianchi S, Catarzi S, Risso GG, Bulgaresi P, et al. Accuracy of Needle Biopsy of Breast Lesions Visible on Ultrasound: Audit of Fine Needle Versus Core Needle Biopsy in 3233 Consecutive Samplings with Ascertained Outcomes. Breast 2012; 21: 449-454 (PMID: 22088803) [CrossRef]
12. Lacambra MD, Lam CC, Mendoza P, Chan SK, Alex MY, Tsang JY, et al. Biopsy Sampling of Breast Lesions: Comparison of Core needle-and Vacuum-assisted Breast Biopsies. Breast Cancer Res Treat 2012; 132:917-923. (PMID: 21698409) [CrossRef]
13. Wei X, Li Y, Zhang S, Zhu Y, Fan Y. Experience in Large-core Needle Biopsy in the Diagnosis of 1431 Breast Lesions. Med Oncol 2011; 28: 429-433. (PMID:20339957) [CrossRef]
14. Schueller G, Schueller-Weidekamm C, Helbich TH. Accuracy of Ultrasound-guided, Large-core Needle Breast Biopsy. Eur Radiol 2008; 18: 1761 (PMID: 18414872) [CrossRef]
15 Luechakiettisak P, Rungkaew P. Breast Biopsy: Accuracy of Core Needle Biopsy Compared with Excisional or Incisional Biopsy: A Prospective Study. Thai Journal of Surgery 2008; 29: 6-10.
16. Lee AH, Carder P, Deb R, Howe M, Knox F, Shrimankar J, et al. Guidelines for Non-operative Diagnostic Procedures and Reporting in Breast Cancer Screening. London, UK: The Royal College of Pathologists. 2016.
17. Mitra S, Dey P. Fine-needle Aspiration and Core Biopsy in the Diagnosis of Breast Lesions: A Comparison and Review of the Literature. Cytojournal 2016; 13:18. (PMID: 27651820) [CrossRef]
18. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977; 1:159-174 (PMID: 843571) [CrossRef]
19. Caswell-Smith P, Wall M. Ductal Carcinoma in Situ: Is Core Needle Biopsy Ever Enough? J Med Imaging Radiat Oncol 2017; 61: 29-33 (PMID: 27554420) [CrossRef]
20. Parker SH, Burbank F, Jackman RJ, Aucreman CJ, Cardenosa G, Cink TM, et al. Percutaneous Large-core Breast Biopsy: A Multi-institutional Study Radiology. 1994; 193: 359-364. (PMID: 7972743) [CrossRef]
21. Melotti MK, Berg WA. Core Needle Breast Biopsy in Patients Undergoing Anticoagulation Therapy: Preliminary Results. AJR Am J Roentgenol. 2000; 174: 245-249 (PMID: 10628487) [CrossRef]
22. Park HL, Kim LS. The Current Role of the Vacuum-assisted Breast Biopsy System in Breast Disease. J Breast Cancer. 2011; 14: 1-7 (PMID: 21847387) [CrossRef]

Original Article

Eur J Breast Health 2020; 16(3): 177-182
DOI: 10.5152/ejbh.2020.5114

The Effect of Systemic Chemotherapy on Ovarian Function: A Prospective Clinical Trial

Filiz Çelebi[1], Çetin Ordu[2], Serkan Ilgün[3], Alper Öztürk[4], Zeynep Erdoğan Iyigün[5], Gül Alço[6], Tomris Duymaz[7], Fatma Aktepe[8], Gürsel Soybir[9], Bülent Baysal[10], Vahit Özmen[11]

[1]Department of Radiology, Gayrettepe Florence Nightingale Hospital, İstanbul, Turkey
[2]Department of Oncology, Gayrettepe Florence Nightingale Hospital, İstanbul, Turkey
[3]Department of General Surgery, Demiroğlu Bilim University School of Medicine, İstanbul, Turkey
[4]Department of General Surgery, Biruni University Hospital, İstanbul, Turkey
[5]Department of Physical Therapy and Rehabilitation, Demiroğlu Bilim University School of Medicine, İstanbul, Turkey
[6]Department of Radiation Oncology, Gayrettepe Florence Nightingale Hospital, İstanbul, Turkey
[7]Department of Physical Therapy and Rehabilitation, Bilgi University, İstanbul, Turkey
[8]Department of Pathology, Gayrettepe Florence Nightingale Hospital, İstanbul, Turkey
[9]Department of General Surgery, Memorial Etiler Hospital, İstanbul, Turkey
[10]Department of Obstetrics and Gynecology, İstanbul Florence Nightingale Hospital, İstanbul, Turkey
[11]Department of General Surgery, İstanbul Florence Nightingale Hospital, İstanbul, Turkey

ABSTRACT

Objective: Premenopausal women with breast cancer are at risk of developing ovarian failure after chemotherapy. The aim of this study was to investigate the negative effects of systemic chemotherapy on ovarian function in premenoupausal women with breast cancer.

Materials and Methods: Thirty-one premenopausal women with operable breast cancer aged between 26-48 years were enrolled in this prospective cohort study to investigate preliminary results. Additional 69 patients' data will be included after the completion of all five measurements. The change in serum Antimullerian Hormone (AMH) levels, mean ovarian volumes (MOV) and antral follicle counts (AFCs) at 3–month intervals were recorded to evaluate ovarian function. Women who had at least one pretreatment and four post-treatment measurements in one year follow-up period were included in the study. Decision of chemotherapy regimen was taken by the Tumor Board.

Results: Thirty-one patients had all five AMH, MOV and AFCs results. There was a statistically significant negative correlation between 1st - 5th AMH levels (p=0.006) and 1st - 5th AFCs during the follow-up period (p<0.0001). However pre- and post-chemotherapy measurements of MOVs did not demonstrate any significant correlation (p=0.799). BMI, parity, lactation, histopathology and molecular subtypes of breast cancer, alcohol intake, smoking and type of chemotherapy regimen were not significantly correlated with AMH, AFC and MOV.

Conclusion: Pretreatment AMH levels and AFC were shown to have a significant role in early prediction of ovarian-reserve after chemotherapy.

Keywords: AMH, ovarian reserve, breast cancer, chemotherapy

Cite this articles as: Çelebi F, Ordu Ç, İlgün S, Öztürk A, Erdoğan İyigün Z, Alço G, et al. The Effect of Systemic Chemotherapy on Ovarian Function: A Prospective Clinical Trial. Eur J Breast Health 2020; 16(3): 177-182

Introduction

Breast cancer is the most common malignancy in women, and the incidence increases with age. The majority of breast cancer patients (75%) are postmenopausal, and about 7% are diagnosed before the age of 40 in developed countries (1). In Turkey, 45% of patients with breast cancer are premenopausal, and 20% are underage of 40 years (2). Most premenopausal women with breast cancer receive cytotoxic chemotherapy and there is an increased risk of ovarian failure (3). Gonadal suppression and ovarian failure manifests as early onset of menopause, chemotherapy-related amenorrhea and infertility (4, 5).

Since direct measurement of ovarian-reserve is difficult, it is usually determined as the number of non-growing follicles in the ovaries (6, 7). Antral follicle count, follicle stimulating hormone (FSH), inhibin and antimullerian hormone (AMH) levels are also used to estimate ovarian-reserve (7, 8). FSH and inhibin indirectly represent ovarian- reserve, but the changes in their levels during the ovarian cycle make the estimation difficult. Although counting antral follicles by ultrasonography is the most effective method, it depends on physician's experience, time consuming and also more expensive than blood tests (9).

It has been showed that, the Gonadotropin-releasing hormone (GNRH)analogs combined with chemotherapy decrease the rate of ovarian failure in the patients with HR negative breast cancer (10). In the other publications limited number of patients with HR positive breast cancer, it's thought that the combined therapy also decreases the rates of ovarian failure (11).

Corresponding Author :
Filiz Çelebi; elbuken.filiz@gmail.com

Received: 17.07.2019
Accepted: 25.11.2019
Avialible Online Deta: 17.03.2020

This protective effect of GNRH analogs may occur with indirect or direct impacts. In indirect impact it may lead the ovaries to the situation like as in silent and prepubertal term that makes them less sensitive to chemotherapeutic agents. In direct impact it may prevent the ovaries damaged by chemotherapy through intracellular pathways leading the receptors on follicle cells (12).

Although there is an initial decrease in the level of AMH with the effect of GNRH followed by an increase, there are hypotheses supporting that the sudden decrease in AMH levels is independent of the effect of GNRH analogues (13). AMH is the best biomedical marker for ovarian function and to be an early and sensitive plasma marker after chemotherapy for the evaluation of ovarian- reserve (14). There are limited data demonstrating the long term effect of chemotherapy on AMH levels in premenopausal breast cancer patients (15).

Determination of dysfunction of ovaries due to chemotherapy is very important for patients with breast cancer who want to maintain fertilization (16). The predictive value of factors that determine ovarian-reserve before and after chemotherapy, such as AMH, AFC and MOV, should be determined. In this way the fertility preservation of patients can be predicted. Knowing that the ovarian failure causes problems such as osteoporosis in the postmenopausal period by Henry et al. (14).

In this study, we investigated the negative effects of systemic chemotherapy on ovarian function in premenopausal women with breast cancer.

Materials and Methods

Between April 2015 and November 2016, 31 premenopausal women with breast cancer were enrolled in this prospective cohort study to investigate preliminary results. Additional 69 patients' data will be included after all five measurements completed in an attempt to reach 100 patients as planned at the beginning of the study. Local ethic committee approval was obtained and all subjects were recruited to the study after giving informed consent. AMH levels, antral follicle counts and ovarian volumes were recorded before chemotherapy. Serum AMH levels, mean ovarian volumes and antral follicle counts at 3 months intervals were measured. Demographic information and clinical data (surgical methods, tumor histopathology and molecular subtypes, hormone receptor status including estrogen, progesterone and human epidermal growth factor receptor-2 (HER2) and chemotherapy regimens) were collected from the database.

Patients with a history of other malignancy and prior chemotherapy or pelvic radiation, bilateral oophorectomy and hysterectomy were excluded.

Chemotherapy regimens were described as adriamycin and cyclophosphamide (AC), docetaxel-cyclophosphamide (TC), of anthracycline-cyclophosphamide and taxanes (AC+T) given sequentially, 5-fluorouracil-epirubicin- cyclophosphamide (FEC), FEC and taxanes (FEC+T).

There are 23 patients with Luminal type breast cancer, which are hormone receptor-positive included in the study. The patients with hormone receptor-positive breast cancer had adjuvant hormone therapy with selective oestrogen receptor modulators (SERMs) with/without ovarian suppression (e.g., tamoxifen ± LHRH-analogues). The patients who did not have chemotherapy induced amenorrhea were given GNRH analogues. AMH levels were measured using enzyme-linked immunosorbent assay (ELISA). AMH assays were performed by USCN Life Science, Inc (Buckingham, UK).

Transvaginal ultrasonography (EV9-4 probe, Siemens Acuson S2000, Erlangen, Germany) was performed to determine ovarian volume and AFC by an expert obstetrician in assisted reproductive techniques (ART) and the images were evaluated with a radiologist experienced in women's imaging. Mean ovarian volume (MOV) was calculated with the use of this formula (A x B x C x 0.52). AFC was determined as the number of follicles 2-10 mm in average diameter for both ovaries. AFC recorded as sum of antral follicles counted from both ovaries. Transvaginal sonograpy was preferred as a standard method. But for one patient transabdominal sonography was used due to her preference.

Statistical analysis

Variables are given as mean ± standard deviations. Median and minimum-maximum were calculated unless otherwise specified. The distribution of variables was analysed with Kolmogorov-Smirnov Test and the quantitative analysis of variables was done with chi-square test.

Pearson test was used to calculate the correlation between AMH, MOV and AFCs. A p value less than 0.5 was considered to indicate a significant difference. For all statistical analyses, IBM Statistical Package for the Social Sciences software, version 20.0 (IBM SPSS corp.; Armonk, NY, USA) was used.

Table 1. Histopathological characteristics of patients

Characteristics	Number of patients
Histopathology	
Invasive ductal ca	25
Others	6
Molecular subtypes	
Luminal A	3
Luminal B	20
TNBC	5
HER-2 positive	3
Stage	
I	6
II	21
III	4
Grade	
I-II	11
III	20
SLNB	26
ALNB	14
Unifocal	22
Multifocal-multiscentric	9

HER2: Human epidermal growth factor receptor-2; SLNB: Sentinel lymph node biopsy; ALNB: Axillary lymph node biopsy

Table 2. Chemotherapy regimens and number of patients

Chemotherapy regimen	Number of patients (n)	Cycles (n)
Adriamycin and cyclophosphamide (AC)	13	4 cycles AC
Docetaxel-cyclophosphamide (TC)	3	4 cycles TC
Anthracycline-cyclophosphamide + taxanes (AC+T)	11	4 cycles AC + 4 cycles (AC+T)
5-fluorouracil-epirubicin- cyclophosphamide (FEC)	1	6 cycles FEC
5-fluorouracil-epirubicin- cyclophosphamide (FEC) + taxanes	1	6 cycles FEC+ 3 cycles taxanes

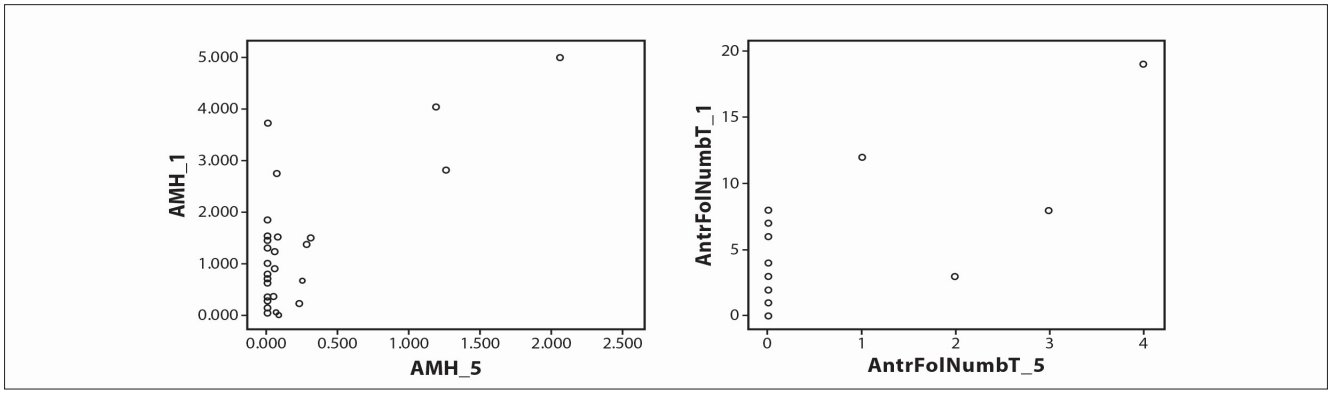

Figure 1. There is statistically significant correlation between 1st-5th AMH levels (p=0.006), AFCs showed statistically significant correlation between 1st-5th measures during follow-up period (p<0.0001)

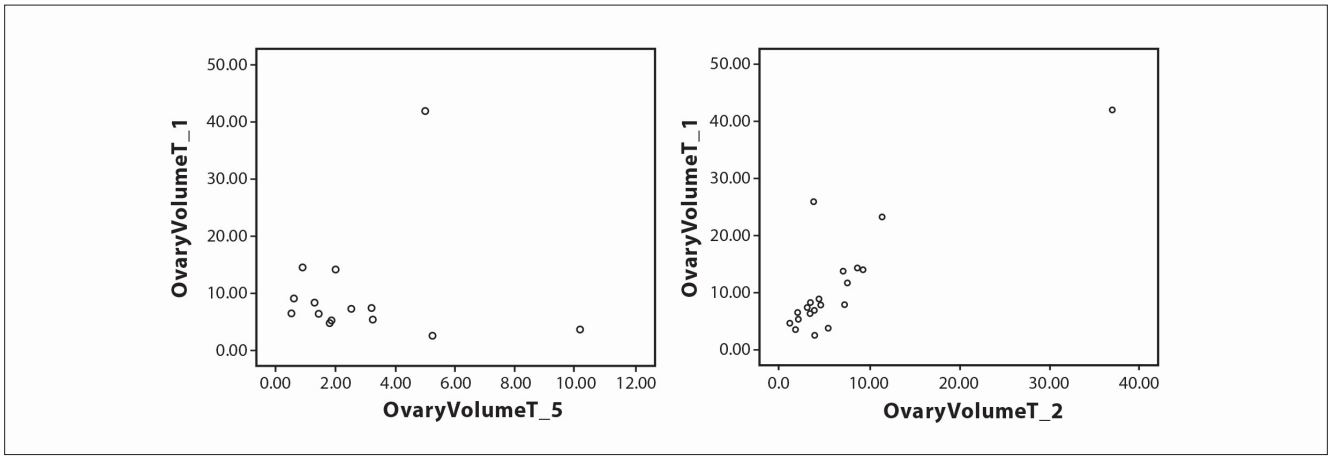

Figure 2. There is minimal negative correlation between MOV measures between 1st-5th measures between 1st-5th measures and this can represent reversal of ovarian volumes to the initial values (r= -0.49, p=0.799)

Results

Thirty-one patients with median age of 38 years (range: 26-48) were included in the study. Histopathologic characteristics of the study population are shown in Table 1.

BMI score was 30.8% normal (19-24), 46.2% overweight (24-29) and 23.1% obese (29-33). 25.8% of the patients were smokers.

Thirty-one patients had all five AMH, MOVs and AFCs results and the results were recorded prospectively. Initial serum AMH levels, AFCs and MOVs were compared with 2nd, 3rd,4th and 5th values. All measures of ovarian reserve showed acute impairment after chemotherapy. AMH levels decreased sharply and rapidly.

There was a statistically significant correlation between 1st- 5th AMH levels (p=0.006). Conversely, there was no association between 1st- 2nd (p=0.976), 1st- 3rd (p=0.076) and 1st - 4rd results (p=0.065). The recovery of AMH levels showed renewal of follicle growth after therapy (Figure 1).

AFCs showed a statistically significant correlation between the 1st- 5th measurements during the follow-up period (p<0.0001) (Figure 1).

There was a minimal negative correlation between MOV measurements between the 1st - 5th measurements and this could represent reversal of ovarian volumes to the initial values (r=-0.49, p=0.799) (Figure 2).

Prechemotherapy AMH, MOV and AFCs showed a statistically significant negative correlation with age (the values were measured respec-

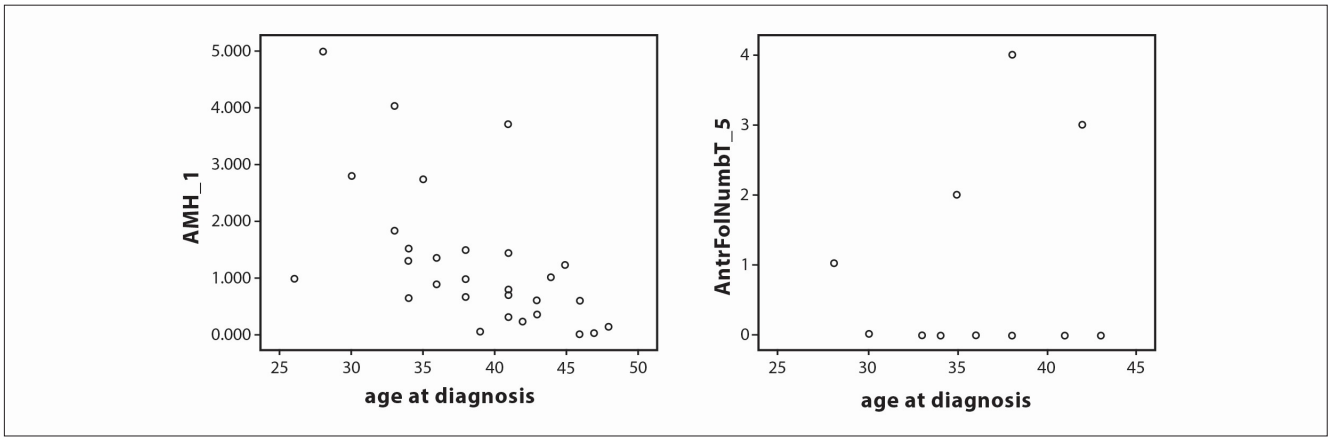

Figure 3. 1st AMH and AFCs showed statistically significant negative negative correlation with the age (The values were measured respectively, r=-0.507, p=0.004; r=-0.401, p=0.025). Also there is significant negative correlation between 5th AMH level and age (r=-0.505, p=0.004)

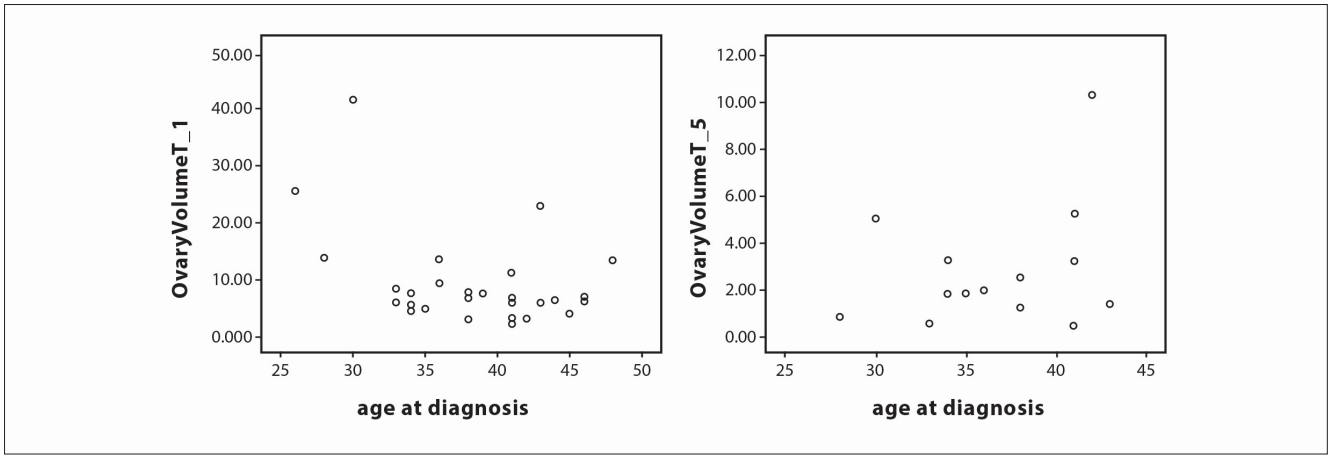

Figure 4. 1st MOV showed statistically significant negative correlation with the age (r=-0.429, p=0.016). Also there is a significant negative correlation between 5th MOV level and age

tively as r=-0.507, p=0.004; r=-0.429, p=0.016; r=-0.401, p=0.025). There was also a significant negative correlation between the 5th AMH level and age (r=-0.505, p=0.004) (Figure 3, 4).

Chemotherapy regimens and number of patients were described in Table 2. There was no significant difference (p>0.05) between the effects of adriamycin-cyclophosphamide, docetaxel-cyclophosphamide and adriamycin-cyclophosphamide-taxane on AFC, MOV and AMH values.

BMI, parity, lactation, histopathology and moleculary subtypes of breast cancer, alcohol intake and smoking were not found to be significantly correlated with AMH, AFC and MOV.

Discussion and Conclusion

Cancer treatments have adverse effects on female reproductive function due to damage to the ovarian follicles and increase the risk of infertility (17). Future fertility and treatment management are important factors for young women and better methods are needed to predict long term ovarian reserve in individual patients (18, 19).

Many prospective studies in breast cancer patients have mentioned the importance of predicting chemotherapy-induced amenorrhea. Some studies have shown that pretreatment AMH levels predict ovarian-reserve after treatment (16, 20, 21), but other studies did not (22). Anderson and Cameron (23) showed that AMH levels before adjuvant chemotherapy predicts long term ovarian reserve. Ruddy et al. (24) concluded that AMH, E2 and FSH are promising methods to determine amenorrhea and ovarian reserve. Our results are in concordance with these studies and a statistically significant correlation between pre and post chemotherapy AMH levels was found.

Our data showed a significant association between AFC results. Pretreatment AFC was strongly negatively correlated with the 5th measurements. Similar to our work, in a recently published trial by Wenners et al. (25), AMH, OFC and MOV values were recorded at baseline and at 6-month intervals with a total of 51 patients. AMH and OFC values at the end of the 1st year were significantly different from baseline, but there was no significant difference in MOV values.

Age-related AMH, AFC and MOV values were found to be higher in younger patients in our study, in accordance with the literature. Therefore, preservation against dysfunction for continuation of fertility may not be necessary in patients with higher AMH and AFC values below a certain age. Patients with a post-chemotherapy high percentage of reserve (AMH, OFC) and with younger age may not need fertility preservation. In our study, it was determined that the over-reserve was preserved in patients with younger age and who had high pre-chemotherapy AMH and AFC values, but the number of patients and the follow-up period were limited and insufficient to determine threshold values.

It could not be determined which chemotherapy regimen more adversely affected ovarian-reserve for discontinuation of fertility. Although there is no data in the literature, it was not possible to derive this result from our study due to the heterogenity of the chemotherapy regimens.

AMH, AFC and MOV values were followed in pre- and post chemotherapy periods for 6 month or 1 year intervals in the literature. In our study 31 patients were followed up with intervals of 3 months and the values acquired at the end of the first year were significantly similar with the literature. One of the consequences of this study is the importance of determining initial pre-chemotherapy and end of 1st post-chemotherapy year AFC and AMH values for the possibility of predicting over-reserve, as in the literature by Wenners et al. (25).

Our study has several strengths, including that recall rates were minimized by the prospective design.

In conclusion, pretreatment AMH levels and AFC were shown to have a significant role in the early prediction of ovarian reserve after chemotherapy. The present analyses have several limitations, such as the number of patients included, and further studies with longer follow-up and a larger study population are needed in order to determine regimen-based results of chemotherapy on AMH levels and antral follicle counts.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul Bilim University (04.07.2017/60-8).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Ç., S.İ.; Design - A.Ö., Z.E.; Supervision - V.Ö., B.B.; Resources - F.Ç., A.Ö.; Materials - B.B.; Data Collection and/or Processing - B.B., G.A.; Analysis and/or Interpretation - F.A., G.S.; Literature Search - Ç.O.; Writing Manuscript - F.Ç., Ç.O.; Critical Review - V.Ö.

Acknowledgements: The author wish to acknowledge David Chapman for language editing.

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

Financial Disclosure: The author declared that this study has received no financial support.

References

1. Brinton LA, Sherman ME, Carreon JD, Anderson WF. Recent Trends in Breast Cancer Among Younger Women in the United States. J Natl Cancer Inst 2008; 100: 1643-1648. (PMID: 19001605) [CrossRef]
2. Özmen V. Breast Cancer in Turkey: Clinical and Histopathological Characteristics (Analysis of 13.240 Patients). J Breast Health 2014; 10: 98-105. (PMID: 28331652) [CrossRef]
3. de Pedro M, Otero B, Martin B. Fertility Preservation and Breast Cancer: A Review. Ecancermedicalscience 2015; 9: 503. (PMID: 25729416) [CrossRef]
4. Yu B, Duglas N, Ferin MJ, Nakhuda GS, Crew K, Lobo RA, Hershman DL. Changes in Markers of Ovarian Reserve and Endocrine Function in Young Women with Breast Cancer Undergoing Adjuvant Chemotherapy. Cancer 2010; 116: 2099-2105. (PMID: 20187091) [CrossRef]
5. Dunlop CE, Anderson RA. Uses of Anti-Müllerian Hormone (AMH) Measurement Before and After Cancer Treatment in Women. Maturitas 2015; 80: 245-250. (PMID: 25596814) [CrossRef]
6. Kim HA, Seong MK, Kim JH, Kim YG, Choi HS, Kim JS, Park IC, Jin HO, Lee JK, Noh WC. Prognostic Value of Anti-Müllerian Hormone and inhibin B in Patients with Premenopausal Hormone Receptor-positive Breast Cancer. Anticancer ResMar 2016; 36: 1051-1057.
7. Iliodromiti S, Nelson SM. Biomarkers of Ovarian Reserve. Biomark Med 2013; 7: 147-158. (PMID: 23387496) [CrossRef]
8. Steiner AZ. Biomarkers of Ovarian Reserve as Predictors of Reproductive Potential. Semin Reprod Med 2013; 31: 437-442. (PMID: 24101224) [CrossRef]
9. Holte J, Brodin T, Berglund L, Hadziosmanovic N, Olovsson M, Bergh T. Antral follicle counts are strongly associated with live-birth rates after assisted reproduction with superior treatment outcome in women with polycystic ovaries. Fertil Steril 2011; 96: 594-599. (PMID: 21880276) [CrossRef]
10. Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015; 372: 923-932. (PMID: 25738668) [CrossRef]
11. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, Giordano M, Garrone O, Pronzato P, Bighin C, Levaggi A, Giraudi S, Cresti N, Magnolfi E, Scotto T, Vecchio C, Venturini M. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. JAMA 2011; 306: 269-276 (PMID: 21771987) [CrossRef]
12. Lambertini M, Campbell C, Bines J, Korde LA, Izquierdo M, Fumagalli D, Del Mastro L, Ignatiadis M, Pritchard K, Wolff AC, Jackisch C, Lang I, Untch M, Smith I, Boyle F, Xu B, Barrios CH, Baselga J, Moreno-Aspitia A, Piccart M, Gelber RD, de Azambuja E. Adjuvant Anti-HER2 Therapy, Treatment-Related Amenorrhea, and Survival in Premenopausal HER2-Positive Early Breast Cancer Patients. J Natl Cancer Inst 2019; 111: 86-94. (PMID: 29878225) [CrossRef]
13. Hasky N, Uri-Belapolsky S, Goldberg K, Miller I, Grossman H, Stemmer SM, Ben-Aharon I, Shalgi R. Gonadotrophin-releasing hormone agonists for fertility preservation: unraveling the enigma? Hum Reprod 2015; 30: 1089-1101. (PMID: 25796551) [CrossRef]
14. Henry NL, Xia R, Schott AF, McConnel D, Banerjee M, Hayes DF. Prediction of postchemotherapy ovarian function using markers of ovarian reserve. Oncologist 2014; 19: 68-74. (PMID: 24319018) [CrossRef]
15. Van Rooij IA, BroekmansFJ, Scheffer GJ, Looman CW, Habbema JD, de Jong FH, Fauser BJCM, Themmen APN, te Velde ER. Serum antimullerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: A longitudinal study. Fertil Steril 2005; 83: 979-987. (PMID: 15820810) [CrossRef]
16. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K, American Society of Clinical Oncology. American Society of Clinical Oncology recommendations on fertility in cancer patients. J Clin Oncol 2006; 24: 2917-2931. (PMID: 16651642) [CrossRef]
17. Dillon KE, Sammel MD, Prewitt M Ginsberg JP, Walker D, Mersereau JE, Gosiengfiao Y, Gracia CR. Pretreatment antimüllerian hormone levels determine rate of posttherapy ovarian reserve recovery: acute changes in ovarian reserve during and after chemotherapy. Fertil Steril 2013; 99: 477-483. (PMID: 23084267) [CrossRef]
18. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 1992; 7: 1342-1346. (PMID: 1291557) [CrossRef]
19. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril 2005; 83: 1622-1628. (PMID: 15950628) [CrossRef]
20. Anders C, Marcom PK, Peterson B, Gu L, Unruhe S, Welch R, Lyons P, Behera M, Copland S, Kimmick G, Shaw H, Snyder S, Antenos M, Woodruff T, Blackwell K. A pilot study of predictive markers of chemo-

therapy-related amenorrhea among premenopausal women with early stage breasr cancer. Cancer Invest 2008; 26: 286-295. (PMID: 18317970) [CrossRef]

21. Bozza C, Puglisi F, Lambertini M, Osa EO, Manno M, Del Mastro L. Anti-Mullerian hormone: determination of ovarian reserve in early breast cancer patients. Endocr Relat Cancer 2014; 21: R51-65. (PMID: 24292601) [CrossRef]
22. Wallace WH, Thomson AB, Kelsey TW. The radiosensivity of the human oocyte. Hum Reprod 2003; 18: 117-121. (PMID: 12525451) [CrossRef]
23. Anderson RA, Cameron DA. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab 2011; 96: 1336-1343 (PMID: 21325458) [CrossRef]
24. Ruddy KJ, Partridge AH. Fertility (male and female) and menopause. J Clin Oncol 2012; 30: 3705-3711. (PMID: 23008319) [CrossRef]
25. Wenners A, Grambach J, Koss J, Maass N, Jonat W, Schmutzler A, Mundhenke C. Reduced ovarian reserve in young early breast cancer patients: preliminary data from a prospective cohort trial. BMC Cancer 2017; 17: 632. (PMID: 28877720) [CrossRef]

Original Article

Eur J Breast Health 2020; 16(3): 183-191
DOI: 10.5152/ejbh.2020.5193

Men's Knowledge and Attitudes Towards Breast Cancer: A Descriptive Study

Ayşe Nilüfer Özaydın[1], Emrah Doğan[1], Berk Bozdoğan[2]
[1]Department of Public Health, Marmara University School of Medicine, İstanbul, Turkey
[2]Marmara University School of Medicine, İstanbul, Turkey

ABSTRACT

Objective: Breast cancer (BC) is an important disease for women. BC influences both patient's and relatives' lives. Especially, husbands/boyfriends/lovers are the ones that are affected mostly. In this study, it was aimed to introduce knowledge and attitudes of men toward BC and their sources of information about BC.

Materials and Methods: This descriptive study was conducted with men applied to a University Hospital in Istanbul (Turkey-2018). The ethics permission was obtained from The Clinical Research Ethics Committee. Data regarding socio-demographic characteristics with the knowledge and attitudes towards BC were collected with a questionnaire specific to the research. Statistical significance level was accepted as $p<0.05$.

Results: In the study, 240 men (mean age: 36.2±10.6 years,min: 18.0, max: 63.0) were interviewed. Fifty four percent of men declared that they would not marry someone with BC and/or someone who had mastectomy. Thirty four percent of participants thought that a woman with BC should conceal the disease. The mean BC knowledge score was 234.1±128.0 (median: 227.5, min: 0, max: 571.0) among the total which was 600.

Conclusion: A significant proportion of men did not have sufficient and accurate knowledge about BC. If the BC knowledge scores increase, there was an association with more positive attitudes. Negative attitudes of men related with BC of a woman may be an indicator of stigmatization. If it is aimed to increase support of men for women dealing with BC, it is recommended that BC awareness activities should be prepared to include men in order to increase their knowledge and to change their attitudes into a more positive way.

Keywords: Sexual partner, sexuality, fertility, education

Cite this articles as: Özaydın AN, Doğan E, Bozdoğan B. Men's Knowledge and Attitudes Towards Breast Cancer: A Descriptive Study. Eur J Breast Health 2020; 16(3): 183-191.

Introduction

Cancer is one of major cause of morbidity and mortality worldwide (1). According to the reports of The International Agency for Research on Cancer (IARC), 12.7 million people were estimated to receive a new cancer diagnosis globally in 2008, but this number increased to 18.1 million people in 2018 (2, 3). Fifty seven percent of the new cancer cases and 65% of people who lost their lives because of cancer are in the developing countries, such as Turkey. This indicates that cancer is an important public health problem in developing countries too (4).

Breast cancer (11.9%) is the second most common cancer following the lung cancer (13%) worldwide (1). Breast cancer is by far the most frequently diagnosed cancer and cause of cancer death among women. According to latest estimates of IARC (2018), breast cancer constitutes 24.2% of all female cancers (about one fourth of all new cancer cases in females worldwide are breast cancer) and is the leading cause of cancer death in females (15%). Breast cancer incidence is higher than other cancer incidences in both developed and developing countries (3).

In Turkey, the incidence of breast cancer (age-standardised rate, ASR) was 31.9/100.000 in 2002, and it has increased to 43.8/100.000 (ASR) in 2015. Currently, breast cancer is the most common cancer among women in Turkey (24.7%) (5). While it is in the first place among female cancers in age groups "25-49 years", "50-69 years" and "≥70", in age group "15-24 years" it is placed in 6th place (respectively 34.1%, 25.5%, 15.2% and 4.5%) (6).

Corresponding Author :
Ayşe Nilüfer Özaydın; nozaydin@gmail.com

Received: 24.09.2019
Accepted: 11.01.2020
Avialible Online Deta: 31.03.2020

In addition to the early diagnosis of breast cancer, early access to treatment and early start-up of treatment are crucial. However, the aim of the treatments should be achievement of complete physical, mental and social well-being and not merely absence of disease or infirmity (7). Thanks to the advances in today's medicine, physical well-being in breast cancer is firstly tried to be provided with medicines, surgeries, and mental well-being is provided with psychiatric support when it is necessary. Social well-being, which is another component of full well-being, is influenced by many cultural and economic factors belonging to the individual, family and society (8).

In social and daily life, "female body and sexuality" are constructed and reproduced by cultural and social elements. The factors such as beauty, glamour and temptation imposed on the female body cause the woman to be seen as a sexual object. When the woman, who is seen as a sexual object, loses her breast due to mastectomy she has, she perceives this as a loss of femininity, fertility, attractiveness and sexuality. This damage in the body image of the woman can cause various psychosocial problems. The problem here is that, because of the sexist attitude towards women, the woman herself and her body are seen as the source of seduction, temptation and shame (9, 10).

The value, respectability or acceptability among her peers or in her society of a woman is measured with the degree of sexual attraction of her body in modern societies. Because the capitalist consumer market and the culture it creates have standardized the female body. The bodies that are out of the norm are described as inferior, disgusting and unkempt. Such bodies are considered as a category that should not be present in interpersonal areas (on the street, in the workplace, in peer groups, near spouses or lovers, on special occasions) (9). It is known that these thoughts are established in the society and that after the diagnosis of cancer, the patient herself, her family and spouses' experiences difficulties and these difficulties may result in divorces (11-13). This situation arouses curiosity about attitudes of men towards breast cancer which is the most common female cancer in Turkey.

Despite extensive research on breast cancer, authors have had difficulty in accessing researches in the English literature in which attitudes and knowledge of men towards breast cancer are assessed. Also, in the

Key Points

- Breast cancer is the most incident cancer among women. Not only effects women, but also people around them. Despite the establishment of effect of men on the health of women, men seem to have a small share of the effort made in breast cancer researches.
- Men have a great and important place in women's lives and are dominant on women's life choices. On account of that, the knowledge and the attitude of men towards breast cancer should be assessed carefully.
- It has been shown that breast health occupies a large and important area in the decision making of men about woman.
- The breast cancer knowledge score the knowledge score and positive attitudes were directly proportional. This shows that efforts to increase knowledge level of the men would effects women health in a positive manner.
- In this descriptive study, authors tried to establish some main points which thought to be related with attitudes of men towards breast cancer. Since the reasons of the attitudes and opinions were not areas of interest of this study, designing and conducting qualitative studies to reveal the background of this area are strongly recommended.

Table 1. Socio-demographic characteristics of participants

Socio-demographic characteristics	n	%
Age Groups (Year)		
≤29	73	30.4
30-39	94	39.2
40-49	41	17.1
≥50	32	13.3
Marital Status		
Married	159	66.3
Divorced/ Separated/ Widowed/Living together	18	7.5
Never married	63	26.3
Education		
Illiterate/Literate/Primary School	38	15.8
Middle School	33	13.8
High School	92	38.3
University and higher degree(s)	77	32.1
Income ($)*		
According to Monthly Income		
≤1603 (267.6)	27	11.3
1604-3206 (267.7-535.2)	107	44.6
3207-4809 (535.4-802.8)	45	18.8
≥4810 (803)	61	25.4
According to Hunger Threshold		
≤1857 (310)	43	17.9
≥1858 (310.2)	197	82.1
According to Poverty Threshold		
≤6424 (1072.4)	213	88.8
≥6425 (1072.6)	27	11.3
Having Children** (n=177)		
Yes	143	80.8
No	34	19.2
Having a Relative with Breast Cancer		
Yes	18	7.5
No	222	92.5
Kinship to the Individual with Cancer		
Mother	6	33.3
Sister	4	22.2
Wife	8	44.4
Total	240	100.0

The Central Bank of Turkey, 2018 September 28. Available from: URL: http://www.tcmb.gov.tr/kurlar/201809/28092018.xml
* It was changed from Turkish Liras to USD with indicative exchanges rates announced by the Central
**Participants who had never experienced marriage were not included

Turkish literature, researchers could not source any research about this subject. It is aimed in this article to shed light on subjects of knowledge and attitudes of men towards breast cancer and their sources of information about breast cancer.

Materials and Methods

This is a descriptive study. It was conducted in Marmara University Hospital in Istanbul, Turkey in September-October 2018. The ethics permission was obtained from Marmara University School of Medicine Clinical Research Ethics Committee (September 02, 2018, protocol no: 09.2018.611), all participants were informed and their consents were obtained.

For the study, a special questionnaire was developed by the researchers: A preliminary test was conducted and then the necessary questions were revised. The questionnaire consisted of 48 questions in total. The first part was 8 questions about the socio-demographic characteristics of the participants and the next 32 questions were specific questions to assess the knowledge about breast cancer. In these questions, the correct and incorrect answers were scored and a "total breast cancer knowledge score" was calculated (max: 600, min: 0). There were also 7 questions about attitude of participants toward breast cancer and 1 more question was sources of breast cancer information of participants.

Due to the challenges of being in a hospital environment, the volunteer participants were interviewed face to face and their answers were recorded.

Statistical analysis

Data from the study were analyzed in Statistical Package for the Social Sciences (SPSS 11.0, IBM Corp.; Armonk, NY, USA) programme. Normality test, Student's T-test, Chi-Square test, correlation tests were performed and $p<0.05$ was accepted for the statistical significance level.

Results

In this study, 240 volunteer males were interviewed. The mean age of the participants was 36.2±10.6 years (median: 36.0, min: 18.0 max: 63.0). 70.4% of the participants were graduated from high school and above. The average monthly income was 3947.1±3132.2 Turkish Liras (median: 3000.0, min: 800, max: 30.000). Socio-demographic characteristics of the participants are presented in Table 1.

Table 2. Breast cancer knowledge score distribution of men according to some basic characteristics

Socio-demographic characteristics	Knowledge Score of Breast Cancer						
	n	Mean	SD	Median	Min.	Max.	p
Age Groups(Year)							
≤29	73	239.3	151.5	210.0	0	570.0	0.574
30-39	94	221.4	109.4	220.0	0	460.0	
40-49	41	236.9	138.2	230.0	30.0	535.0	
≥50	32	255.9	106.6	275.0	40.0	520.0	
Education							
Illiterate/Literate/Primary School	38	200.4	124.3	200.0	20.0	500.0	0.002
Middle School	33	189.7	107.9	190.0	0.0	470.0	
High School	92	226.3	131.9	215.0	0.0	570.0	
University and higher degree(s)	77	279.0	121.4	295.0	30.0	535.0	
Monthly Income ($)							
(According to Poverty Threshold)							
≤1072.4	213	227.3	126.9	220.0	0.0	570.0	0.020
≥1072.6	27	287.9	125.8	270.0	60.0	525.0	
Marital Status							
Married	159	225.5	117.3	220.0	0.0	535.0	0.381
Divorced/ Separated/ Widowed/Living together	18	224.2	125.2	230.0	60.0	520.0	
Never married	63	258.7	151.6	250.0	10.0	570.0	
Having Children (n:177)							
Yes	143	237.5	115.4	240.0	0.0	535.0	0.004
No	34	174.1	115.2	170.0	0.0	460.0	
Having a Relative with Breast Cancer							
Yes	18	202.2	151.3	155.0	40.0	505.0	0.273
No	222	236.7	125.9	230.0	0.0	570.0	

Breast cancer knowledge scores

The knowledge score of males was assessed with a questionnaire developed by researchers. According to this form, the mean score was 234.1±128.0 (median: 227.5, min: 0, max: 571.0). The distribution of knowledge scores according to socio-demographic characteristics of men is shown in Table 2.

Table 3. The declared attitudes of men about breast cancer

Attitude Questions	n	%
Would you marry someone with breast cancer?		
No. I would not	46	19.2
I do not know	84	35.0
Yes. I would	110	45.8
Would you marry someone who had a mastectomy?		
No	49	20.4
I do not know	81	33.8
Yes	110	45.8
What would you do if your wife was diagnosed with breast cancer?		
I would consider divorce.	8	3.3
It's none of my business. I'm going back to where I left off.	1	0.4
I don't know what to say right now.	28	11.7
I would support her and fight together to cure the disease.	199	82.9
What would you do if your wife had a mastectomy?		
I would consider divorce.	7	2.9
It's none of my business. I would go back to where I left off.	4	1.7
I don't know what to say right now.	27	11.3
I would try to give her support and comfort.	198	82.5
If your wife had a mastectomy and she wanted breast reconstruction surgery, what would be your attitude?		
I would oppose	14	5.8
It would not matter	66	27.5
I don't know what to say right now.	63	26.3
I would encourage her	93	38.8
If your wife/spouse/mother had breast cancer, would you conceal it from other people?		
Yes	14	5.8
I do not know	75	31.3
No	151	62.9
Should a woman with breast cancer conceal her disease?		
Yes	11	4.6
I do not know	71	29.6
No	158	65.8
Total	240	100.0

Attitude assessment

Results of the participants' attitudes towards breast cancer are given in Table 3.

Eighty one percent of men who thought that breast cancer would affect fertility of woman and 94.0% of men who thought that breast cancer would not affect fertility said that they would support their wives if their wives had breast cancer (p:0.016) (Table 4).

Eighty four percent of the men who have children said that they would support their wives if they had mastectomy. On the other hand, 67.6% of men who do not have children said that they would support their wives if they had a mastectomy (p:0.03) (Table 5).

In addition to the results presented in the tables, some of the important findings are given in the following paragraphs.

While 5% of participants who had not any spouse or first degree relative with breast cancer said that "A woman should conceal that she has breast cancer", none of the participants with a spouse or first degree relative with breast cancer agreed with this idea (p>0.05).

While only 40.6% of men who were 50 years and older stated that they could marry someone with breast cancer, nearly half of (47.9%) ≤29 age group stated that they could marry someone with breast cancer (p>0.05).

Fifty one percent of university graduates and 39.4% of middle school graduates stated that they could marry someone with breast cancer (p: 0.068).

While 50.8% of men who never married said that they could marry someone with breast cancer, only 33.3% of men with marriage experience said they could marry someone with breast cancer (p>0.05).

While 63% of those whose income status is above the "poverty threshold" stated that they could marry a person with breast cancer, this ratio was 43.7% of those below the poverty threshold (p>0.05).

Only 55.6% of males with any breast cancer cases in their family and 45% of those without breast cancer cases in their family said that they could marry someone with breast cancer (p:0.02).

While 52.1% of participants under 29 years of age declared that they could marry someone who had a mastectomy, this ratio was 40.6% in the ≥50 age group (p:0.019).

Eighty five percent of participants who thought that sexual life of a woman with breast cancer would be impaired and 92,0% of those who thought it would not be impaired stated that they would support their wives (p:0.014).

Breast cancer knowledge scores of participants who stated that they would support their wives were significantly higher than those who would not support their wives [respectively 254.1±124.9 (median: 250.0, min: 0, max: 570.0) and 136.8±95.1 (median: 110.0, min: 10.0, max: 360.0)] (p: 0.0001), if their wives were diagnosed with breast cancer.

Similar to previous results, breast cancer knowledge scores of participants who stated that they would support their wives were significantly higher than those who would not support their wives [respectively 263.4±116.3 (median: 280.0, min: 0, max: 520.0) and 215.5±131.9 (median: 200.0, min: 0, max: 570.0)] (p: 0.004), if their wives had a mastectomy.

Information source of participants

The participants' sources of information were questioned and results were presented in Table 6.

The mean breast cancer knowledge score of participants whose source of information was newspaper/magazine (mean: 273.7±119.4) was higher than those whose source of information was not newspaper/magazine (mean: 212.4±127.7) (p: 0.006).

Table 4. The distribution of the situation of supportiveness of men, when their wives had breast cancer

	What would a man do if their wives were diagnosed with breast cancer?						
	Would Support		Would Not Support		Total		
Socio-demographic Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Age Groups (Year)							
≤29	58	79.5	15	20.5	73	100.0	0.820
30-39	79	84.0	15	16.0	94	100.0	
40-49	35	85.4	6	14.6	41	100.0	
≥50	27	84.4	5	15.6	32	100.0	
Education							
Illiterate/Literate/Primary School	31	81.6	7	18.4	38	100.0	0.399
Middle School	25	75.8	8	24.2	33	100.0	
High School	75	81.5	17	18.5	92	100.0	
University and higher degree(s)	68	88.3	9	11.7	77	100.0	
Monthly Income ($)(According to Poverty Threshold)							
≤1072.4	175	82.2	38	17.8	213	100.0	0.284
≥1072.6	24	88.9	3	11.1	27	100.0	
Marital Status							
Married	130	81.8	29	18.2	159	100.0	0.779
Divorced/ Separated/ Widowed/Living together	15	83.3	3	16.7	18	100.0	
Never married	54	85.7	9	14.3	63	100.0	
Having Children							
Yes	121	84.6	22	15.4	143	100.0	0.053
No	24	70.6	10	29.4	34	100.0	
Having a Relative with Breast Cancer							
Yes	14	77.8	4	22.2	18	100.0	0.370
No	185	83.3	37	16.7	222	100.0	
Breast Cancer Disturbs a Woman's Sexual Life							
No	80	90.9	8	9.1	88	100.0	0.014
I do not know	79	75.2	26	24.8	105	100.0	
Yes	40	85.1	7	14.9	47	100.0	
Breast Cancer Affects Woman's Fertility							
No	63	94.0	4	6.0	67	100.0	0.016
I do not know	107	78.1	30	21.9	137	100.0	
Yes	29	80.6	7	19.4	36	100.0	
Breast Cancer Knowledge Score							
≤200	72	69.2	32	30.8	104	100.0	0.0001
201-400	106	92.2	9	7.8	115	100.0	
≥401	21	100.0	0	0.0	21	100.0	
Total	199	82.9	4	17.1	240	100.0	

Table 5. The distribution of the situation of supportiveness of men, when their wives had a mastectomy

	What would a man do if their wives had mastectomy?						
	Would Support		Would Not Support		Total		
Socio-demographic Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Age Groups (Year)							
≤29	58	79.5	15	20.5	73	100.0	0.827
30-39	79	84.0	15	16.0	94	100.0	
40-49	35	85.4	6	14.6	41	100.0	
≥50	26	81.2	6	18.8	32	100.0	
Education							
Illiterate/Literate/Primary School	30	78.9	8	21.1	38	100.0	0.753
Middle School	26	78.8	7	21.2	33	100.0	
High School	76	82.6	16	17.4	92	100.0	
University and higher degree(s)	66	85.7	11	14.3	77	100.0	
Monthly Income ($)(According to Poverty Threshold)							
≤1072.4	174	81.7	39	18.3	213	100.0	*
≥1072.6	24	88.9	3	11.1	27	100.0	
Marital Status							
Married	128	80.5	31	19.5	159	100.0	0.483
Divorced/ Separated/ Widowed/Living together	15	83.3	3	16.7	18	100.0	
Never married	55	87.3	8	12.7	63	100.0	
Having Children (n:177)							
Yes	120	83.9	23	16.1	143	100.0	0.03
No	23	67.6	11	32.4	34	100.0	
Having a Relative with Breast Cancer							
Yes	14	77.8	4	22.2	18	100.0	*
No	184	82.9	38	17.1	222	100.0	
Breast Cancer Disturbs a Woman's Sexual Life							
No	80	90.9	8	9.1	88	100.0	0.004
I do not know	77	73.3	28	26.7	105	100.0	
Yes	41	87.2	6	12.8	47	100.0	
Breast Cancer Affects Woman's Fertility							
No	63	94.0	4	6.0	67	100.0	0.006
I do not know	106	77.4	31	22.6	137	100.0	
Yes	29	80.6	7	19.4	36	100.0	
Breast Cancer Knowledge Score							
≤200	71	68.3	33	31.7	104	100.0	0.0001**
201-400	106	92.2	9	7.8	115	100.0	
≥401	21	100.0	0	0.0	21	100.0	
Total	198	82.5	42	17.5	240	100.0	

*Chi-Square testing cannot be performed because of Cochrane rules

**Student-T Test was performed

Table 6. Information sources of men related to breast cancer

Information source*	n	%
TV	127	52.9
Physicians	92	38.3
Newspapers and magazines	85	35.4
Friends. relatives and neighbours	67	27.9
Advertisement	54	22.5
Brochure	54	22.5
Nurses	37	15.4

*More than one answer was acceptable

The mean breast cancer knowledge score of men who stated that they had gathered their information from brochures (mean: 276.0±108.5) was higher than who had not read brochures (mean: 221.9±130.9) (p: 0.006).

The mean knowledge score of participants who said they had been informed by a doctor (mean: 254.9±134.6) was higher than who had not been informed by a doctor (p: 0.047).

Discussion and Conclusion

Breast cancer is ranked first among female cancers and is one of the most important diseases for women in Turkey as well as in the world. While breast cancer is in the first place among female cancers in age groups "25-49 years", "50-69 years" and "≥70", in the age group "15-24 years" it is placed in 6th place (respectively 34.1%, 25.5%, 15.2% and 4.5%) (6). When women are diagnosed with this disease, they are mostly in the reproductive age, where they may be married and/or engaged and/or have a boyfriend. Not only the organ in which the disease is seen is perceived as a mere body part, but also is perceived by both men and women as a special organ for female sexuality in many different cultures and societies (14). This approach affects both attendance of women's screening for early diagnosis and causes psychosocial problems after treatment (12). The target group of studies related with breast cancer is mostly women, since breast cancer is mostly seen in women. Few studies which evaluate the knowledge, attitudes and behaviors of men with women in their lives during breast cancer diagnosis and treatment have been reached. In order to shed light on the subject scientifically, this study was planned and data was collected successfully. This study, when conducted with men who have applied to a university hospital and who have voluntarily participated in the study, is one of the pioneering studies in this field of research. Although, breast cancer is the most important disease for females, authors have had difficulty in accessing studies for comparison that evaluate knowledge and attitudes of men towards breast cancer in English literature. Unfortunately, no other published article in the Turkish literature could be reached.

In our study, 54.2% of men declared that they would not marry someone that had breast cancer and/or someone whose breast(s) had been removed. In our study, questions regarding the reasons for this situation were not asked. The authors thought that this is an important area of interest and strongly recommended that qualitative studies should be conducted to find the reason: men do not want to marry as to whether she is not healthy or whether she is not considered attractive anymore.

Thirty four percent of our participants thought that a woman with breast cancer should conceal her disease. Although, details about the reason(s) for this opinion could not be obtained, it may be related with the perception of the breast mainly as a sexual organ. Because of this, it is seen as an inappropriate subject to talk about by society. Since it is accepted as a sexual organ, people, both men and women, in Turkey prefer to use the word "chest" instead of "breast". Also, the reason might be related with the fear of cancer and its consequences, such as death.

In our study, if wives of the participants were diagnosed with breast cancer, 82.9% of men stated that they would support their wives, 11.7% were undecided and only 3.3% declared that they would think of divorce. In a study conducted in Saudi Arabia, 90.6% of men stated that they would never leave their wives if they were diagnosed with breast cancer, while 9.4% said they would leave. However, despite this finding, researchers from Saudi Arabia emphasized that this may not be the case when it comes to reality (15). Similarly, we believe that if a study was conducted in a specific population who had breast cancer cases it may reflect a more realistic situation. Fear of being abandoned by husbands or partners of women may affect negatively the behaviors of women to attend breast cancer screening programmes.

An interesting finding in our study is that the knowledge of breast cancer in men of different age groups was similar. However, it was found that the knowledge of breast cancer was significantly higher in males with children than those without any children. In our study, the knowledge of men about breast cancer was positively affected by being educated at high school and above, having higher income from poverty threshold and having children, but the age, marital status and having any relatives with breast cancer did not affect their breast cancer knowledge scores.

In our study, the breast cancer knowledge of men who had any relative with breast cancer did not show any difference compared to those without any relative with breast cancer. The reason(s) behind this has aroused curiosity. Do men not try to obtain information about disease of their relatives or do they avoid communication with the person who has breast cancer because the breast is perceived as a sexual organ?

While 85.1% of the men who thought that the sexual life of a woman with breast cancer would be deteriorated declared that they would support their wives if women are diagnosed with breast cancer, 91% of the men who did not think this way declared they would support their wives. Eighty one percent of the participants who believed that breast cancer would affect a woman's fertility said that they would support their wives in case of a breast cancer diagnosis, this ratio was 94.0% in men who did not believe breast cancer would affect a woman's fertility.

In our study group it was found there was a directly proportional relationship between education level and breast cancer knowledge scores of the participants. Similar relationship was also found between breast cancer knowledge scores and positive attitudes in the breast cancer diagnosis and mastectomy situations. However, there was not any significant relationship between education level and positive attitudes of men. It is unknown as to why positive attitudes were observed with extreme high scores such as ≥401 points and scores which were completely independent of the education level. This important result may shed light on the necessity and the importance of the breast cancer awareness activities specifically designed for the men.

It has been thought that the health of the breast, which generally is considered as a sexual organ of women, is seen an important criterion for marriage by our participants. In addition to this, it is thought that sexuality and fertility are important criteria for man in marriage. In case of a negative health status stemming from women in these subjects, lack of support of the men may affect both women's health and the couples' marriage in a negative way.

Until International Conference on Population and Development-1994, men had not been considered as a target group for reproductive health issues and no awareness activities for men were conducted. In this conference, it was accepted that one of the biggest reasons of the lack of expected effects of different interventions at national and / or international level in order to increase the reproductive health status in a society would be the exclusion of men in this field, and after 1994, reproductive health services have been given in a holistic approach which included both sexes from birth to death (16, 17). As a disease, breast cancer mostly occurs in the female body, however, it is a chronic disease which affects life of patients and their families in terms of physical and psychiatric well-being. Therefore, it is recommended to carry out similar holistic approaches in breast cancer activities to enhance knowledge and attitude of men and women positively.

The men who participated in our study stated that they obtained their knowledge about breast cancer most often from TV programmes, physicians and newspapers/magazines respectively. Similar to our findings, it was reported that males used TV/radio, newspapers/magazines and doctors/nurses as their source of information respectively (18). In a study, men's major sources of information were physicians, internet and the media (15). Another study parallel to our findings, TV and newspapers represented major sources of information for men (19).

It is a limitation that this study could be conducted with only voluntary participants who were relatives of patients who applied to hospital for any complaint. It is recommended to conduct a research in a larger sample group that can be more representative of the Turkish society. Due to lack of a specific attitude scale in this area, attitude questions were developed by the researchers. It is recommended to researchers working in this field, that there is a need to produce a standardized attitude scale. In addition, due to the importance and characteristics of the subject, it is considered and suggested that it should be evaluated together with a gender attitude scale.

In conclusion, when the attitudes of men towards women with breast cancer are questioned, more than half of the participants declared that they would not marry a woman with breast cancer and/or who had mastectomy, while the majority of men stated that if their wife was diagnosed with breast cancer they would support her, and only 3% of the men reported that they would get divorced from their wives. However, with a hypothetical questioning, the possibility of responding in favour of social expectations should be kept in mind, and it should be taken into consideration that their behavior may be very different in the case of 'real life'. One in ten men stated that if his wife's breast had to be removed, he was undecided about whether or not to leave, which could in fact be regarded as a sincere and open confession.

In order to change the attitudes of men on these issues in a positive way, it is necessary to demolish the stereotypes and transfer the correct information to all men by media. By developing positive attitudes of men, early and effective participation of women in diagnosis and treatment processes can be ensured and social isolation of women can be prevented. Therefore, it is recommended the organization of breast cancer awareness activities which is not only targeted at healthy/diseased women, but also for men.

Ethics Committee Approval: Ethics committee approval was received for this study from Marmara University School of Medicine Clinical Research Ethics Committee (September 02, 2018, protocol no: 09.2018.611).

Informed Consent: Written informed consent was obtained from all participants' themselves who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.N.Ö., E.D., B.B.; Design – A.N.Ö., E.D., B.B.; Supervision – A.N.Ö., E.D., B.B.; Resources – A.N.Ö.; Materials – A.N.Ö., E.D., B.B.; Data Collection and/or Processing – A.N.Ö., E.D.; Analysis and/or Interpretation – A.N.Ö., B.B.; Literature Search – A.N.Ö., E.D., B.B.; Writing Manuscript – A.N.Ö., B.B.; Critical Review – A.N.Ö., E.D., B.B.

Acknowledgements: Authors would like to thank Dr. Abdullah Mercan, Dr. Ali Nofal, Dr. Bahadır Emre Soylu, Dr. Osman Çolak and all the voluntary participants.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Stewart BW, Wild CP, editors. World cancer report 2014. Lyon: IARC; 2014. ISBN 978-92-832-0429-9.
2. Boyle P, Levin B, editors. World cancer report 2008. Lyon; IARC; 2008. ISBN 978-92-832-0423-7.
3. The International Agency for Research on Cancer. Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. Press Release No: 263 2018. (cited 2019 July 25). Available from: URL:https://www.iarc.fr/wp-content/uploads/2018/09/pr263_E.pdf.
4. Ozmen V, editor. Breast cancer in Turkey. Turkey: Cinius; 2017. ISBN 978-605-296-077-6.
5. Bora Başara B, Soytutan Çağlar İ, Aygün A, Özdemir TA, editors, General Directorate of Health Information Systems, Ministry of Health. Health Statistics Yearbook 2017. Ankara; 2018. (cited 2019 July 25). Available from: URL:https://dosyasb.saglik.gov.tr/Eklenti/30148,ingilizcesiydijiv1pdf.pdf?0.
6. Sencan I, Keskinkilic B, editors, Public Health Institution of Turkey, Ministry of Health.Turkey Cancer Statistics. Ankara; 2017. (cited 2019 July 25). Available from: URL:https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/2014-RAPOR._uzuuun.pdf.
7. World Health Organization. Basic documents-48th ed. WHO; 2014. ISBN 978 92 4 165048 9 (cited 2019 July 25). Available from: URL:http://apps.who.int/gb/bd/PDF/bd48/basic-documents-48th-edition-en.pdf#page=1.
8. Akin A, editor. Toplumsal cinsiyet, sağlık, kadın. Hacettepe University; 2003. ISBN: 975-491-141-X.
9. Bilgin R. Body and sexuality of women in traditional and modern society. Fırat Univ J Social Sci 2016; 26: 219-243. [CrossRef]
10. Çavdar İ. Sexual problems of the patients who suffer from breast carcinoma. Eur J Breast Health 2006; 2: 64-66.
11. Woloski-Wruble AC, Ganz FD, Jiang Y, Qiang W, Kadmon I. Israeli and Chinese partners of women with breast cancer: a cross-cultural view of marital issues. Psycho-oncology 2012; 21: 324- 331. (PMID: 22383274) [CrossRef]

12. Babacan Gumus A. Psychosocial issues in breast cancer and supportive interventions. Eur J Breast Health 2006; 2: 108-114.
13. Bahar S. Hastalıktan geriye kalan tarifsiz acı terk eden kocalar. Economics News, Sabah Gazetesi; 2018. (cited 2019 July 25). Available from: URL:https://www.sabah.com.tr/ekonomi/2018/06/24/hastaliktan-geriye-kalan-tarifsiz-aci-terk-eden-kocalar.
14. Denizgil T, Sonmez I. Comparison of self esteem, body image, sexual satisfaction and sexual experiences between women who had mastectomy or breast conserving surgery for breast carcinoma. Yeni Symposium 2015; 53: 17-25.
15. Al-Amoudi SM, Abduljabbar HS. Men's knowledge and attitude towards breast cancer in Saudi Arabia: a cross-sectional study. Saudi Med J 2012; 33: 547-550. (PMID: 22588817)
16. United Nations [Internet]. New York (NY): UN. Report of the International Conference on Population and Development, Cairo, 5-13 September 1994 1995. (cited 2019 July 25). Available from: https://www.unfpa.org/sites/default/files/event-pdf/icpd_eng_2.pdf.
17. Akin A, Bahar Ozvaris S, Özgülnar N, Dilbaz B, Gülersoy-Özaydin N. Üreme Sağlığına Giriş. T.C. Sağlık Bakanlığı Ana Çocuk Sağlığı ve Aile Planlaması Genel Müdürlüğü. Ankara: 2005. ISBN: 975-590-132-9.
18. McMenamin M, Barry H, Lennon AM, Purcell H, Baum M, Keegan D, McDermott E, O'Donoghue D, Daly L, Mulcahy H. A survey of breast cancer awareness and knowledge in a Western population: lots oflight but little illumination. Eur J Cancer 2005; 41: 393-397. (PMID: 15691638) **[CrossRef]**
19. Najdyhor E, Krajewska-Kułak E, Krajewska-Ferishah K. Knowledge of women and men about breast cancer prevention. Ginekol Pol 2013; 84: 116-125. (PMID: 23668058) **[CrossRef]**

Original Article

Eur J Breast Health 2020; 16(3): 192-197
DOI: 10.5152/ejbh.2020.5332

Associated Features with Non-Sentinel Lymph Node Involvement in Early Stage Breast Cancer Patients who Have Positive Macrometastatic Sentinel Lymph Node

Hakan Ataş[1], Buket Altun Özdemir[1], Ebru Menekşe[1], Sabri Özden[1], Yunus Nadi Yüksek[1], Gül Dağlar[2]

[1]Clinic of Breast and Endocrine Surgery, Ankara City Hospital, Ankara, Turkey
[2]Clinic of Breast and Endocrine Surgery, Ankara Numune Research and Training Hospital, Ankara, Turkey

ABSTRACT

Objective: The main goal of this study is to determine the clinico-pathological factors that correlate non-sentinel lymph nodes (LNs) involvement in clinically node negative breast cancer (BC) patients with positive macrometastatic sentinel lymph node (SLN) in order to derive future evidence to define a subgroup where completion axillary lymph node dissection (cALND) might not be recommended.

Materials and Methods: Total 289 SLN biopsies were performed in clinically node negative BC patients between March 2014 and April 2017. Seventy patients who performed cALND due to positive macrometastatic SLN were retrospectively selected and classified into two groups, according to non-SLN involvement (NSLNI). Clinico-pathological features of patients were examined computerized and documentary archives.

Results: Extracapsular extension (ECE) of SLN, number of harvested SLNs, metastatic rate of SLNs, absence of ductal carcinoma in situ (DCIS) and presence of multilocalization were significantly associated with the likelihood of non-SLN involvement after univariate analysis ($p<0,05$). Absence of DCIS and presence of multilocalization were found to be significant after multivariate analysis.

Conclusion: Careful examination of clinico-pathological features can help to decide avoiding cALND if enough LNs are removed and the rate of SLN metastases is low, particularly in case DCIS accompanying invasive cancer in patients without multi localized tumour.

Keywords: Breast cancer, lymphatic metastasis, sentinel lymph node biopsy

Cite this articles as: Ataş H, Altun Özdemir B, Menekşe E, Özden S, Yüksek YN, Dağlar G. Associated Features with Non-Sentinel Lymph Node Involvement in Early Stage Breast Cancer Patients who Have Positive Macrometastatic Sentinel Lymph Node. Eur J Breast Health 2020; 16(3): 192-197.

Introduction

The axillary nodal status is the most important prognostic factor in predicting the clinical outcomes in breast cancer (BC) patients. In recent years, sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) for an accurate staging and also to determine the prognosis and necessity of adjuvant therapies in BC patients with clinically negative axillary lymph nodes (1, 2). SLNB is a minimally invasive technique and safe, as well as lower morbidity compared with axillary dissection (2, 3). It is reported that the complication rates were, especially lymphedema, respectively 19.9% vs. 5.6% following ALND than SLNB during long-term follow-up (4).

When the sentinel lymph nodes (SLNs) are negative, ALND can be omitted due to the remaining axillary nodes were found free of disease (2). But it is still controversial to perform completion axillary lymph node dissection (cALND) in patients with SLN metastases (5). After the publishing ACASOG Z0011 and AMAROS studies, the importance of the non SLN involvement is considered less important (6, 7). However, cALND remains important for patients who have undergone mastectomy and cannot receive radiotherapy. After the IBCSG 23-01 study, the contribution of axillary dissection for micrometastatic lymph nodes to disease-free survival has not been demonstrated and there is still no standardization for axillary treatment (8). However, in most of the studies, while SLN positivity was identified, micro or macrometastasis was not differentiated (5, 6, 9). Therefore, knowing the specific factors affecting NSLNI in patients with macrometastasis in SLN may make a difference in approach to axilla. In terms of refraining from morbidity of ALND and also keeping in oncological safety, it is important to identify the related factors with additional nodal disease in BC with SLN macrometastasis.

Corresponding Author :
Hakan Ataş; drhakanatas@gmail.com

Received: 07.12.2019
Accepted: 28.01.2020
Available Online Date: 17.04.2020

The main goal of this study is to determine the clinico-pathological factors that correlate non-sentinel lymph nodes involvement in clinically node negative BC patients with positive SLN in order to derive future evidence to define a subgroup where cALND might not be recommended.

Materials and Methods

The clinically early stage BC patients with the clinically axillary node negative, who underwent SLNB at Breast and Endocrine Surgery Unit of Ankara Numune Research and Training Hospital between March 2014 to April 2017, were reviewed as retrospectively from the our computerized and documentary archives. Informed consent was obtained from patients at the time of enrolment in the registry. Institutional ethical committee of Ankara Numune Research and Training Hospital approved the study (Number of ethics committee approval: E-17-1429).

Patients, who underwent to ALND due to positive SLN were taken into this study. The cases with receiving neoadjuvant chemotherapy, micrometastases in SLN, isolated tumour cells and more than 6 removed SLNs were excluded from the study. All patients carried out ultrasounds of both breast and axilla and the patients aged more than 40 years underwent to mammography (MMG) for the purpose of diagnosis and treatment planning. Patients were diagnosed as BC according to excisional & stereotactic biopsy, tru-cut biopsy and fine needle aspiration biopsy (FNAB) from suspicious breast mass. All the SLNB procedures were conducted via the use of blue dye such as patent blue, isosulfan blue and methylene blue. After the induction of anaesthesia, the blue dye was injected into the subareolar and perilesional areas in 10 mL volume and performed a massage to stimulate lymphatic drainage, for 10-12 minutes. Identified all blue nodes were accepted as SLNs and harvested. Pathologic evaluation of SLNs was performed with frozen section analysis intraoperatively, included sectioning at 2-mm intervals and staining with haematoxylin and eosin (H&E). If lymph nodes were negative with H&E, immunohistochemistry using cytokeratin antibody was performed. The determination of macrometastatic cells (>2 mm) within this period was described as a 'positive SLN' and further ALND was performed. Micrometastasis (0.2-2 mm), cell clusters and isolated tumour cells of <2 mm diameter were not accepted as a 'positive SLN' and so no more ALND performed.

Patient characteristics including age, side, localization and multilocalization of the tumour, presence of microcalcification on MMG, tumour characteristics including histological type, histological grade via the modified Bloom and Richardson system, tumour size, presence of lymphovascular invasion (LVI) and perineural invasion (PNI) and status of estrogen receptor (ER), progesterone receptor (PR), cerb-B2, p53, Ki67 and presence of DCIS accompanying invasive cancer, number of harvested SLNs and non-SLNs, SLN metastatic rate and extracapsular extension (ECE) of SLNs were assessed as possible estimated factors of axillary lymph node involvement. Multilocalization was defined as tumours that showed either or both multicentricity and multifocality. SLN metastatic rate was defined as the ratio of positive SLNs to total harvested SLNs.

After the final examination of enrolled surgical data and histopathological results, these patients with cALND were classified in two groups [(Group 1: non-sentinel lymph node involvement-, NSLNI (-) and Group 2: non-sentinel lymph node involvement, NSLNI (+).

Statistical analysis

The relationship between clinico-pathological variables and groups which was divided according to axillary lymph node involvement was initially evaluated using univariate analysis. Continuous data are presented as mean±SD while differences between groups were analysed by means of ANOVA test. Categorical variables were analysed with $\chi 2$ tests. Logistic regression was used to significant dependent variables associated with NSLNI. According to the number of risk factors which was independent variables, NSLNI rates was calculated by $\chi 2$ tests. A p-value less than 0.05 was considered statistically significant. All statistical tests were performed using IBM Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA), version 18.0, software.

Key Points

- cALND in breast cancer patients with positive SLN still remains important for patients who have undergone mastectomy and can not receive radiotherapy.
- In order to avoid overtreatment due to morbidity of ALND, it is crucial to identify the factors associated with NSLNI.
- However, the problem with the practical use of existing nomograms was that some parameters used, such as LVI or ECE of SLN, were not known during the operation.
- This study suggests that cALND is less necessary in breast cancer patients with positive SLN accompanied by DCIS but without multilocalization.

Results

SLN biopsies were performed in 289 clinically early stage BC patients. cALND were performed in 85 patients with positive SLN. Of these, 76 had macrometastases (26.3%), 8 had micrometastases (2.7%) and 1 (0.3%) had isolated tumour cells. And six other patients with more than 6 SLN excluded from the study. The remaining 70 patients were classified in two groups according to the involvement of non-SLN. A total of 32 patients in group 1 and 38 patients in group 2 were analysed. The age range was 21-80 years (mean: 51.4±12.8). There was no significant difference between groups in terms of age. We placed the diagnosis of malignancy with a tru-cut biopsy in 43 (62%) and with excisional & stereotactic biopsy in 27 (38%). SLND was applied to all patients with the use of blue dye. Three types of blue dyes were used. Patent blue in 53 (76%), isosulfan blue in 9 (13%) and methylene blue in 8 (11%). Multilocalization was seen in 11 (15.7%) of 70 patients and was found significantly associated with NSLNI (p=0.046). Forty-nine (70%) patients were underwent breast-conserving surgery that included lumpectomy and 21 (30%) modified radical mastectomy. The mean pathological tumour size was 2.400.98 cm. A total of 29 (41.42%) had a T1 tumor size while 41 (58.57%) patients with T2 tumor. The histological types of tumors were invasive ductal carcinoma (IDC) in 53 (76%), invasive lobular carcinoma (ILC) in 11 (16%), mixed invasive ductal and invasive lobular carcinoma in 3 (4%) and other in 3 (4%). Presence of DCIS accompanying invasive cancer histologically detected in 29 (41.4%), and absence of DCIS accompanying invasive cancer found statistically significant correlation with nodal involvement (p=0.021). Additional positive lymph nodes after ALND were identified in 38 of 70 (54.3%) patients with positive SLNs. The number of harvested SLN was minimum 1 and maximum 6 (mean: 2.921.42). SLN metastatic rate was 49% and 71.8% in group1 (NSLNI-) and group 2 (NSLNI+), respectively. ECE of SLNs was detected in 16 (22.8%) and all patients with ECE of SLNs were in group 2.

Clinicopathologic characteristics and results of the histopathological examination of the primary tumor and axillary lymph nodes are shown in Table 1 and Table 2.

ECE of SLNs (p<0.001), number of harvested SLNs (p=0.015), metastatic rate of SLNs (p=0.01), absence of DCIS accompanying invasive cancer (p=0.021) and multilocalization (p=0.046) were significantly associated with NSLNI on univariate analysis (p<0.05). These factors which were found to be significantly associated with NSLNI underwent to multivariate analysis. Multivariate analysis of potential risk factors showed that absence of DCIS accompanying invasive cancer (p=0.024) and presence of multilocalization (p=0.046) were independently associated with NSLNI in the present study (Table 3). If none, 1 or 2 of the risk factors is present, the estimated risks of NSLNI are found as 29.2%, 63.4% and 100 %, respectively (Table 4).

Discussion and Conclusion

Many studies investigated the different factors to predict the non-sentinel lymph node metastases in patients with positive SLN (5, 9). The present study revealed that ECE of SLNs, number of harvested SLNs, metastatic rate of SLNs, absence of DCIS and presence of multilocalization were significantly associated with the likelihood of NSLNI in BC patients on univariate analysis. Of these, only absence of DCIS accompanying invasive cancer and multilocalization were found to be independent factors that effect NSLNI. Presence of DCIS was negatively associated with NSLNI. This parameter has not been examined and reported as the independent predictor of NSLNI previously. But Ramjeesingh et al. (9) reported the negatively association of DCIS and SLN involvement and suggested that women with DCIS and small

Table 1. Patient characteristics associated with NSLNI

Characteristics	Group 1: NSLNI (-) n=32 (45.7%)	Group 2: NSLNI (+) n=38 (54.3%)	p
Age (mean±SD)	48.4±11	54.0±13.9	0.07
Tumor localization %, (n)			
Right	50% (16)	31.5% (12)	
Left	50% (16)	68.5% (26)	0.117
Multilocalization %, (n)			
No	93.7% (30)	76.3% (29)	
Yes	6.3% (2)	23.7% (9)	0.046
Microcalcification %, (n)			
No	65.6% (21)	68.4% (26)	
Yes	34.4% (11)	31.6% (12)	0.804
Number of harvested SLNs (mean±SD)	3.37±1.58	2.55±1.17	0.015
Number of harvested axillary nodes (mean±SD)	19.31±10.83	19.21±5.89	0.960
Number of total positive lymph node (mean±SD)	1.33±0.54	8.28±8.55	<0.01

NSLNI: non-sentinel lymph node involvement; MMG: mammography; SLN: sentinel lymph node

Table 2. Pathologic characteristics breast cancer patients

Characteristics	Group 1: NSLNI (-) n=32 (45.7%)	Group 2: NSLNI (+) n=38 (54.3%)	p
Tumour size (cm) (mean±SD)	2.32±0.75	2.46±1.15	0.549
DCIS %, (n)			
Absent	43.7% (14)	71% (27)	
Present	56.3% (18)	29% (11)	0.021
pT %, (n)			
T1	43.7% (14)	39.5% (15)	
T2	56.3% (18)	60.5% (23)	0.717
pN %, (n)			
N1	100% (32)	34.2% (13)	
N2	0% (0)	63.1% (24)	
N3	0% (0)	2.7% (1)	<0.001
HG %, (n)			
HG 1	28.1% (9)	18.4% (7)	
HG 2	40.6% (13)	50% (19)	
HG 3	31.3% (10)	31.6% (12)	0.591
ER %, (n)			
Negative	34.4% (11)	26.3% (10)	
Positive	65.6% (21)	73.7% (28)	0.464
PR %, (n)			
Negative	31.3% (10)	31.6% (12)	
Positive	68.7% (22)	68.4% (26)	0.591
Cerb-B2 %, (n)			
Score 1	78.1% (25)	71% (27)	
Score 2	6.3% (2)	10.6% (4)	
Score 3	15.6% (5)	18.4% (7)	0.753
Ki 67 %, (n)			
≤%15	31.3% (10)	15.7% (6)	
>%15	25% (8)	31.6% (12)	
Unknown	43.7% (14)	52.7% (20)	0,180
LVI %, (n)			
No	56.3% (18)	34.2% (13)	
Yes	43.7% (14)	65.8% (25)	0,064
PNI %, (n)			
No	87.5% (28)	71% (27)	
Yes	12.5% (4)	29% (11)	0,095
SLN metastatic rate (%)*	49.0	71.8	0.01
ECE of SLNs %, (n)			
No	100% (32)	57.9% (22)	
Yes	0% (0)	42.1% (16)	<0.001

*SLN metastatic rate =positive SLNs/ harvested SLNs. NSLNI: non-sentinel lymph node involvement; DCIS: ductal carcinoma in situ; ER: estrogen receptor; PR: progesterone receptor; Cerb-B2: epidermal growth factor receptor 2; LVI: lymphovascular invasion; PNI: perineural invasion; SLN: sentinel lymph node; ECE: extracapsular extension; HG: histologic grade.

Table 3. Multivariate analysis of clinical and pathological characteristics associated with NSLNI

Characteristic	Odds Ratio	95% CI	p
Presence of multilocalization	8.285	0.02-0.92	0.046
Absence of DCIS accompanying invasive cancer	5.464	0.042-0.802	0.024
Number of harvested SLNs	-	-	0.163
SLN metastatic rate (%)	-	-	0.781
ECE of SLNs	-	-	0.998

NSLNI: non-sentinel lymph node involvement; CI: confidence interval; DCIS: ductal carcinoma situ; SLN: sentinel lymph node; ECE: extracapsular extension.

Table 4. Correlation of risk factors (Presence of multilocalization and DCIS accompanying invasive cancer)

Number of risk factors	Group 1: NSLNI (-) (n=32, 45.7%)	Group 2: NSLNI (+) (n=38, 54.3%)	p
0	53.1% (17)	18.4% (7)	0.03
1	46.9% (15)	68.4% (26)	
2	0% (0)	13.2% (5)	

NSLNI: non-sentinel lymph node involvement; DCIS: ductal carcinoma situ

low-grade tumours may not require assessment of SLNs, intraoperatively. Another parameter that we examined was multilocalization. Multifocal/multicentric tumours are described as a presence of two or more discrete tumours in the same breast (in the same quadrant for multifocal tumours and different quadrants for multicentric tumours). As emphasized in the literature, multifocal/multicentric BCs have a higher rates of lymph node metastasis. Andea et al. (10) reported the relation between multifocality and axillary metastases. Similarly, we found multilocalization of the primary tumour as a predictor of NSLNI in the present study. Moreover 81.8% of patients with multilocality had additional axillary metastases. Although the number of patients in this study is low, if all independent predictive factors were present, 100% of cases with positive SLNs were found to have NSLNI+.

The relationship between tumour size and possibility of NSLNI has been reported in many studies. Ozmen et al. (11) found that tumour size larger than 2 cm was associated with higher risk of NSLNI. Also, Joseph et al. (12) demonstrated that primer tumour size was a predictor of NSLNI. The rates of metastatic non-SLNs were 0%, 12% and 47% for patients with T1a, T1b and T1c, respectively. But in the present study we could not find it as a statistically significant feature in both univariate and multivariate analysis. Similarly, Boler et al. (13), Abdessalam et al. (14) and Rahusen et al. (15) could not find an association between tumour size and NSLNI. High histological grade is another parameter that associated with an increased risk of NSLN (16, 17). But we could not find histological grade as a statistically significant predictive factor like previously demonstrated (18, 19).

Although many studies (14, 17) have reported similar results that LVI was enough to predict NSLNI, the univariate analyses revealed no significant differences between LVI and NSLNI in the current study.

Status of steroid receptors (particularly PR, not ER), Her-2 neu and Ki 67 mentioned as an independent predictive factors of axillary lymph node metastases previously (20). Also, we could not demonstrate any association between these parameters and NSLNI in our study.

Hwang et al. (18) reported that an increasing number of harvested SLNs is another parameter that associated with the likelihood of having additional lymph node metastases. Our study validated this association also. Number of positive SLNs and SLN metastatic rate (positive SLNs/ harvested SLNs) are the other demonstrated parameters that associated with NSLNI by two different studies (21, 22). The present study did not examine the number of positive SLNs as a predictor of NSLNI. But the univariate analyses revealed significant differences between two groups in terms of metastatic rate of SLN. Additionally, the significance rates were higher in patients with three or more harvested SLNs. However, the significance was lost in the multivariate analysis.

Size of the metastases in SLNs were usually defined as macrometastases (≤2 mm), micrometastases (≤2 mm) and isolated tumor cells (>2 mm) with the rates of non-SLN positivity, 48%, 23% and 12.5%, respectively (23). Due to the low metastatic rates, in our clinic we do not perform cALND in patients with micrometastases and isolated tumour cells in SLNs already. Therefore, these subjects were not studied in the present study. Besides size of the metastases, ECE of SLNs concerns us about the tumour cells in transit to other sites. ECE in SLN was demonstrated as a significant predictor of increased NSLNI for many times (24). In concordance with previous reports, in our study 100% of patients with ECE had NSLNI while 40.7% of patients without ECE were found to have additional axillary nodal metastases.

Based upon the most of clinicopathological features that mentioned above, many different nomograms have been developed, previously. In 2003, a nomogram by Van Zee et al. (22) from the Memorial Sloan Kettering Cancer Center (MSKCC) was published. This nomogram was based on eight parameters (type, size and grade of tumour, detection method of SLN, LVI, multifocality, ER status and SLN metastatic rate). Stanford model was reported in 2008, for predicting the NSLNI in SLN positive BC patients as another one, Cambridge model (25, 26). In fact, all of these nomograms were based on the synergistic interaction of these factors. But the problem in the practical use of nomograms was that some of the parameters used were not known during the operation such as LVI, ECE of SLN, ER status. Moreover, these nomograms based on the populations own features where they developed so they are in need to be validated in different patient populations. In different studies it was shown that Gur et al. (27) reported that the MSKCC nomogram, Cambridge Formula and Stanford nomogram were good discriminators for Turkish population, in their validation study. However, some other validation studies did not find nomograms reliable particularly for SLNs with micrometastatic involvement (28, 29).

The strengths of this study can be stated as follows. All the operations were applied by experienced surgeons of General Surgery Clinic, Breast and Endocrine Surgery Department. And pathological examinations were done by pathologists with the help of surgeons. Patients with neoadjuvant chemotherapy and more than 6 removed SLNs, who were thought to be able to influence the results of the statistical

analysis were excluded from the study. cALND was performed to all patients with a positive SLN.

On the other hand, the current study reflects the typical features of BC patients. The most important limitations of this study are, insufficient number of patients, the retrospective nature and detection method of SLN. We used only blue dye as a signing method of SLN. But also emphasized in the literature, both radioisotope and blue dye can be used to identify the SLNs in ESBC patients with the rate of 99% (30). With the use of the combined technique, the number of sentinel lymph nodes removed could be increased, which could affect the results in different ways.

In conclusion, this retrospective study demonstrated absence of DCIS accompanying invasive cancer as an independent predictor of NSLNI that has not mentioned in literature previously. Also, presence of multilocalization was found another important predictive factor of the lymph node metastasis. Careful examination of clinicopathologic features can help to decide avoiding cALND if enough lymph nodes are removed and the rate of SLN metastases is low, particularly in patients with presence of DCIS accompanying invasive cancer but without multilocalization. Finally, this study cannot be used to predict the NSLNI in daily clinical practice but may provide insight into new studies. Because there is still an ongoing argument on the predictive factors of axillary LN involvement. Future studies are needed to reveal more accurate subgroups of patients that might be avoided of axillary overtreatment in BC patients with SLN positive.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research Hospital (Number of ethics committee approval: E-17-1429).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.A., B.A.Ö., E.M.; Design – B.A.Ö., E.M., Y.N.Y.; Supervision – Y.N.Y., G.D.; Data Collection and/or Processing – H.A., B.A.Ö., S.Ö.; Analysis and/or Interpretation –E.M., S.Ö., Y.N.Y.; Literature Search – H.A., B.A.Ö., S.Ö.; Writing Manuscript – H.A., E.M.; Critical Review – E.M., Y.N.Y., G.D.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Hennigs A, Köpke M, Feißt M, Riedel F, Rezai M, Nitz U, Moderow M, Golatta M, Sohn C, Schneeweiss A, Heil J. Which patients with sentinel node-positive breast cancer after breast conservation still receive completion axillary lymph node dissection in routine clinical practice? Breast Cancer Res Treat 2019; 173: 429-438. (PMID: 30315437) [Crossref]
2. Karahallı Ö, Acar T, Atahan MK, Acar N, Hacıyanlı M, Kamer KE. Clinical and Pathological Factors Affecting the Sentinel Lymph Node Metastasis in Patients with Breast Cancer. Indian J Surg 2017; 79: 418-422. (PMID: 29089701) [Crossref]
3. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, Ashikaga T, Weaver DL, Mamounas EP, Jalovec LM, Frazier TG, Noyes RD, Robidoux A, Mc Scarth H, Wolmark N. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 11: 927-933. (PMID: 20863759) [Crossref]
4. Janni W, Kühn T, Schwentner L, Kreienberg R, Fehm T, Wöckel A. Sentinel node biopsy and axillary dissection in breast cancer: the evidence and its limits. Dtsch Arztebl Int 2014; 111: 244-249. (PMID: 24766712)
5. Zendejas B, Hoskin TL, Degnim AC, Reynolds CA, Farley DR, Boughey JC. Predicting four or more metastatic axillary lymph nodes in patients with sentinel node-positive breast cancer: assessment of existent risk scores. Ann Surg Oncol 2010; 17: 2884-2891. (PMID: 20429038) [Crossref]
6. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Morrow M, Hunt KK. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. Ann Surg 2016; 264: 413-420. (PMID: 27513155) [Crossref]
7. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijl JHG, Orzalesi L, Bouma WH, van der Mijle HCJ, Nieuwenhuijzen GAP, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JWS, Belkacemi Y, Petignat P, Schinagl DAX, Coens C, Messina CGM, Bogaerts J, Rutgers EJT. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15(12), 1303-1310. (PMID: 25439688)
8. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U; International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013; 14: 297-305. (PMID: 23491275) [Crossref]
9. Ramjeesingh R, Quan ML, Gardner S, Holloway CM. Prediction of involvement of sentinel and nonsentinel lymph nodes in a Canadian population with breast cancer. Can J Surg 2009; 52: 23-30. (PMID: 19234648)
10. Andea AA, BouwmanD, Wallis T, Visscher DW. Correlation of tumor volume and surface area with lymph node status in patients with multifocal/multicentric breast carcinoma. Cancer 2004; 100: 20-27. (PMID: 14692020) [Crossref]
11. Ozmen V, Karanlik H, Cabioglu N, Igci A, Kecer M, Asoglu O, Tuzlali S, Mudun A. Factors predicting the sentinel and non-sentinel lymph node metastases in breast cancer. Breast Cancer Res Treat 2006; 95: 1-6. (PMID: 16322900) [Crossref]
12. Joseph KA, El-Tamer M, Komenaka I, Troxel A, Ditkoff BA, Schnabel F. Predictors of nonsentinel node metastasis in patients with breast cancer after sentinel node metastasis. Arch Surg 2004; 139: 648-651. (PMID: 15197092) [Crossref]
13. Boler DE, Uras C, Ince U, Cabioglu N. Factors predicting the non-sentinel lymph node involvement in breast cancer patients with sentinel lymph node metastases. Breast 2012; 21: 518-523. (PMID: 22410110) [Crossref]
14. Abdessalam SF, Zervos EE, Prasad M, Farrar WB, Yee LD, Walker MJ, Carson WB, Burak WE Jr. Predictors of positive axillary lymph nodes after sentinel lymph node biopsy in breast cancer. Am J Surg 2001; 182: 316-320. (PMID: 11720662) [Crossref]
15. Rahusen FD, Torrenga H, van Diest PJ, Pijpers R, van der Wall E, Licht J, Meijer S. Predictive factors for metastatic involvement of nonsentinel nodes in patients with breast cancer. Arch Surg 2001; 136: 1059-1063. (PMID: 11529831) [Crossref]
16. Bader AA, Tio J, Petru E, Bühner M, Pfahlberg A, Volkholz H, Tulusan AH. T1 breast cancer: identification of patients at low risk of axil-

lary lymph node metastases. Breast Cancer Res Treat 2002; 76: 11-17. (PMID: 12408371) [Crossref]
17. Syed A, Eleti S, Kumar V, Ahmad A, Thomas H. Validation of Memorial Sloan Kettering Cancer Center nomogram to detect non-sentinel lymph node metastases in a United Kingdom cohort. Il G Chir 2018; 39: 12-19. (PMID: 29549676) [Crossref]
18. Hwang RF, Krishnamurthy S, Hunt KK, Mirza N, Ames FC, Feig B, Kuerer HM, Singletary SE, Babiera G, Meric F, Akins JS, Neely J, Ross MI. Clinicopathologic factors predicting involvement of nonsentinel axillary nodes in women with breast cancer. Ann Surg Oncol 2003; 10: 248-254. (PMID: 12679309) [Crossref]
19. Cserni G, Gregori D, Merletti F, Sapino A, Mano MP, Ponti A, Sandrucci S, Baltás B, Bussolati G. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg 2004; 91(10): 1245-1252. (PMID: 15376203) [Crossref]
20. Mustać E, Matušan-Ilijaš K, Marijić B, Smokvina M, Jonjić N. Predicting the likelihood of additional nodal metastases in breast carcinoma patients with positive sentinel node biopsy. Int J Surg Pathol 2010; 18: 36-41. (PMID: 19448065) [Crossref]
21. Wada N, Imoto S, Yamauchi C, Hasebe T, Ochiai A. Predictors of tumor involvement in remaining axillary lymph nodes of breast cancer patients with positive sentinel lymph node. Eur J Surg Oncol 2006; 32: 29-33. (PMID: 16269227) [Crossref]
22. Van Zee KJ, Manasseh DME, Bevilacqua JL, Boolbol SK, Fey JV, Tan LK, Borgen PI, Cody HS 3rd, Kattan MW. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol 2003; 10: 1140-1151. (PMID: 14654469) [Crossref]
23. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, Clark G, Edge SB, Hayes DF, Hughes LL, Hutter RV, Morrow M, Page DL, Recht A, Theriault RL, Thor A, Weaver DL, Wieand HS, Greene FL. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002; 20: 3628-3636. (PMID: 12202663) [Crossref]
24. Gooch J, King TA, Eaton A, Dengel L, Stempel M, Corben AD, Morrow M. The extent of extracapsular extension may influence the need for axillary lymph node dissection in patients with T1-T2 breast cancer. Ann Surg Oncol 2014; 21: 2897-2903. (PMID: 24777858) [Crossref]
25. Kohrt HE, Olshen RA, Bermas HR, Goodson WH, Wood DJ, Henry S, Rouse RV, Bailey L, Philben VJ, Dirbas FM, Dunn JJ, Johnson DL, Wapnir IL, Carlson RW, Stockdale FE, Hansen NM, Jeffrey SS; Bay Area SLN Study. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. BMC Cancer 2008; 8: 66. (PMID: 18315887) [Crossref]
26. Pal A, Provenzano E, Duffy SW, Pinder SE, Purushotham AD. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. Br J Surg 2008; 95: 302-309. (PMID: 17876750) [Crossref]
27. Gur AS, Unal B, Ozbek U. Validation of breast cancer nomograms for predicting the non-sentinel lymph node metastases after a positive sentinel lymph node biopsy in a multi-center study. Eur J Surg Oncol 2010; 36: 30-35. (PMID: 19535217) [Crossref]
28. Alran S, De Rycke Y, Fourchotte V, Charitansky H, Laki F, Falcou MC, Benamor M, Freneaux P, Salmon RJ; Institut Curie Breast Cancer Study Group, Sigal-Zafrani B. Validation and limitations of use of a breast cancer nomogram predicting the likelihood of non-sentinel node involvement after positive sentinel node biopsy. Ann Surg Oncol 2007; 14: 2195-2201. (PMID: 17294071) [Crossref]
29. van la Parra RF, Ernst MF, Bevilacqua JL, Mol SJ, Van Zee KJ, Broekman JM, Bosscha K. Validation of a nomogram to predict the risk of non-sentinel lymph node metastases in breast cancer patients with a positive sentinel node biopsy: validation of the MSKCC breast nomogram. Ann Surg Oncol 2009; 16: 1128-1135. (PMID: 19252954) [Crossref]
30. Newman EA, Newman LA. Lymphatic mapping techniques and sentinel lymph node biopsy in breast cancer. Surg Clin North Am 2007; 87: 353-364. (PMID: 17498531) [Crossref]

Original Article

Eur J Breast Health 2020; 16(3): 198-200
DOI: 10.5152/ejbh.2020.5180

Does Gross Margin Examination Reduce Re-excision Rate in Breast Conservation for Invasive Carcinoma? CALLER Review

Suzanne Hoekstra[1], Diane Stoller[1], Haya Raef[2]
[1]Mercy Hospital, Breast Care Specialists of Maine, Portland, ME, USA
[2]Tufts University, Boston, MA, USA

ABSTRACT

Objective: Determine if Gross Margin Examination reduces margin re-excision rate. Our institutional practice is to perform Gross Margin Examination (GME) with Real-time re-excision (RRE) for all breast conservation specimens with Invasive Carcinoma.

Materials and Methods: Chart review was done to determine if this practice is helpful. 51 CALLER charts were reviewed from December 2016 to December 2017.

Results: Thirty-three underwent margin RRE based on the GME. 11 had cancer in the re-resected margin, 6 of which were cleared with the RRE. The other 5 were reoperated on to clear the margin because on final pathology a margin other than the re-resected margin was positive for malignancy. GME was helpful in preventing reoperation in 55%. None of the remaining 22 patients receiving were found to have a positive margin on final pathology, with 1.6 margins on average re-resected. 13/18 patients did not have RRE and had a final clear margin, but of the other 5, final margin was positive for DCIS in 2 and Invasive Cancer in 3. GME missed invasive disease at the margin in 3 of these 18 patients.

Conclusion: GME was helpful in preventing reoperation in 6 of 11 patients who would have had a positive margin. However, this resulted in the unnecessary removal of additional normal breast tissue in 22 patients. 3 patients' positive margins were missed with GME and required reoperation. 13 patients were able to avoid re-excision and 11 were able to clear their margin in real-time, improving outcomes 24/51 patients. GME therefore does appear useful.

Keywords: CALLER, gross margin examination, re-excision

Cite this articles as: Hoekstra S, Stoller D, Raef H. Does Gross Margin Examination Reduce Re-excision Rate in Breast Conservation for Invasive Carcinoma? CALLER Review. Eur J Breast Health 2020; 16(3): 198-200.

Introduction

Breast-conserving surgery (BCS) is the established standard approach for women with early-stage invasive breast cancers. During BCS, the breast tumor is excised with negative margins, yielding a better cosmetic result. Various factors are associated with tumor recurrence after BCS, including margin status, which has been shown to be a very important prognostic factor for local recurrence (1). A positive margin is correlated with a twofold increase in ipsilateral breast tumor recurrence (2). This risk is not completely eliminated with the addition of local or systemic adjuvant therapy. In addition, patients who develop local recurrence have an increased risk of distant disease, which can impact survival (3).

Delays in adjuvant therapy can also occur when additional surgical procedures are needed to obtain clear margins after breast conservation. Cosmesis is also impacted, and up to 50% of patients requiring multiple re-excisions will opt for completion mastectomy (4, 5).

The assessment of lumpectomy margins is an ongoing issue for breast surgeons. Various techniques and technology have been utilized in an attempt to reduce margin re-excision rates. These include imaging techniques such as margin scans, and specimen radiograph and pathological assessment such as frozen section or cytology. To date, none of these intraoperative approaches have been successful in reliably identifying clear margins, resulting in a global re-excision rate of approximately 25% (6). Intraoperative pathologic techniques have the highest sensitivity and specificity on meta-analysis (7).

Corresponding Author :
Suzanne A. Hoekstra; hoekstras@northernlight.org

Received: 20.12.2019
Accepted: 09.02.2020
Available Online Date: 30.03.2020

The simplest intraoperative pathological technique for evaluating lumpectomy margins is examination of the specimen for gross evidence of the tumor. This method is quick, inexpensive, simple, and any additional suspicious margins can be immediately resected.

We sought to determine if our institution's protocol for intraoperative gross margin assessment was successful in reducing the number of patients requiring re-operation.

Materials and Methods

In 2015, the American Society of Breast Surgeons held a multidisciplinary consensus conference entitled a "Collaborative Attempt to Lower Lumpectomy Reoperation rates" (CALLER) and composed a "toolbox" of options to reduce lumpectomy reoperations (8). They then offered surgeons the opportunity to participate in the CALLER Registry, a one-year period during which patients undergoing breast conservation were entered into a special section of the Mastery of Breast Surgery where certain data points regarding re-excision were captured. We performed a retrospective analysis of our institution's patients entered in the CALLER registry during this time.

The most recent consensus for a clear margin for invasive cancer is "no tumor on ink," and this was utilized as our definition of a clear margin for patients with invasive disease (9). We reviewed the operative notes and surgical pathology for all CALLER registry patients. Notation was made regarding the results of intraoperative margin assessment as well as whether reoperation was needed, and why.

Table 1. Patient cohort

Number of patients	51
Median age group	60-69
Median tumor size group (mm)	10-19 mm
ER positivity	43 (84%)
Triple negative	5 (10%)

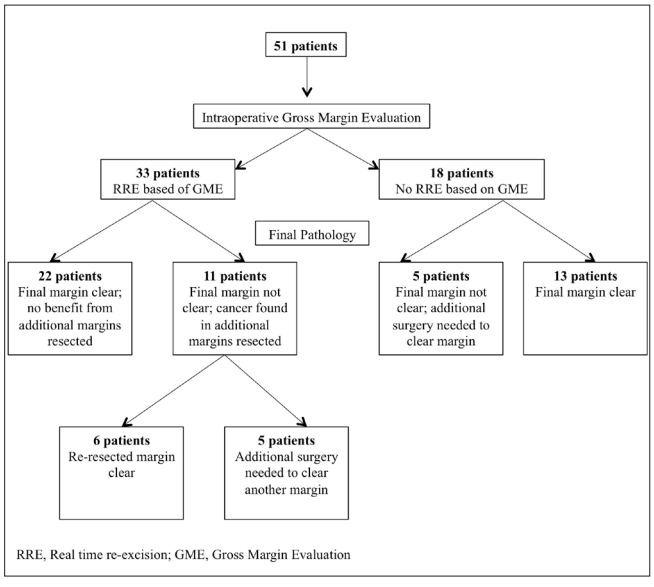

Figure 1. Summary of patient outcomes following gross margin evaluation

Our institutional standard of care is to perform gross margin evaluation (GME) of all lumpectomy specimens done for invasive breast cancer. Each lumpectomy specimen is removed, marked with sutures for orientation, and sent fresh to the pathologist for examination. All lumpectomy specimens were evaluated by a single pathologist. The pathologist inks and sections the specimen. The sections are grossly examined to determine if the tumor appears to be close to or abutting a margin. The pathologist then calls into the operating room and reports the findings, making a recommendation about any margins that might grossly appear to benefit from re-excision. No tissue is frozen or evaluated microscopically. Based on this evaluation, additional margins may be re-resected in real time (RRE) in hopes of avoiding a second operation.

Results

A total of 61 patients were entered into the CALLER Registry from December 2016 to December 2017. 10 of these patients were excluded because they had pure DCIS, resulting in a total of 51 cases of invasive disease analyzed for review. Information on the patient cohort is provided in Table 1.

Of these 51 patients, 33 (65%) underwent margin RRE based on the results of the GME. 11 were found to have cancer in the newly resected margin, and 6 of these had the margin cleared with the RRE. However, the other 5 required a second surgical procedure to completely clear the margins. In all 5 cases this was due to a positive margin other than the one re-excised based on GME based on final pathology. Thus, the GME was helpful in preventing a second operation in only 6 of the 11 patients who had a real-time re-excision.

However, of the other 22 patients who were recommended for and received RRE based on GME, none were found to have a positive margin on the final pathology. The average number of margins resected on these patients was 1.6 as the majority had 1 or 2 margins resected. Thus, the GME did not actually improve the outcome for these patients and increased tissue removed and operative time.

Therefore, of the 33 patients who did receive RRE based on GME, only 6 (18%) of these received a true benefit from the protocol.

Conversely, 18 patients were not recommended to undergo RRE based on GME. Of these patients, the margin was clear on final pathology report in 13 (72%). However, the remaining 5 patients were found to have positive margins at final pathology. Two of these were for DCIS and 3 were for invasive cancer. All but one underwent additional surgery to clear the margins (this patient's margin was anterior and beneath de-epithelialized skin so was felt not to be a candidate for re-excision). Consequently, 3/18 (17%) of patients with invasive disease at the margin were missed during GME.

Overall, of the 51 patients who underwent gross margin evaluation, a total of 19 patients (37%) benefitted from intraoperative gross margin evaluation. This includes the 6 out of 33 patients who underwent RRE based on GME and had a true benefit, and the 13 out of 18 patients who were correctly not recommended for RRE based on GME (Figure 1).

Discussion and Conclusion

Ongoing efforts to decrease the rate of positive margins for patients have been challenging and despite several techniques being explored worldwide, the positive margin continues to be a struggle for patients

who choose breast conservation. Patients must then undergo additional surgical procedures which may reduce cosmesis or delay adjuvant therapy. A number of methods of reducing re-excision rates have been developed. Our institution has a longstanding practice of intraoperative gross margin evaluation with real-time re-excision based on the findings. In our experience, this process does decrease the need for a return to operating room for re-excision for those with invasive disease. A margin positive for DCIS presents an even greater challenge because it is not visualized on GME.

We performed an analysis using data collected from our Mastery of Breast Surgery CALLER registry to determine whether GME reduces re-excision rates for invasive carcinoma. Our analysis revealed an 18% reoperation rate, which compares favorably with other studies, and is below the reported national database average of 25% (6). Balch and colleagues reported a 25% re-excision rate with gross margin assessment, with tumors <2 mm from a margin considered as margin positive (10). Fleming et al. (11) reports a lower re-excision rate of 9.1% with utilization of gross margin assessment, adopting a margin of 10 mm as an acceptable margin. Differences in definitions of margin negativity may influence re-excision rates.

Other intraoperative pathological techniques include frozen section analysis (FSA) of biopsies or cytological examination. A recent systemic review of the literature reported lower re-excision rates with FSA (12). However these methods are more time-consuming, and require further technology or training that may not be necessary if a low margin-positive rate can be achieved with gross evaluation alone.

Ultimately, the use of gross margin examination with real-time re-excision it is not as foolproof and helpful as hoped. It may result in excess tissue removal and increased operative time. Additionally, the specimen needs to be directly transferred to the pathology department for real-time consultation, which is not available in every institution. It also depends on reliable orientation of the specimen by the surgeon to ensure that the correct margin is being excised; incorrect orientation has been shown to lead to incomplete resection (13).

Therefore, each surgeon should consider this option and discuss whether it would be helpful in their institution. Because at least 37% of our patients did benefit from this process, we do plan to continue our current practice of intraoperative gross margin evaluation and remain mindful of its limitations.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.H., D.S.; Design – S.H., D.S.; Supervision – S.H.; Resources – S.H.; Materials – S.H., D.S.; Data Collection and/or Processing - S.H., D.S. H.R.; Analysis and/or Interpretation – S.H., D.S., H.R.; Literature Search – S.H., D.S., H.R.; Writing Manuscript – S.H., D.S., H.R.; Critical Review – S.H., D.S., H.R.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, Gamagami P, Colburn WJ. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 1999; 340: 1455-1461. (PMID: 31774979) [CrossRef]
2. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 2014; 21: 717-730. (PMID: 24473640) [CrossRef]
3. Vicini FA, Kestin L, Huang R, Martinez A. Does local recurrence affect the rate of distant metastases and survival in patients with early-stage breast carcinoma treated with breast-conserving therapy? Cancer 2003; 97: 910-919. (PMID: 12569590) [CrossRef]
4. Cellini C, Huston TL, Martins D, Christos P, Carson J, Kemper S, Simmons RM. Multiple re-excisions versus mastectomy in patients with persistent residual disease following breast conservation surgery. Am J Surg 2005; 189: 662-666. (PMID: 15910716) [CrossRef]
5. Heil J, Breitkreuz K, Golatta M, Czink E, Dahlkamp J, Rom J, Schuetz F, Blumenstein M, Rauch G, Sohn C. Do reexcisions impair aesthetic outcome in breast conservation surgery? Exploratory analysis of a prospective cohort study. Ann Surg Oncol 2012; 19: 541-547. (PMID: 21761099) [CrossRef]
6. Wilke LG, Czechura T, Wang C, Lapin B, Liederbach E, Winchester DP, Yao K. Repeat surgery after breast conservation for the treatment of stage 0 to II breast carcinoma: a report from the National Cancer Data Base, 2004-2010. JAMA Surg 2014; 149: 1296-1305. (PMID: 25390819) [CrossRef]
7. St John ER, Al-Khudairi R, Ashrafian H, Athanasiou T, Takats Z, Hadjiminas DJ, Darzi A, Leff DR. Diagnostic accuracy of intraoperative techniques for margin assessment in breast cancer surgery: A meta-analysis. Ann Surg 2017; 265: 300-310. (PMID: 27429028) [CrossRef]
8. Landercasper J, Attai D, Atisha D, Beitsch P, Bosserman L, Boughey J, Carter J, Edge S, Feldman S, Froman J, Greenberg C, Kaufman C, Morrow M, Pockaj B, Silverstein M, Solin L, Staley A, Vicini F, Wilke L, Yang W, Cody 3rd H. Toolbox to reduce lumpectomy reoperations and improve cosmetic outcome in breast cancer patients: the American Society of Breast Surgeons Consensus Conference. Ann Surg Oncol 2015; 22: 3174-3183. (PMID: 26215198) [CrossRef]
9. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, Klimberg S, Chavez-MacGregor M, Freedman G, Houssami N, Johnson PL, Morrow M. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014; 21: 704-716. (PMID: 24515565) [CrossRef]
10. Balch GC, Mithani SK, Simpson JF, Kelley MC. Accuracy of intraoperative gross examination of surgical margin status in women undergoing partial mastectomy for breast malignancy. Am J Surg 2005; 71: 22-28. (PMID: 15757052)
11. Fleming FJ, Hill AD, Mc Dermott EW, O'Doherty A, O'Higgins NJ, Quinn CM. Intraoperative margin assessment and re-excision rate in breast conserving surgery. Eur J Surg Oncol 2004; 30: 233-237. (PMID: 15028301) [CrossRef]
12. Esbona K, Li Z, Wilke LG. Intraoperative imprint cytology and frozen section pathology for margin assessment in breast conservation surgery: a systematic review. Ann Surg Oncol 2012; 19: 3236-3245. (PMID: 22847119) [CrossRef]
13. Molina MA, Snell S, Franceschi D, Jorda M, Gomez C, Moffat FL, Powell J, Avisar E Breast specimen orientation. Ann Surg Oncol 2009; 16: 285-288. (PMID: 19050966) [CrossRef]

Original Article

Eur J Breast Health 2020; 16(3): 201-207
DOI: 10.5152/ejbh.2020.5536

Features, Outcomes, and Management Strategies of Male Breast Cancer: A Single Institution Comparison to Well-Matched Female Controls

Joseph Liu[1,2], Anupama Suresh[1,2], Marilly Palettas[3], Julie Stephens[3], Akaansha Ganju[1,2], Evan Morgan[1,2], Mahmoud Kassem[1,2], Yanjun Hou[4], Anil Parwani[4], Anne Noonan[1,2], Raquel Reinbolt[1,2], Jeffrey VanDeusen[1,2], Sagar Sardesai[1,2], Nicole Williams[1,2], Mathew Cherian[1,2], Gary Tozbikian[4], Daniel G. Stover[1,2], Maryam Lustberg[1,2], Zaibo Li[4], Bhuvaneswari Ramaswamy[1,2], Robert Wesolowski[1,2]

[1]Stefanie Spielman Comprehensive Breast Cancer, The Ohio State University, Columbus, OH, USA
[2]Division of Medical Oncology, Comprehensive Cancer Center, The Ohio State University Medical Center, Columbus, OH, USA
[3]Center for Biostatistics, Department of Biomedical Informatics, The Ohio State University, Columbus, OH, USA
[4]Department of Pathology, The Ohio State University, Columbus, OH, USA

ABSTRACT

Objective: The primary objective of this study was to delineate differences in management, overall and distant disease-free survival in males diagnosed with breast cancer and treated at The Ohio State University Comprehensive Cancer Center as compared to comprehensively matched female subjects. Secondary objectives included assessment of clinical and histopathologic features and recurrence score, as measured by Oncotype DX and the modified Magee equation #2.

Materials and Methods: This single institution retrospective study compared male and comprehensively matched female patients (1:2) with stage I-III breast cancer between 1994 and 2014. Recurrence risk was estimated using a modified Magee equation. Overall survival and distant disease-free survival were estimated and compared using Kaplan-Meier and Log-rank methods.

Results: Forty-five male breast cancer patients were included (stage I: 26.7%; stage II: 53.3%; stage III: 20.0%; hormone receptor positive: 97.8%; human epidermal growth factor receptor 2 negative: 84.4%) with a median age of 63.8 (43.0-79.4) years at diagnosis. Intermediate and low recurrence scores were most common in male and female patients respectively; mean score was similar between groups (20.3 vs. 19.8). The proportion of male breast cancer patients treated with adjuvant chemotherapy and post-mastectomy radiation was lower compared to female patients (42.2% vs. 65.3%, p=0.013; 22.7% vs. 44.4%, p=0.030, respectively). Overall survival and distant disease-free survival between male and female patients were similar.

Conclusion: Male breast cancer patient outcomes were similar compared to well-matched female patients suggesting that breast cancer specific factors are more prognostic than gender.

Keywords: Male breast cancer, matched-pair analysis, rare disease, recurrence score, survival analysis

Cite this article as: Liu J, Suresh A, Palettas M, Stephens J, Ganju A, Morgan E, et al. Features, Outcomes, and Management Strategies of Male Breast Cancer: A Single Institution Comparison to Well-Matched Female Controls. Eur J Breast Health 2020; 16(3): 201-207.

Introduction

Male breast cancer (MBC) is a rare disease, accounting for approximately 1-2% of all documented breast cancer cases (1). Compared to female breast cancer, MBC generally presents at an older age and later stage, with larger tumor sizes, higher nuclear grades and higher frequency of lymph node involvement (2, 3). Such differences may arise due to the rarity of MBC, resulting in lower patient awareness and subsequent delays in proper diagnostic workup. In addition, there is a lack of level-one evidence for the best management strategies of MBC, as it is exceedingly difficult to accrue sufficient numbers of MBC patients to prospective clinical trials. To date, many MBC studies have been retrospective and descriptive in nature and do not have a formal comparison to female subjects. Larger studies often rely on unmatched population-level comparisons and lack detailed patient management information (4, 5). The few MBC studies that have used matched female cohorts, have often not sufficiently controlled for potential cofounding factors, such as date of diagnosis, age at diagnosis and hormone (HR) or human epidermal growth factor receptor 2 (HER2) receptors status (6-8). As such, current treatment practices for patients with MBC are largely based on extrapolation from clinical trials enrolling female breast cancer patients with a similar stage and histopathologic subtype.

Furthermore, in the MBC literature, it is uncertain whether prognostic genomic tests, such as Oncotype DX recurrence score (RS) (RS; Genomic Health, Redwood City, CA), can be used to help estimate prognosis and identify MBC patients who will benefit from chemotherapy, given that these scores are based on studies performed in female breast cancer patients (9-11). Limited data exists on the utility of

Corresponding Author :
Robert Wesolowski; Robert.Wesolowski@osumc.edu

Received: 24.02.2020
Accepted: 19.04.2020
Available Online Date: 20.05.2020

Oncotype DX for MBC (12-15). As a result, there have been greater strides for women in breast cancer detection, incidence, and mortality compared to men (1, 2).

The main objective of this study was to compare clinical characteristics, treatment practices and outcomes between male and comprehensively matched female patients with breast cancer treated at a single institution, The Ohio State University Comprehensive Cancer Center (OSUCCC). We also obtained the results of Oncotype DX in male and female cohorts, when available, and calculated RS based on modified Magee scores (University of Pittsburgh Medical Center (UPMC) Magee-Women's Hospital), a less expensive and well-validated alternative that estimates RS based on several pathological variables and semi-quantitative immunohistochemical results (16, 17).

Materials and Methods

Study design

This study was a retrospective chart review of clinical and histopathologic data from breast cancer patients seen at the OSUCCC between 1994 and 2014.

Ethical Committee: The study was approved by the Ohio State University Cancer Institutional Review Board (OSU IRB 2015C0153).

Informed Consent: Due to the retrospective nature of the study, a full waiver of the informed consent process was obtained from the Ohio State University Cancer Institutional Review Board.

Eligibility: Eligible patients were identified by ICD-9 code (174.0-174.9) and included MBC patients who received treatment at this institution. Patients with incomplete clinical data and those treated at other institutions were excluded. The MBC cohort was comprehensively matched in a 1:2 ratio to a female cohort (see "Statistical Methods" below for details).

Data collection

Data were initially queried and obtained from The Ohio State University Information Warehouse and uploaded into Research Electronic Data Capture (REDCap) (18). Data missing from the initial query were populated using manual review of each patient's electronic medical record. The following data were extracted from patients' records: demographic information, stage at diagnosis (based on the American Joint Committee on Cancer (AJCC) 7th edition), tumor grade, estrogen receptor (ER) and progesterone receptor (PR) and HER2 status, Oncotype DX RS, location and date of distant metastases, locoregional and systemic management information, date of death and last known follow-up.

Outcomes measures

The primary objective of this study was to delineate differences in management, overall and distant disease-free survival in males diagnosed with breast cancer and treated at the OSUCCC as compared to comprehensively matched female subjects. Secondary objectives included assessment of clinical and histopathologic features and the RS, as measured by Oncotype DX and the modified Magee equation #2. Oncotype DX is a commonly used 21-gene reverse transcription, polymerase chain reaction assay performed on breast tumor tissue that estimates the 10-year risk of recurrence and predicts benefit from chemotherapy (the details have been extensively described previously) (11). The modified Magee equation #2 incorporates tumor grade (based on Nottingham Score), ER and PR expression (based on H-Score), HER2 amplification, and tumor size to give a validated estimate of Oncotype DX RS (16, 19). The equation was derived from a linear regression analysis of a large single-institution patient cohort (n=800). RSs are reported on a scale of 0-100 and used to be categorized into low (<18), intermediate (18-30) and high (>30) (11). More recently, a large prospective study demonstrated that RS of ≤25 and ≤15 were associated with excellent prognosis and lack or benefit from adjuvant chemotherapy in women aged >50 years and ≤50 years respectively (20).

Key Points

- Well matched study between male and female breast cancer with regard to clinical features, management and outcomes.
- Assessment of overall survival and distant disease free survival in both cohorts.
- Description of differences in treatment modalities in both male and female breast cancer cohorts.

Statistical analysis

The MBC cohort included 45 men diagnosed with non-metastatic breast cancer from 1994-2014. The female cohort included randomly selected female breast cancer patients that were matched at a male-to-female ratio of 1:2 (if matched female breast cancer patients were available) on the following criteria: age of diagnosis, year of diagnosis (both within 5 years), stage at diagnosis, ER, PR, and HER2 status. Matching was done using variable optimal matching (vmatch macro) (21). Two female matches were identified for 34 males, one female match for seven males and there were no matches found for four male patients.

Demographic and clinical characteristics as well as treatment modalities were summarized for the two cohorts using descriptive statistics. Comparisons between males and females included treatment management for patients, clinical characteristics of patients (see Data Collection section), and RS. Categorical variables were compared between males and females using either a Chi-square test/Fisher's Exact test, and continuous variables were compared with a two sample t-test/Wilcoxon Rank Sum test. Overall survival (OS) was defined as the time from date of diagnosis to date of death, and distant disease-free survival (DDFS) was defined as the time from date of diagnosis to first metastases or death. Patients were censored at the date last known to be alive. OS and DDFS estimates were generated by sex using Kaplan Meier methods and were compared between sexes using Log-rank tests. All data analyses were performed using suite of analytics software (SAS) 9.4 (SAS Institute Inc., Cary, NC, USA) or Stata 14 (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics

A total of 45 male patients and 75 matched female patients were included in this study. A summary of demographic and clinical characteristics is displayed in Table 1. Both males and females were predominately white (77.8% and 85.3%, respectively). The median age at diagnosis for males and females was 63.8 years and 63.1 years, respectively, and the median body mass index at diagnosis was 31.0 and 29.9, respectively. Male patients were predominantly HR positive and HER2 negative (97.8% were ER and/or PR positive; 8.9% HER2+; 6.7% HER2 unknown; 2.3% Triple Negative) and the majority were stage II at the time of diagnosis (stage I: 26.7%; stage II: 53.3%; stage III: 20.0%). The proportion of patients with pathologically positive

lymph nodes was lower in males than females (46.7% and 57.3%, p=0.225, respectively). Male patients also had a higher proportion of intermediate and high-grade tumors compared to female patients (Low: 13.3% vs. 30.7%; Intermediate: 64.4% vs. 46.7%; High: 22.2% vs 18.7%, respectively). In patients who experienced distant recurrence (n=45 for males and n=75 for females), bone, brain, and liver metastases were more common in women, whereas lung metastases were more common in men (Table 2).

Table 1. Demographic and clinical characteristics of male and female breast cancer patients

Characteristics	Males (n=45) No. (%)	Females (n=75) No. (%)
Age at diagnosis, median (range)	63.8 (43.0-79.4)	63.1 (42.0-79.0)
BMI at diagnosis, median (range)	31.0 (20.0-45.5)	29.9 (16.1-48.5)
Race		
White	35 (77.8)	64 (85.3)
Black	7 (15.6)	9 (12.0)
Other	3 (6.7)	2 (2.7)
Stage		
1	12 (26.7)	21 (28.0)
2	24 (53.3)	37 (49.3)
3	9 (20.0)	17 (22.7)
Grade		
1	6 (13.3)	23 (30.7)
2	29 (64.4)	35 (46.7)
3	10 (22.2)	14 (18.7)
Unknown	0 (0.0)	3 (4.0)
Lymph node status		
Positive	21 (46.7)	43 (57.3)
Negative	24 (53.3)	31 (41.3)
Unknown	0 (0.0)	1 (1.3)
ER status		
Positive	44 (97.8)	73 (97.3)
Negative	1 (2.2)	2 (2.7)
PR status		
Positive	38 (84.4)	64 (85.3)
Negative	5 (11.1)	11 (14.7)
Unknown	2 (4.4)	0 (0.0)
HER2 status		
Positive	4 (8.9)	5 (6.7)
Negative	38 (84.4)	70 (93.3)
Unknown	3 (6.7)	0 (0.0)

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor; SD: standard deviation

Treatment modalities

Table 3 summarizes treatment management of the study cohorts. There were several differences in the management observed between the male and female cohorts. As expected, use of breast-conserving surgery differed significantly, with male patients undergoing mastectomies more frequently than female patients (97.8% vs. 60.0%, p<0.001). No male patients had breast-conserving surgery, compared to 27 female patients (36.0%). Of the patients who underwent a mastectomy, fewer males were treated with radiotherapy compared to matched female patients (22.7% vs. 44.4%; p=0.030). In addition, a lower percentage of males received chemotherapy compared to females (42.2% vs. 65.3%; p=0.013), with similar proportions receiving anthracycline-containing chemotherapy (33.3% vs. 46.7%; p=0.152). However, these observa-

Table 2. Clinical summary of male and female patients with metastatic disease

	Males (n=45) No. (%)	Females (n=75) No. (%)
Site of metastases		
Bone	3 (6.7)	14 (18.7)
Brain	0 (0.0)	3 (4.0)
Liver	2 (4.4)	8 (10.7)
Lung	3 (6.7)	3 (4.0)
Other	0 (0.0)	3 (4.0)

Table 3. Summary of treatment management of male and female breast cancer patients

Treatment	Males (n=45) No. (%)	Females (n=75) No. (%)	p
Surgery			
Complete mastectomy	44 (97.8)	45 (60.0)	
Lumpectomy	0 (0.0)	27 (36.0)	<0.0001
None	1 (2.2)	3 (4.0)	
Radiotherapy	11 (24.4)	47 (62.7)	<0.0001
Post-mastectomy	10 (22.7)	20 (44.4)	0.0302
Chemotherapy	19 (42.2)	49 (65.3)	0.0134
Anthracyclines	15 (33.3)	35 (46.7)	0.1515
Endocrine therapy	41 (91.1)	69 (92.0)	1.0000
Tamoxifen	38 (84.4)	19 (25.3)	<0.0001
AI	10 (22.2)	64 (85.3)	<0.0001
SERD	1 (2.2)	4 (5.3)	0.6492
GnRH agonists	4 (8.9)	3 (4.0)	0.4228
Median (range) duration, months	59.7 (7.7-186.1)[a]	59.5 (0.4-122.3)[b]	0.8141

AI: aromatase inhibitor; GnRH: gonadotropin releasing hormone; SD: standard deviation; SERD: selective estrogen receptor degrader. [a]n=40; [b]n=69

tions may be the result of lower proportion of MBC patients with node positive disease, thus not meeting standard criteria for post-mastectomy radiation and adjuvant chemotherapy.

There was no significant difference in the proportion of endocrine therapy use between male and female patients (91.1% vs. 92.0%, p=0.999). Compared to females, the majority of male patients received tamoxifen (84.4% vs. 25.3%, p<0.001), whereas most female patients received an aromatase inhibitor (AI) (85.3% vs. 22.2%, p<0.001). Crossover between tamoxifen and AI therapy occurred in 8 female patients. There was no difference in median duration of adjuvant hormonal therapy between male and female patients (59.7 months vs. 59.5 months, p=0.814). Adherence to endocrine therapy was similar between the 2 groups with 72.5% MBC patients completing at least 48 months of tamoxifen compared to 63.8% of matched female breast cancer (p=0.350).

Survival

Survival results are summarized in Table 4 and Figure 1 and 2. No difference in the Kaplan-Meier curves was found between males and females in OS or DDFS (OS: p=0.287; DDFS: p=0.318; Figure 1). Among patients receiving chemotherapy, marginal differences were detected in OS and DDFS between males and females favoring male patients (p=0.054 for OS; p=0.045 for DDFS; Figure 2a and b) and no differences were detected in OS or DDFS between males and females treated without chemotherapy (p=0.172; p=0.102; Figure 2c and d).

Table 4. Survival analysis of male and female breast cancer patients

Treatment	Males (n=45) No. (%)	Females (n=74) No. (%)	p
Overall Survival			
Death	8 (17.8)	16 (21.6)	0.287
Median TTD, years	N/A	12.9	
Distant Disease-Free Survival			
Disease progression	9 (20.0)	18 (24.3)	0.318
Median TTP, years	N/A	11.1	

TTD: time to death; TTP: time to progression

Table 5. Recurrence risk calculation using Oncotype DX and the modified Magee equation

	Males	Females	p
Oncotype DX	n=5	n=12	
RS; mean (SD)	18.8 (5.7)	13.7 (9.4)	0.2777
Range	11 - 26	0 - 33	
Modified Magee	n=26	n=47	
RS; mean (SD)	20.3 (6.3)	19.8 (8.1)	0.8222
Low; n (%)	9 (34.6)	23 (48.9)	
Intermediate; n (%)	16 (61.5)	18 (38.3)	0.1620
High; n (%)	1 (3.9)	6 (12.8)	

RS: recurrence score; Low: RS<18; Intermediate: 18≤RS≤30; High: RS>30

Oncotype DX and modified Magee recurrence scores

Table 5 provides the summary of Oncotype DX and Magee scores in the study cohorts. Oncotype DX RSs were available for 5 men (11.1%) and 12 women (16.0%). Due to the low number of Oncotype DX testing performed, the modified Magee equation was used to estimate recurrence risk. The modified Magee recurrence scores could be calculated for 26 men (57.8%) and 47 women (62.7%). Mean scores were similar between male and female cohorts (20.3, range 7.5-31.2, SD 6.3 vs. 19.8, range 8.8-39.4, SD 8.1; p=0.822). There was also no statistically significant difference in the categorized Magee score distribution between males and females, although, the intermediate score was most common in male subjects, while the low score was most common in female subjects (Low: 34.6%; Intermediate: 61.5%; High: 3.9% for males and Low: 48.9%; Intermediate: 38.3%; High: 12.8% for females, p=0.162).

Discussion and Conclusion

This single institution, retrospective study compared clinical and histopathologic features, management, and outcomes between patients with stage I-III MBC and a well-matched female breast cancer cohort. As expected, MBC patients in our study primarily presented with a higher rate of HR-positivity (97.8%) and a lower rate of HER2 amplification (8.9%) compared to historical female breast cancer data (approximately 75% HR+; 18-25% HER2+) (6, 22, 23). Results sug-

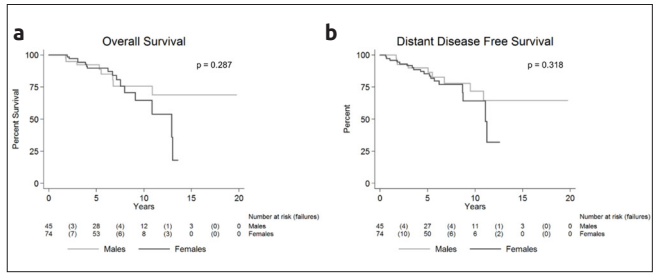

Figure 1. a, b. Survival estimates in male and female study subjects. (a) Overall survival. (b) Distant disease-free survival

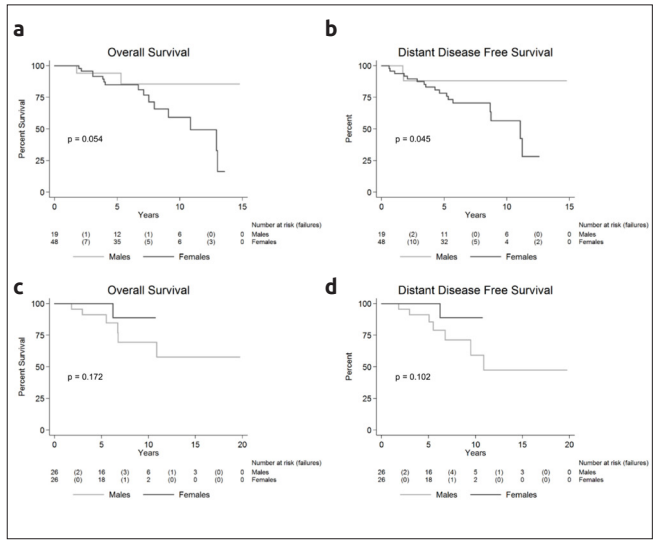

Figure 2. a-d. Overall and distant disease-free survival between male and female patients based on receipt of chemotherapy. (a) Overall survival in patients treated with chemotherapy. (b) Distant disease-free survival in patients treated with chemotherapy. (c) Overall survival of patients not treated with chemotherapy. (d) Distant disease-free survival of patients not treated with chemotherapy

gested no overall differences in OS or DDFS, but there were important differences in the management of cancer between the two cohorts. For instance, while the use of hormone therapy overall did not differ between the male and female cohorts (as expected tamoxifen was used much more frequently in male subjects) the rate of breast conserving surgery and adjuvant chemotherapy was significantly lower in male patient compared to well match female subjects.

Use of tamoxifen as adjuvant endocrine therapy for MBC is in line with contemporary best practices as evidenced by a strong preference for tamoxifen use over AIs in most previously published reports (2, 7, 24). The median duration of endocrine therapy was similar between MBC and female breast cancer patients and approached the 5-year standard of care at the time. Furthermore, 72.5% MBC patients in our study completed at least 48 months of tamoxifen compared to 63.8% of matched female breast cancer (p=0.350). Tamoxifen adherence (defined as ≥ 80%) in female breast cancer is associated with improved OS (25). Local treatment for breast cancer differed between the two cohorts, with every male patient in this study who had breast surgery for operable cancer undergoing a mastectomy, a finding comparable to existing literature (24, 26). There are several explanations for this finding, including the scarcity of breast tissue and tendency for men to present with more advanced disease, including larger tumor size and higher rates of chest wall and retro-areolar infiltration (27). Furthermore, the results show that the proportion of males on adjuvant radiotherapy after mastectomy was much lower compared to females. Existing literature has reported anywhere between 3-100% of male patients received adjuvant radiotherapy and are largely heterogeneous in their conclusions, some of which are artifacts of high prevalence of advanced disease with axillary nodal involvement (28-33). The lower proportion of lymph node positivity in male patients relative to female patients in our study may confound our observations. There was no significant difference in OS or DDFS between male and female cohorts in this study. Previous retrospective studies also found no difference in OS or progression-free survival in MBC compared to female breast cancer when matched by age and stage (3, 4, 34, 35). Therefore, long-term outcomes of male patients may not be significantly different from female patients when matched for stage, HR and HER2 status, age of diagnosis, and other prognostic factors, despite significant differences in management.

Since most prognostic tests are based on female study populations and do not account for sex-based genomic or molecular disparities, differences in RS as determined by Oncotype DX for male and female breast cancer are an important area of active research (13, 36, 37). A recent study of 322 men demonstrated that MBC patients are dissimilar in terms of prognostic information contained within the Oncotype DX RS results. Among breast cancer patients with high RSs (RS ≥31), the 5-year breast cancer-specific survival was significantly lower for MBC than female patients (12). In order to address RS discrepancies between the male and female breast cancer patients, we assessed RSs with a modified Magee equation (16). We found that overall, modified Magee scores were similar between male and female cohorts. However, male patients more commonly had intermediate RSs, while matched female patients more commonly had low RSs. These minor differences may be attributed to variation in tumor biology as measured by the unmatched Magee score parameters, namely H-score and tumor grade. Unfortunately, due to a small sample size, we were unable to compare DDFS and OS between low, intermediate and high Magee recurrence scores. Interestingly, there was discrepancy in chemotherapy use based on RS as calculated by Magee equation with higher proportion of female breast cancer patients treated with adjuvant chemotherapy across all RS categories. Within the low RS group, 22% of MBC patients (2 out of 9) and 35% female patients (8 of 23) had chemotherapy. In the intermediate category, 50% of males and 83% of female patients had chemotherapy. The high RS group had no MBC patient who had chemotherapy, while 5 out of 6 female patients (83%) had adjuvant chemotherapy.

We feel that the biggest strength of present study is the use of a cohort of female breast cancer patients that were well-matched to the male patients: the majority of male patients were matched with two females based on age of diagnosis (within five years), year of diagnosis (within five years), stage at diagnosis, ER, PR, and HER2 status. There are, however, some limitations of this analysis that are worth noting. The study spans a large time frame, during which standard therapies for breast cancer have changed. However, we attempted to minimize the effect of the diagnosis date by matching patients that were diagnosed within 5 years of each other. Despite this comprehensive matching used in this study, less stage IIA MBC patients had node positive disease than stage IIA female patients, which could explain imbalances in the proportion of patients receiving post-mastectomy radiation and adjuvant chemotherapy. In addition, although a broad time frame was used to capture cases, the number of male cases was relatively small which prevented analysis of the association between survival and RSs and limits the generalizability of the survival analysis. Furthermore, the paucity of histopathological data in certain patients limited our use of the modified Magee equation and resulted in about 45% of cases missing RSs.

In conclusion, the rarity of MBC makes it very challenging to study this population in either randomized clinical trials or cohort studies. Aside from the International Male Breast Cancer Program of the European Organization for Research and Treatment of Cancer (EORTC), this study is one of the largest matched cohort studies to date. Results highlight that there is no significant difference in overall or distant disease-free survival, despite some differences in management of the disease between male and well-matched female breast cancer patients. This suggests that breast cancer specific factors rather than gender play a role in patient outcome and early detection and appropriate treatment are critical factors affecting survival of male patients with breast cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ohio State University Cancer Institutional Review Board (OSU IRB 2015C0153).

Informed Consent: Due to the retrospective nature of the study, a full waiver of the informed consent process was obtained from the Ohio State University Cancer Institutional Review Board.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.W., B.R.; Design – J.L.; Supervision – R.W., B.R.; Resources – R.W.; Materials – J.L., M.P., J.S.; Data Collection and/or Processing – J.L., A.S., A.G., E.M., M.K.; Analysis and/or Interpretation – J.S., M.P., J.L., E.M., M.K.; Literature Search – J.L., A.S., A.G., E.M., M.K.; Writing Manuscript – J.L., A.S., M.P., J.S., A.G., E.M., M.K., Y.H., A.P., A.N., R.R., J.vD., S.S., N.W., M.C., G.T., D.G.S., M.L., Z.L., B.R., R.W.; Critical Review – Y.H., A.P., A.N., R.R., H.V., S.S., N.W., M.C., G.T., D.S., M.L., Z.L., B.R., R.W.

Acknowledgements: The project described was supported by the Stefanie Spielman Fund for Breast Cancer Research. Additional support was provided by the National Center for Advancing Translational Sciences [grant number UL1TR002733]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Surveillance E. End Results (SEER) Program Research Data (1973-2015), (www.seer.cancer.gov). 2018.
2. Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male breast cancer: a population-based comparison with female breast cancer. JCO 2010; 28: 232-239. (PMID:19996029) [CrossRef]
3. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population- based study. Cancer 2004; 101: 51-57. (PMID:15221988) [CrossRef]
4. Bradley KL, Tyldesley S, Speers CH, Woods R, Villa D. Contemporary systemic therapy for male breast cancer. Clin Breast Cancer 2014; 14: 31-39. (PMID:24220158) [CrossRef]
5. Leone JP, Leone J, Zwenger AO, Iturbe J, Vallejo CT, Leone BA. Prognostic significance of tumor subtypes in male breast cancer: a population-based study. Breast Cancer Res Treat 2015; 152: 601-609. (PMID: 26126972) [CrossRef]
6. Scott-Conner CE, Jochimsen PR, Menck HR, Winchester DJ. An analysis of male and female breast cancer treatment and survival among demographically identical pairs of patients. Surgery 1999; 126: 775-781. (PMID:10520928) [CrossRef]
7. Eggemann H, Altmann U, Costa SD, Ignatov A. Survival benefit of tamoxifen and aromatase inhibitor in male and female breast cancer. J Cancer Res Clin Oncol 2018; 144: 337-341. (PMID:29098396) [CrossRef]
8. Cui Q, Kong D, Li Z, Ahiable P, Wang K, Wu K, Wu G. Dachshund 1 is differentially expressed between male and female breast cancer: a matched case-control study of clinical characteristics and prognosis. Clin Breast Cancer 2018; 18: e875-882. (PMID:29478945) [CrossRef]
9. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, Cronin M, Baehner FL, Watson D, Bryant J, Costantino JP, Geyer Jr CE, Wickerham DL, Wolmark N. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006; 24: 3726-3734. (PMID:16720680) [CrossRef]
10. Nguyen MT, Stessin A, Nagar H, D'Alfonso TM, Chen Z, Cigler T, Hayes MK, Shin SJ. Impact of oncotype DX recurrence score in the management of breast cancer cases. Clin Breast Cancer 2014; 14: 182-190. (PMID:24486121) [CrossRef]
11. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004; 351: 2817-2826. (PMID:15591335) [CrossRef]
12. Massarweh SA, Sledge GW, Miller DP, McCullough D, Petkov VI, Shak S. Molecular characterization and mortality from breast cancer in men. J Clin Oncol 2018; 36: 1396. (PMID:29584547). [CrossRef]
13. Shak S, Palmer G, Baehner FL, Millward C, Watson D, Sledge Jr GW. Molecular characterization of male breast cancer by standardized quantitative RT-PCR analysis: first large genomic study of 347 male breast cancers compared to 82,434 female breast cancers. J Clin Oncol 2009; 27: 549.
14. Rayson D, Erlichman C, Suman VJ, Roche PC, Wold LE, Ingle JN, Donohue JH. Molecular markers in male breast carcinoma. Cancer 1998; 83: 1947-1955. (PMID: 9806653).
15. Piscuoglio S, Ng CK, Murray MP, Guerini-Rocco E, Martelotto LG, Geyer FC, Bidard FC, Berman S, Fusco N, Sakr RA, Eberle CA, De Mattos-Arruda L, Macedo GS, Akram M, Baslan T, Hicks JB, King TA, Brogi E, Norton L, Weigelt B, Hudis CA, Reis-Filho JS. The genomic landscape of male breast cancers. Clin Cancer Res 2016; 22: 4045-4056. (PMID: 26960396) [CrossRef]
16. Klein ME, Dabbs DJ, Shuai Y, Brufsky AM, Jankowitz R, Puhalla SL, Bhargava R. Prediction of the Oncotype DX recurrence score: use of pathology-generated equations derived by linear regression analysis. Mod Pathol 2013; 26: 658-664. (PMID: 23503643) [CrossRef]
17. Equations M. Available at: http://path.upmc.edu/onlineTools/magee-equations.html. 2018.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42: 377-381. (PMID: 18929686) [CrossRef]
19. Flanagan MB, Dabbs DJ, Brufsky AM, Beriwal S, Bhargava R. Histopathologic variables predict Onco type DX™ Recurrence Score. Mod Pathol 2008; 21: 1255-1261. (PMID: 18360352) [CrossRef]
20. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer Jr CE, Dees EC, Goetz MP, Olson Jr JA, Lively T, Badve SS, Saphner TJ, Wagner LI, Whelan TJ, Ellis MJ, Paik S, Wood WC, Ravdin PM, Keane MM, Moreno HLG, Reddy PS, Goggins TF, Mayer IA, Brufsky AM, Toppmeyer DL, Kaklamani VG, Berenberg JL, Abrams JA, Sledge Jr GW. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018; 379: 111-121. (PMID: 29860917)
21. Division of Biomedical Statistics and Informatics - Locally Written SAS Macros. Mayo Clinic Available at: http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros. (Accessed: 8th June 2018).
22. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. Breast Cancer Res Treat 2002; 76: 27-36. (PMID: 12408373) [CrossRef]
23. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, Levin WJ, Stuart SG, Udove J, Ullrich A. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989; 244: 707-712. (PMID: 2470152) [CrossRef]
24. Cutuli B, Le-Nir CC, Serin D, Kirova Y, Gaci Z, Lemanski C, De Lafontan B, Zoubir M, Maingon P, Mignotte H, Tunon de Lara C, Edeline J, Penault-Llorca F, Romestaing P, Delva C, Comet B, Belkacemi Y. Male breast cancer. Evolution of treatment and prognostic factors. Analysis of 489 cases. Crit Rev Oncol Hematol 2010; 73: 246-254. (PMID: 19442535) [CrossRef]
25. McCowan C, Shearer J, Donnan PT, Dewar JA, Crilly M, Thompson AM, Fahey TP. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. Br J Cancer 2008; 99: 1763-1768. (PMID: 18985046) [CrossRef]
26. Fogh S, Kachnic LA, Goldberg SI, Taghian AG, Powell SN, Hirsch AE. Localized therapy for male breast cancer: functional advantages with comparable outcomes using breast conservation. Clin Breast Cancer 2013; 13: 344-349. (PMID: 23891587) [CrossRef]
27. Patten DK, Sharifi LK, Fazel M. New approaches in the management of male breast cancer. Clin Breast Cancer 2013; 13: 309-314. (PMID: 23845572) [CrossRef]
28. Cutuli B, Lacroze M, Dilhuydy JM, Veiten M, De Lafontan B, Marchal C, Resbeut M, Graic Y, Campana F, Moncho-Bernier V. Male breast cancer: results of the treatments and prognostic factors in 397 cases. Eur J Cancer 1995; 31: 1960-1964. (PMID: 8562148) [CrossRef]
29. Chakravarthy A, Kim CR. Post-mastectomy radiation in male breast cancer. Radiother Oncol. 2002; 65: 99-103. (PMID: 12443805) [CrossRef]
30. Borgen PI, Wong GY, Vlamis VA, Potter CH, Hoffmann BR, Kinne DW, Osborne MP, McKinnon WM. Current management of male breast cancer. A review of 104 cases. Ann Surg 1992; 215: 451-9. (PMID: 1319699) [CrossRef]

31. Stierer M, Rosen H, Weitensfelder W, Hausmaninger H, Teleky B, Jakesz R, Fruhwirth H, Dünser M, Beller S, Haid A. Male breast cancer: Austrian experience. World J Surg 1995; 19: 687-692. (PMID: 7571664) [CrossRef]
32. Stranzl H, Mayer R, Quehenberger F, Prettenhofer U, Willfurth P, Stöger H, Hackl A. Adjuvant radiotherapy in male breast cancer. Radiother Oncol 1999; 53: 29-35. (PMID: 10624850) [CrossRef]
33. Hultborn R, Friberg S, Hultborn KA, Peterson LE, Ragnhult I. Male Breast Carcinoma: II. A study of the total material reported to the Swedish Cancer Registry 1958--1967 with respect to treatment, prognostic factors and survival. Acta Oncol 1987; 26: 327-341. (PMID: 3322330) [CrossRef]
34. Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, Bartlett JMS, Gelmon K, Nahleh Z, Bergh J, Cutuli B, Pruneri G, McCaskill-Stevens W, Gralow J, Hortobagyi G, Cardoso F. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010; 28: 2114-2122. (PMID: 20308661) [CrossRef]
35. Ribeiro GG, Swindell R, Harris M, Banerjee SS, Cramer A. A review of the management of the male breast carcinoma based on an analysis of 420 treated cases. Breast 1996; 5: 141-146. [CrossRef]
36. Grenader T, Yerushalmi R, Tokar M, Fried G, Kaufman B, Peretz T, Geffen DB. The 21-gene recurrence score assay (Oncotype DX™) in estrogen receptor-positive male breast cancer: experience in an Israeli cohort. Oncology 2014; 87: 1-6. (PMID: 24970679) [CrossRef]
37. Turashvili G, Gonzalez-Loperena M, Brogi E, Dickler M, Norton L, Morrow M, Wen HY. The 21-gene recurrence score in male breast cancer. Ann Surg Oncol 2018; 25: 1530-1535. (PMID: 29520654) [CrossRef]

Original Article

Eur J Breast Health 2020; 16(3): 208-212
DOI: 10.5152/ejbh.2020.5659

Breast Cancer in Patients 80 Years-Old and Older

Aaron Bertolo[1], Christopher Rosso[2], Ioannis A. Voutsadakis[3,4]

[1]St. George University School of Medicine, Grenada
[2]Algoma University, Sault Ste. Marie, Ontario, Canada
[3]Algoma District Cancer Program, Sault Area Hospital, Sault Ste. Marie, Ontario, Canada
[4]Section of Internal Medicine, Division of Clinical Sciences, Northern Ontario School of Medicine, Sudbury, Ontario, Canada

ABSTRACT

Objective: Breast cancer is the most common cancer in women and one in ten patients affected are over age 80. However, this age group is mostly excluded from clinical trials and data to inform their care is sparse.

Materials and Methods: Medical records of all patients aged 80 years-old and older diagnosed and treated for breast cancer in a single center over a six-year period were retrospectively reviewed. A cohort of patients aged 65 to 75 treated for breast cancer at the same center during the same period was also reviewed for comparison.

Results: Patients in the 80 and over age group were commonly diagnosed with stage II or III disease (39.2%) compared to younger patients who were diagnosed more commonly (61.6%) with stage I disease. Sub-types of breast cancer had a similar representation in the two groups. Hormonal therapy was used equally in the two groups, but significantly fewer patients in the 80 and over age group had radiation therapy and chemotherapy as part of their treatment. Despite these differences, recurrence rates were not significantly different between the two groups.

Conclusion: Individualized treatments taking into consideration the patient's general status, comorbidities and life expectancy are feasible in the older breast cancer population and result in outcomes similar to those of younger patients in the short and intermediate terms.

Keywords: Breast cancer, chemotherapy, geriatric, octogenarians, radiotherapy, retrospective

Cite this articles as: Bertolo A, Rosso C, Voutsadakis IA. Breast Cancer in Patients 80 Years-Old and Older. Eur J Breast Health 2020; 16(3): 208-212.

Introduction

Cancer is commonly a disease of the old and the median age at diagnosis of all sites is 65 years-old, according to U.S. SEER data (1). Several common cancers, such as lung carcinomas, prostate cancer, and gastrointestinal cancer, present at the median age of 65 years and older. Although the median age at presentation of breast cancer is 61 years, 45% of breast cancer patients are 65 years and older (2). Older patients (≥80 years-old) constitute a significant percentage of these patients. About one in four patients with breast cancer above age 65 or 10.6% of the total breast cancer population is 80 years-old or older (3). This age group often presents challenges in their treatment because of comorbidities and frailty. Studies have also found that diagnosis is commonly delayed due to reduced screening (4). Challenges include cardiovascular and cerebrovascular comorbidities that preclude general anesthesia for surgical treatment and may increase adverse effects of chemotherapy treatment. Many patients, especially in the older part of the age spectrum (>85 years-old), would not be considered for chemotherapy treatment by most oncologists, even when an oncologic indication exists, because of a perceived or actual increase in adverse effects of such therapy. Elderly patients may also be more prone to the adverse effects of hormonal treatment, such as neurocognitive function decline and aromatase inhibitor-associated osteoporosis. Overall, these challenges could lead to inferior outcomes of breast cancer in the elderly, and such outcomes may be improved by better-tailored therapies that take into consideration the functional status and organ reserves of the individual patient rather than the numeric age (5).

A few older and more contemporary studies have addressed the particular presentation and treatment characteristics of breast cancer in the older population (6-9). Breast cancer in this population tends to present later and may receive less than standard surgical treatment due to comorbidities or perceptions of the surgeon (5). They also tend to receive less often chemotherapy or radiation (7).

Corresponding Author :
Ioannis A. Voutsadakis; ivoutsadakis@yahoo.com; ivoutsadakis@nosm.ca

Received: 27.03.2020
Accepted: 24.04.2020
Available Online Date: 21.05.2020

Further information on clinical, sub-type and therapy characteristics in a modern series of elderly breast cancer patients is presented in this paper and comparisons are drawn with younger patients treated concomitantly in a single center. As options of systemic treatment beyond hormonal therapy and chemotherapy increase in breast cancer and include targeted treatments and immunotherapy, an improved understanding of the disease in the elderly will help with better tailoring of therapies (10, 11).

Materials and Methods

A retrospective review of patient case records was performed to identify patients over 80 years-old treated for breast cancer at our center between August 2013 and March 2019. Charts were reviewed, and data on key demographic and tumor characteristics of interest were recorded and analyzed. A similar group of patients with breast cancer but aged 65 to 75 treated at the same period were selected and analyzed for comparison. For each patient older than 80 years of age, a patient aged 65 to 75 included in the database and diagnosed as close as possible was selected for inclusion in the comparison group. Demographic data were captured from patient medical records, as well as data on the histologic characteristics of tumors, stage, tumor markers and molecular characteristics, including Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) expression. Histoscores for ER and PR were calculated as the product of the percentage of cells staining positive for the receptors multiplied by the staining intensity (strong intensity= 3, moderate intensity = 2, weak intensity of staining= 1). Data on patient treatments and outcomes were also extracted from electronic medical records.

Statistical analysis

Descriptive statistics were used for the summary of the variables of interest. The x^2 test or Fisher's exact test was used to evaluate differences in clinical and biologic characteristics of patients with or without outcomes of interest. Continuous parameters were compared with the t test. The Kaplan-Meier method was used for the construction of OS and PFS curves. All resulting p values were considered to be significant at the level of $p<0.05$.

The protocol of the study was approved by the Research Ethics Board of the institution (# 2019-07-01).

Results

Ninety-seven patients 80 years-old and older (older group) were treated for a breast cancer and are analyzed. A similar group of breast cancer patients age 65 to 75 (younger group) treated over the same period were analyzed as a comparison. The median age of the older group was 85 years-old (range, 80-97). Eighty-five patients (87.6%) were 80 to 89 years-old, and 12 patients (12.4%) were 90 years-old and older. The median age of the younger group was 70 years-old (range, 65-75) (Table 1). A significantly higher percentage of older patients (88.7%) had their cancer diagnosed clinically as opposed to diagnosis through screening compared with the younger patient group in whom the cancer was most commonly (54.5% of cases) diagnosed with screening. Consistently, there was also a difference in the two groups in the stage of cancer at diagnosis. Most breast cancers in the younger group (67.7%) were diagnosed as in situ disease or stage I, whereas in the older group, this percentage was 43.3% (p=0.01, Table 1). A significant proportion of the older patients (15.4%) were not completely staged pathologically as no intervention beyond the biopsy of the primary tumor was performed. No significant differences were observed between the groups in tumor grade, histologic type or biologic sub-type. There were also no significant differences between the groups regarding ER and PR positivity.

The older group also exhibited a heavier comorbidity burden than the younger group, including heart disease and kidney disease and a trend (although not statistically significant) for higher rates of hypertension and diabetes (Table 2). The median number of comorbidities was 3 (range, 0-10) in the older group and 2 (range, 0-10) in the younger group ($p<0.0001$). Patients in the older age group were receiving a higher average number of medications (median: 5, range: 0-14) than patients in the younger group (mean: 3, range: 0-13, p=0.001).

The older group of patients received more commonly a mastectomy (33% of patients versus 23.2% of patients in the younger group), whereas the reverse was true for a lumpectomy (p=0.02, Table 3). Older patients had also more commonly no surgical intervention at all (15.5% of patients) or no axillary intervention (sentinel node biopsy or dissection). Among adjuvant therapies, hormonal therapy was equally used between the groups; however, adjuvant radiation and chemotherapy were less used in the older group (33% versus 75.8% for radiation and 11.3% versus 35.4% for chemotherapy, Table 3).

The median follow-up in the older group was 22.6 months (range, 0-120 months), and the median follow-up in the younger group was 34.8 months (range, 0-135 months). Outcomes were overall positive in both groups, with 13 patients in the older group and four patients in the younger group having tumor recurrence or progression. Overall Survival (OS) was acceptable for both groups but better for the younger group due to competing causes of death in the older patients (Figure 1).

Key Points

- Occurrence of breast cancer should not be underestimated in the population of women above 80 years of age.
- Breast cancer is diagnosed more commonly clinically rather than with screening in women older than 80 years of age.
- The biology of breast cancer is not significantly different in women 80 years-old and older compared with younger post-menopausal women.
- Breast cancer patients 80 years-old and older receive hormonal therapies in a comparative rate with younger patients but they receive radiation therapy and chemotherapy less commonly than younger counterparts.

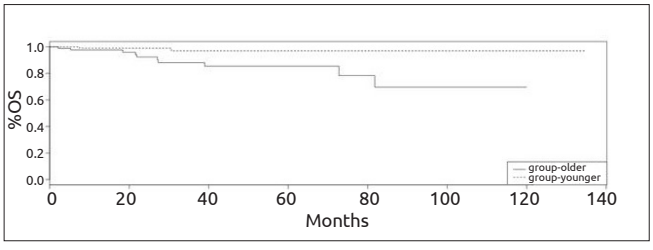

Figure 1. Overall Survival of patients with breast cancer over 80 years-old (group-older) versus patients 65 to 75 years-old (group-younger). Log Rank p=0.007

Table 1. Patient and disease characteristics in patients with breast cancer over 80 years-old versus patients 65 to 75 years-old

	Group >80	Group 65-75	p
Age			
Median age at diagnosis (range)	85 (80-97)	70 (65-75)	
Mode of Detection			
Screening	11 (11.3%)	54 (54.5%)	<0.000
Clinical	86 (88.7%)	45 (45.5%)	
Stage			
0	8 (8.2%)	6 (6.1%)	0.01
I	34 (35.1%)	61 (61.6%)	
II	35 (36.1%)	22 (22.2%)	
III	3 (3.1%)	8 (8.1%)	
IV		2 (2.1%)	1 (1%)
N/A	15 (15.4%)	1 (1%)	<0.000
Size			
Median size (cm) (range)	2.4 (0.5-10)	2.0 (0.2-11.2)	0.13
Grade			
1	8 (8.2%)	13 (13.1%)	0.82
2	36 (37.1%)	43 (43.5%)	
3	28 (28.9%)	34 (34.3%)	
N/A	25 (25.8%)	9 (9.1%)	
Histology			
Ductal	67 (69.1%)	63 (63.6%)	0.10
Lobular	9 (9.2%)	15 (15.2%)	
Mixed	3 (3.1%)	11 (11.1%)	
Other	6 (6.2%)	10 (10.1%)	
N/A	12 (12.4%)	0	
Sub-Type			
ER+/HER2-	71 (73.2%)	72 (72.7%)	0.74
HER2+	12 (12.4%)	12 (12.1%)	
Triple Negative	6 (6.2%)	9 (9.1%)	
N/A	8 (8.2%)	6 (6.1%)	

The second comparison in stage refers to all patients clinicopathologically staged versus not staged
N/A: not available; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2

Table 2. Comorbidities and polypharmacy in the group of patients with breast cancer over 80 years-old versus patients 65 to 75 years-old

Comorbidities	Group >80	Group 65-75	p
Heart disease	37 (38.1%)	13 (13.1%)	<0.000
Diabetes	25 (25.8%)	15 (15.2%)	0.065
Hypertension	58 (59.8%)	47 (47.5%)	0.08
Lung disease	18 (18.6%)	17 (17.2%)	0.80
Kidney disease	10 (10.3%)	2 (2%)	0.01
Previous cancer	13 (13.4%)	11 (11.1%)	0.62
Median number of comorbidities (range)	3 (0-10)	2 (0-10)	<0.00
Polypharmacy			
Median number of medications (range)	5 (0-14)	3 (0-13)	0.001

Table 3. Cancer treatments in the group of patients with breast cancer over 80 years-old versus patients 65 to 75 years-old

Treatment	Group >80	Group 65-75	p
Surgery			
Lumpectomy	50 (51.5%)	74 (74.8%)	0.02
Mastectomy	32 (33%)	23 (23.2%)	
None	15 (15.5%)	2 (2%)	<0.000
No axillary intervention	19 (19.6%)	7 (7.1%)	0.01
Hormonal therapy	69 (71.1%)	74 (74.7%)	0.56
Radiation	32 (33%)	75 (75.8%)	<0.000
Chemotherapy	11 (11.3%)	35 (35.4%)	<0.000

In the surgery comparisons the first comparison refers to lumpectomy versus mastectomy and the second comparison refers to any surgery (lumpectomy or mastectomy) versus no surgery

Discussion and Conclusion

Octogenarians represent about one in ten patients with breast cancer. In the age group 80 to 84 years-old the incidence of breast cancer per 100,000 people is about 400, which is similar to the incidence for the 75 to 79 age range and much higher than the incidence in women 50 to 54 years-old in whom the incidence is just above 200 per 100,000 people (12). The disease may differ biologically in patients 80 years old and older. In addition, treatments in this instance have to take into consideration the particularities of this older population.

In this report, we investigated the characteristics, treatment and outcomes of breast cancer in octogenarians and nonagenarians and compared them with a similar group of younger patients aged 65 to 75 who were treated at our center during the same period. The main findings included that older patients were more commonly diagnosed clinically and with a stage II or III disease compared with younger patients who were diagnosed more commonly with screening and with stage I disease. Additionally, there were no significant differences in the histology or sub-type of tumors in the two groups. Older patients, as expected, had a higher number of comorbidities and took on average 1.5 more medications than younger patients. Regarding therapy, the group aged 80 and older underwent more commonly a mastectomy or no surgery

as their primary surgical treatment, and a significant proportion, about one in five patients, did not have an axillary intervention. Radiation and chemotherapy were also used less in the older group compared with younger counterparts, aged 65 to 75.

Given that guidelines do not advocate for the screening of breast cancer in women older than 75 or with a life expectancy of fewer than 10 years (13, 14), the finding of more advanced stage at diagnosis in older patients should not come as a surprise and is consistent with a higher percentage of clinically diagnosed cancers in these patients. Randomized trials of screening mammography have not included women above age 75 and only one trial included women above age 70 (15). Thus, benefit of screening in reducing mortality in women age 80 and above is uncertain.

Molecular characteristics of breast cancer in patients 80 years-old and older are similar in the older and younger group. This finding is consistent with the results of another series that compared 83 octogenarian breast cancer patients with a group of 249 breast cancer patients 60 to 70 years-old (7). In this series, hormone receptor-positive cancers were equally prevalent in patients older than 80 compared with patients aged 60 to 70 and similar to the prevalence of hormone receptor positivity in the current series. HER2 positivity was also not significantly different in the two groups (7). An additional report of 124 patients 80 years-old and older also confirmed HER2 positivity in 12% (16). Another series compared women with breast cancer above 60 years-old with counterparts between ages 40 and 59 and those below age 40 (16). It found that the group diagnosed at age above 60 years-old had a higher percentage of ER/ PR positive tumors than patients aged 40 to 60 or younger. HER2 positive tumors were equally prevalent in the three groups (17). In contrast, a study from the Netherlands showed a higher prevalence of HER2 positive tumors (22%) in women younger than 40 years-old compared with women over 70 years old who had HER2 positive tumors in 10% of cases (18). The basal-like phenotype was observed in 13.4% of the breast cancers in patients older than 60 as opposed to 22.6% in patients 40 to 60 years-old (17). Regarding specific mutations, the tumor suppressor p53 gene was more commonly mutated in patients in the 40- to 60-year age group (41.5% versus 29.1%). However, mutations of the E-cadherin gene (CDH1) commonly associated with lobular histology and the luminal phenotypes were more prevalent in patients above age 60 (19.3% versus 12.2% in younger patients) (17). Together, these findings suggest that there is a similarity between the breast cancer sub-type landscape in patients over 80 years of age and younger post-menopausal counterparts. Conversely, peri-menopausal and pre-menopausal patients have higher percentages of HER2 positive and triple-negative cancers.

Despite similarities of breast cancer biologic sub-types between women over 80 years-old and younger post-menopausal women, their treatment needs to be tailored due to increased comorbidities associated with decreased organ function reserves and frailty. We have observed a significant increase in comorbidities and polypharmacy in our older patients, which is consistent with previous research (7). As a result, decreased use of radiation therapy has been observed. However, in our series, this may also be justified by increased mastectomy use in older patients. A significantly decreased use of chemotherapy, despite similar tumor biology and higher tumor stage, is certainly due to concerns about the tolerability of treatment and possible effects for the performance status and self-sufficiency of patients (19). This finding is a legitimate concern even for patients in this age group who are initially entirely independent, as their ability to metabolize the drugs may be sub-optimal and exposure levels disproportionate (20). Geriatric assessment is an integral part of the care of older cancer patients and may accurately predict patients at higher risk for treatment toxicity (21-24). Reassuringly, although the Overall Survival of older patients was lower than that of the younger group, competing causes rather the breast cancer was more commonly the cause of their demise and, the recurrence rates were not different. In addition, the benefit of chemotherapy may not be as extensive in older patients, which would make the balance of risk- benefit less favorable (8, 25).

The main limitations of the current study include the retrospective nature of its design that may have introduced selection and recording bias and the moderate size that may have precluded detection of smaller differences between the groups. In addition, despite the fact that the study population is contemporary, new therapies that have been introduced recently such as CDK inhibitors, PI3K inhibitors and immune checkpoint inhibitors (10, 26-29) have not been included in the treatments that the patients, either in the older or the younger group, have received.

In conclusion, this study has shown that breast cancer in women who are 80 years-old and older is biologically similar to the disease in younger post-menopausal women but tends to present in more advanced stages possibly due to lower rates of screening in this population. Despite lower use of radiation and chemotherapy in patients 80 years-old and older, disease recurrence rates remain low, at least in the short-term. Individualized therapies that consider the patient's general status, comorbidities, and life expectancy remain the key for optimal outcomes, both from a cancer outcome perspective and from the perspective of preserving the quality of life and independence of the patient. Novel targeted cancer treatments with a better safety profile than standard chemotherapy will provide further opportunity for improving outcomes, especially for sub-types with limited options currently, such as triple-negative disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Saullt Area Hospital (#2019-07-01).

Informed Consent: Written informed consent was not required or obtained from patients who participated in this study, as this was a retrospective investigation.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - I.A.V.; Design - I.A.V.; Supervision - I.A.V.; Resources - I.A.V.; Materials - I.A.V.; Data Collection and/or Processing - A.B., C.R.; Analysis and/or Interpretation - A.B., I.A.V.; Literature Search - A.B., I.A.V.; Writing Manuscript - I.A.V.; Critical Review - C.R., I.A.V.

Acknowledgements: The authors thank the Sault Ste. Marie Academic Medical Association, Sault Ste. Marie, Canada for administrative support.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Howlander N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2012. Available from: www.seer.cancer.gov
2. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, Jemal A. Cancer treatment and survivorship statis-

tics, 2016. CA Cancer J Clin 2016; 66: 271-289. (PMID: 27253694) [Crossref]
3. American College of Surgeons National Cancer Database Benchmark Reports. Available from: http://cromsell.org/ BMarks/BMPub
4. Butler AN. Screening mammography for older women: a case of mixed messages. Arch Intern Med 1992; 152: 922-925. (PMID: 1580716) [Crossref]
5. Ulcickas Yood M, Owusu C, Buist DSM, Geiger AM, Field TS, Thwin SS, Lash TL, Prout MN, Wei F, Quinn VP, Frost FJ, Silliman RA. Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg 2008; 206: 66-75. (PMID: 18155570) [Crossref]
6. Guilfoyle C, Keller D, Sariego J. Breast cancer in the octogenarian. Breast J 2012; 18: 650-651. (PMID: 23110369) [Crossref]
7. Kuzan TY, Koca E, Dizdar O, Arslan C, Eren T, Yalcin S, Kucukoztas N, Aksoy S, Rahatli S, Dede DS, Altundag O, Zengin N, Ozyilkan O, Altundag K. Breast cancer in octogenarian women: clinical characteristics and outcome. J BUON 2013; 18: 328-334. (PMID: 23818342)
8. Martinez-Ramos D, Simon-Monterde L, Queralt-Martin R, Suelves-Piqueres C, Menor-Duran P, Escrig-Sos J. Breast cancer in octogenarian. Are we doing our best? A population-registry based study. Breast 2018; 38: 81-85. (PMID: 29274475) [Crossref]
9. Mamtani A, Gonzalez JJ, Neo DT, Friedman RS, Recht A, Hacker MR, Sharma R. Treatment strategies in octogenarians with early-stage, high-risk breast cancer. Ann Surg Oncol 2018; 25: 1495-1501. (PMID: 29427213) [Crossref]
10. Voutsadakis IA. Immune blockade inhibition in breast cancer. Anticancer Res 2016; 36: 5607-5622. (PMID: 27793883) [Crossref]
11. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016; 375: 1925-1936. (PMID: 27959613) [Crossref]
12. Strulov Shachar S, Hurria A, Muss HB. Breast cancer in women older than 80 years. J Oncol Practice 2016; 12: 123-132. (PMID: 26869650) [Crossref]
13. Cancer Care Ontario Breast Cancer Pathway Map. Available from: www.cancercareontario.ca/en/pathwaymap. Assessed March 12, 2020.
14. Oeffinger KC, Fortham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, Walter LC, Church TR, Flowers CR, LaMonte SJ, Wolf AM, DeSantis C, Lortet-Tieulent J, Andrews K, Manassaram-Baptiste D, Saslow D, Smith RA, Brawley OW, Wender R; American Cancer Society. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA 2015; 314: 1599-1614. (PMID: 26501536) [Crossref]
15. Kotwal AA, Schonberg MA. Cancer screening in the elderly. A review of breast, colorectal, lung, and prostate cancer screening. Cancer J 2017; 23: 246-253. (PMID: 28731949) [Crossref]
16. Ferrigni E, Bergom C, Yin Z, Szabo A, Kong AL. Breast cancer in women aged 80 years or older: An analysis of treatment patterns and disease outcomes. Clin Breast Cancer 2019; 19: 157-164. (PMID: 30819504) [Crossref]
17. Wang MX, Ren JT, Tang LY, Ren ZF. Molecular features in young vs elderly breast cancer patients and the impacts on survival disparities by age at diagnosis. Cancer Medicine 2018; 7: 3269-3277. (PMID: 29761914) [Crossref]
18. de Munck L, Schaapveld M, Siesling S, Wesseling J, Voogd AC, Tjan-Heijnen VC, Otter R, Willemse PH. Implementation of trastuzumab in conjunction with adjuvant chemotherapy in the treatment of non-metastatic breast cancer in the Netherlands. Breast Cancer Res Treat 2011; 129: 229-233. (PMID: 21431871) [Crossref]
19. Balducci L. Treatment of breast cancer in women older than 80 years is a complex task. J Oncol Practice 2016; 12: 133-134. (PMID: 26869651) [Crossref]
20. Wasil T, Lichtman SM. Clinical pharmacology issues relevant to the dosing and toxicity of chemotherapy drugs in the elderly. Oncologist 2005; 10: 602-612. (PMID: 16177284) [Crossref]
21. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, Levine RM, Lubiner ET, Reyes P, Schreiber FJ 3rd, Balducci L. Predicting the risk of chemotherapy toxicity in older patients: The chemotherapy Risk Assessment Scale for High-Age patients (CRASH) score. Cancer 2012; 118: 3377-3386. (PMID: 22072065) [Crossref]
22. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, Lichtman SM, Gajra A, Bhatia S, Katheria V, Klapper S, Hansen K, Ramani R, Lachs M, Wong FL, Tew WP. Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. J Clin Oncol 2011; 29: 3457-3465. (PMID: 21810685) [Crossref]
23. Voutsadakis IA. Clinical tools for chemotherapy toxicity prediction and survival in geriatric cancer patients. J Chemother 2018; 30: 266-279. (PMID: 29943680) [Crossref]
24. Reed M, Patrick C, Quevillon T, Walde N, Voutsadakis IA. Prediction of hospital admissions and grade 3-4 toxicities in cancer patients 70 years-old and older receiving chemotherapy. Eur J Cancer Care 2019; 28: e13144. (PMID: 31429128) [Crossref]
25. Chou HH, Kuo WL, Yu CC, Tsai HP, Shen SC, Chu CH, Yu MC, Lo YF, Dabora MA, Chang HK, Lin YC, Ueng SH, Chen SC. Impact of age on pathological complete response and locoregional recurrence in locally advanced breast cancer after neoadjuvant chemotherapy. Biomed J 2019; 42: 66-74. (PMID: 30987708) [Crossref]
26. Etti J. Management of adverse events due to cyclin-dependent kinase 4/6 inhibitors. Breast Care 2019; 14: 86-92. (PMID: 31798379) [Crossref]
27. Spring LM, Wander SA, Andre F, Moy B, Turner NC, Bardia A. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. Lancet 2020; 395: 817-827. (PMID: 32145796) [Crossref]
28. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu YS, Inoue K, Takahashi M, Pápai Z, Longin AS, Mills D, Wilke C, Hirawat S, Juric D, SOLAR-1 Study Group. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019; 380: 1929-1940. (PMID: 31091374) [Crossref]
29. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Henschel V, Molinero L, Chui SY, Maiya V, Husain A, Winer EP, Loi S, Emens LA, IMpassion130 Investigators. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (Impassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020; 21: 44-59. (PMID: 31786121) [Crossref]

Original Article

Eur J Breast Health 2020; 16(3): 213-218
DOI: 10.5152/ejbh.2020.5487

Evaluation of Pathologic Complete Response (pCR) to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients with Estrogen Receptor Positive and HER2 Negative and impact of predicting variables on pCR

Ramesh Omranipour[1,2], Roghiyeh Jalili[1], Adel Yazdankhahkenary[3], Abdolali Assarian[4], Mehrzad Mirzania[5], Bita Eslami[1]

[1]Breast Disease Research Center (BDRC), Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Surgical Oncology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Trauma and Surgery Research Center, Sina hospital, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran
[5]Department of Hematology and Oncology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Objective: The pathologic complete response (pCR) in the breast and axillary lymph node after neoadjuvant chemotherapy (NAC) would improve outcomes and it is used as a surrogate marker for survival. Our objective was to evaluate the breast and nodal pCR in breast cancer patients with estrogen receptor-positive (ER) and HER2 negative subtypes. Meanwhile, we sought to examine the impact of predicting factors on the rate of pCR.

Materials and Methods: In this multicenter retrospective study, medical records data of 314 women with ER+/HER2- breast cancer subtype who received neoadjuvant chemotherapy was extracted from oncology centers' data between 2011 and 2018. Breast and axillary lymph node pCR were assessed. Meanwhile, receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value for proliferative index (Ki-67%) expression.

Results: Breast pCR was seen in 25.2% (n=79) of the 314 cancer patients and partial response was seen in 47.8% (n=150), too. Nodal pCR was reported in 30.9% (n=97) of the 249 node-positive patients. The overall pCR (both breast & node) was observed in 14.6 % (n=46) of the 272 patients in which the data of breast and nodal were available. We identified 22.5% as the best cut-off value for ki-67 expression in predicting complete response to NAC.

Conclusion: The pCR rate after NAC in ER+/HER2– subtypes of breast cancer is low. Therefore, the optimal therapy for these patients should be further investigated.

Keywords: Breast cancer, HER-2 protein, neoadjuvant therapy

Cite this articles as: Omranipour R, Jalili R, Yazdankhahkenary A, Assarian A, Mirzania M, Eslami B. Evaluation of Pathologic Complete Response (pCR) to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients with Estrogen Receptor Positive and HER2 Negative and impact of predicting variables on pCR. Eur J Breast Health 2020; 16(3): 213-218.

Introduction

Systemic therapy in a newly diagnosed patient with breast cancer is increasing as an integral part of the multi-disciplinary treatment considering primary tumor factors (1, 2). Neoadjuvant chemotherapy (NAC) as a valuable tool, can reduce the size of primary tumors and control loco-regional recurrence rates and eradicate the disease in the regional lymph nodes and convert node-positive disease to node-negative (3). Widespread uses of NAC will downstage the primary tumor in most women and increasing the feasibility of breast-conserving surgery (BCS) in previously mastectomy candidates and decreasing the extent of avoidance of axillary lymph node dissection (ALND) in nodal positive patients (4). In this regard, combination chemotherapy regimens are superior to single-agent chemotherapy (5) and regimens contain both anthracycline and taxane had the highest of complete response.

The pathologic complete response (pCR) in the breast and axillary lymph node after NAC would improve outcomes and it is used as a surrogate marker for survival for some groups (6, 7). Breast cancer subtypes are classified by molecular markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) and these subtypes are associated with different behavior and response to the chemotherapy (8, 9). Several studies have shown pCR rates with some variation up to 40% after NAC based on tumor biologic subtypes (7, 10-12). The pCR rate and a favorable outcome are highest for triple-negative (TN) tumors, followed by HER 2 positive tumors and least for hormone-positive (12).

Some limitations such as a non-standardized pCR definition, presence of non-invasive and invasive cancer, prognostic impact of breast cancer subtypes, and difference in NAC regimens have caused unexpected differences in reported pCR.

Corresponding Author :
Bita Eslami; b-eslami@tums.ac.ir

Received: 20.01.2020
Accepted: 17.05.2020

Since the luminal subtypes of breast cancer (estrogen-receptor and/or progesterone-receptor positive and HER2 negative) were reported about 60% of cases in our country (13), the evaluation of the pathologic response to NAC in this group seems to be necessary.

The first goal of this study was to evaluate the breast and nodal pathologic response in breast cancer patients with ER positive and HER2 negative subtypes and the secondary objective was to examine the impact of predicting factors on the rate of pCR.

Materials and Methods

The present study was approved by the ethics committee of Tehran University of Medical Sciences and patients' consent was available in hospital medical file for research projects considering ethical issues.

This multicenter retrospective study was conducted in the oncology centers of Tehran capital city of Iran. Patients' information (age at the time of diagnosis, initial tumor size with ultrasonography before NAC, tumor type, stage, and nuclear grade, NAC regimen, Ki-67 proliferation marker, and type of surgery) was extracted from their medical records of patients between 2011 and 2018 by the main investigator. All patients with pathologically confirmed invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC) of the breast with stage I to III who received NAC were included in this study.

In order to decrease the false-negative rate of SLNB after NAC as a reliable technique to replace ALND, certain precautions have been applied as a standard protocol in all oncology centers. For all patients, dual tracer radio-labelled colloid and patent blue have been injected for SLN mapping and only patients with at least three reactive SLNs were considered as node negative. None of our patients had nodal localization with clips or tattooing at the time of needle biopsy.

Patients were eligible for inclusion if they were ER positive and HER2 negative based on their diagnostic core biopsy. Hormone positivity was defined as ≥ 1% of cells staining positive for ER or PR. HER2 receptor status was defined at immunohistochemistry (IHC) as negative with staining of 0 or 1+. HER2 amplification was assessed in equivocal (2+) by fluorescence in situ hybridization (FISH). Patients previously had an excisional biopsy for diagnosis or if they had any part of their surgery such as sentinel lymph node biopsy before NAC were excluded from the study. Ki-67 was calculated using scoring systems to estimate a proliferation index (PI); the number of positively stained tumor nuclei divided by the total number of nuclei in a specific region by pathologists. All tumors were unifocal and patients with multifocal and multicentric tumors were excluded from the study.

Key Points

- The rate of pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) in ER+/HER2- subtype of breast cancer is low.
- Younger age, progesterone receptor-negative, and increasing ki-67 (cutoff point: 22.5%) as predicting factors were associated with an increased rate of pCR after NAC.
- Further studies are needed to find the best treatment in ER+/HER2- subtype of breast cancer.

The majority of patients have received combination NAC with AC-T (Doxorubicin, Cyclophosphamide, and Taxane) regimen. After completion of NAC, all patients underwent breast and axillary surgery, and surgical specimens were evaluated by expert pathologists.

Overall pCR was defined as no evidence of residual invasive cancer both in breast and axilla according to the most widely used definition. We assessed pathologic response in the breast regardless of axillary response and in the axilla regardless of breast response, too. Partial response (PR) was considered if there was any response regardless of the amount of changes in breast or axilla. No response (NR) was recorded if there was not any changes and sign of regression in breast and axilla.

Statistical analyses

Statistical analyses were performed using IBM Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Continues variables were reported as mean ± standard deviation (SD) and categorical variables were identified as a number with percentages. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value for Ki-67 expression. The impact of factors such as age at the time of diagnosis (<50, ≥50 years), tumor size (<50, ≥50 mm), pathologic tumor (T) and nodal (N) score, nuclear grade, Ki-67 proliferation index (<22.5, ≥22.5), and progesterone receptor expression on pCR were determined using univariable analysis. Multivariate logistic regression analysis was performed using age category, stage T, ki-67% category, and PR expression based on the univariable analysis (p-value less than 0.05 entered to the model). Odds ratio (OR) and 95% confidence interval (CI) are presented. All tests were two-sided and a p-value less than 0.05 was considered statistically significant.

Results

A total of 314 patients with ER+/ HER2- receiving NAC were identified. The characteristics of study population are shown in Table 1. Median patients' age was 48 years old and median tumor size at baseline was 30 (7-88 mm) by ultrasonography. The majority of the cancers (97.1%) were ductal, and 9 (2.1%) were lobular.

The pathological response data are listed in Table 2. Breast pCR was seen in 25.2% (n=79) of the 314 cancer patients and partial response was seen in 47.8% (n=150), too. Nodal pCR was reported in 30.9% (n=97) of the 249 node-positive patients. Finally, the overall pCR (both breast & node) was observed in 14.6 % (n=46) of the 272 patients in which the data of breast and nodal were available. One hundred twenty-three (39.2%) patients were considered successfully treated with BCS after NAC. Our results showed NAC resulted in avoidance of ALND in 20.7% (n=65) of node-positive cases.

The area under the ROC curve (AUC) for ki-67 expression was 0.67 (p=0.001; 95% CI: 0.58- 0.75). We identified 22.5% as the best cut-off value for Ki-67 expression in predicting a complete response to NAC. This cut-off level was associated with an optimal sensitivity of 72% and specificity 59%.

Table 3 highlighted the association between predicting factors and overall pCR. The results show Ki-67 ≥22.5 and PR negative had more complete breast and nodal response. The adjusted OR of multivariate logistic regression analysis, illustrated a statistically significant positive association between younger age (<50 years), Ki-67 ≥22.5 and PR expression and overall pCR (Table 4).

Table 1. Characteristics of study population (n=314)

Characteristics	
Patient age, years	48.43±11.59*
<50	168 (53.5)
≥50	134 (42.7)
Missing data	12 (3.8)
Tumor type	
IDC	305 (97.1)
ILC	9 (2.9)
Clinical T at presentation	
T1	27 (8.6)
T2	160 (51)
T3	24 (7.6)
T4	54 (17.2)
Missing data	49 (15.6)
Nodal category at presentation	
N0	23 (7.3)
N1	161 (51.3)
N2	88 (28)
N3	0 (0)
Missing data	42 (13.4)
Tumor grade	
1	46 (14.6)
2	223 (71)
3	39 (12.4)
Missing data	6 (1.9)
Ki-67%	26.33±19.56*
Progesterone receptor	
Positive	288 (91.7)
Negative	26 (8.3)
Types of surgery	
BCS +SLNB	47 (15)
BCS +ALND	76 (24.2)
MST +SLNB	29 (9.2)
MST + ALND	162 (51.6)

*Mean±SD. Categorical variables were expressed as number with percentages in parenthesis. IDC: invasive-ductal carcinoma; ILC: invasive-lobular carcinoma; BCS: breast conserving surgery; SLND: sentinel lymph node dissection; ALND: axillary lymph node dissection; MST: mastectomy

Table 2. Pathologic response of breast and node

Pathologic Response	Number (%)
Breast (n=314)	
pCR	79 (25.2)
RR	150 (47.8)
NR	85 (27.1)
Nodal (n= 249)	
pCR	97 (30.9)
PR	35 (11.1)
NR	117 (37.3)
Overall breast & nodal	
pCR	46 (14.6)
PR	168 (53.5)
NR	58 (18.5)
Treated with BCS	123 (39.2)
Avoidance of ALND in node positive	65 (20.7)

pCR: Pathologic Complete Response; PR: partial response; NR: no response; BCS: Breast Conservative Surgery; ALND: Axillary Lymph Node Dissection

Discussion and Conclusion

In this multicenter retrospective study, data of 314 luminal breast cancer patients treated with neoadjuvant chemotherapy were evaluated for pathologic response rate. We found patients with ER positive and HER2 negative breast cancer had a 25.2% pCR rate in breast and 30.9% in axillary lymph nodes. The impact of NAC on pCR in both breast and axilla was 14.6%. Our results demonstrated that ALND can be avoided for 20.7% of patients with nodal metastases. The breast conservation rate of this study was 39.2%. Results of multivariate analysis showed that younger age, PR negative and increasing Ki-67 score were associated with an increased rate of pCR after NAC.

The pCR rate in both breast and axilla of the present study (14.6%) is higher than previously reported by the other studies. The pCR rate of the ACOSOG Z1071 multicenter clinical trial with 317 cases was 11.4% (3) and in I-SPY trial with 93 cases was 9% (14). Von Minckwitz et al. (10) study was reported the pCR rate of 8.9% in luminal A and 15.4% in luminal B/HER2- disease in the German population (n=1994 for these two categories). A pCR rate of 9% has been reported by Caudle and their colleagues from MD Anderson Cancer Center, in 309 patients with HR+ /HER2- subtype (15). However, some studies manifested the lower pCR rate in both breast and axilla as about 5% in Petruolo et al. study and 4.3% in Lips et al. study (16, 17). Petruolo study also showed the overall pCR is more common in ductal than lobular carcinoma (6% vs 1%) and lobular ones were less likely downstage than those with ductal carcinoma (16). Lips et al. have shown that lobular histology was not associated with chemotherapy response when the analysis is restricted to HR+/HER2- tumors, too (17). Despite our small sample size of lobular carcinoma (n=9), our result confirmed by their findings and only one of the lobular patients responded completely to NAC.

A large scale study that analyzed pooled data of 12 international trials with 11,955 patients reported the low pCR rate (7.5%) in HR+ / HER2 - (grade 1,2), 16.2% in HR+/ HER2- (grade 3) compared with another subtypes. They reported the association between pCR and the long-term outcome was weakest for this subtype of breast cancer (6). Our results showed the pCR in grades 1 and 2, and 3 were 16.3% (38/233), and 17.6% (6/34), respectively and the pCR differ-

Table 3. Predictive factors associated with pathologic complete response (pCR)

Variable	pCR	Partial response & No response	p
Age			0.001
<50	34 (80.95)	115 (52.5)	
≥50	8 (19.05)	104 (47.5)	
Tumor Type			0.64
IDC	45 (97.8)	218 (96.5)	
ILC	1 (2.2)	8 (3.5)	
Grade			0.84
1 & 2	38 (86.4)	195 (87.4)	
3	6 (13.6)	28 (12.6)	
Stage T			0.07
1 & 2	37 (82.2)	149 (68.7)	
3 & 4	8 (17.8)	68 (31.3)	
N Score			0.76
0 & 1	32 (69.6)	152 (67.3)	
2	14 (30.4)	74 (32.7)	
Ki-67%			0.006
<22.5	11(30.6)	111 (59)	
≥22.5	25 (69.4)	77 (41)	
PR			0.002
Positive	36 (78.3)	212 (93.8)	
Negative	10 (21.7)	14 (6.2)	
Tumor size (mm)			0.25
<50	36 (78.3)	158 (69.9)	
≥50	10 (21.7)	68 (30.1)	

pCR: Pathologic Complete Response; PR: Progesterone Receptor; IDC: invasive-ductal carcinoma; ILC: invasive-lobular carcinoma

Table 4. Logistic Regression analysis for factors associated with pCR

Variables	Adjusted OR	95%CI	p
Age category (<50 / ≥50)	3.07	1.17-8.08	0.02
Ki-67% (≥22.5 / <22.5)	2.66	1.15-6.16	0.02
PR (Negative/Positive)	3.52	1.24-9.94	0.02

PR: progesterone receptor; OR: odds ratio; CI: confidence interval. Considering univariable analysis age category, stage T, ki-67% category, and PR expression were entered to the model.

ences between grades were not statistically significant. Boughey et al. study revealed the overall pCR was significantly higher in patients with triple-negative (38.2%) and HER2 positive (45.4%) disease than in those with HR+/HER2- (11.4%) (3).

Based on this knowledge and low pathologic response rate in ER+/HER2- breast cancer patients, it should be investigated whether the initial treatment approach would be NAC or surgery.

On the other hand, achieving a pCR is not the only aim of treatment with NAC and some evidence showed the pCR is not valid as a surrogate endpoint for improved event-free survival (EFS) and overall survival (OS) (6). So other benefits such as increasing the eligibility for BCS and decreasing the rate of ALND should be considered. In the present investigation, 38.5% of the patients have treated with BCS. Our result was consistent with another study in this subtype of breast cancer, which reported about 38% of patients could have BCS regardless of patient preference (16). It should be mentioned; in the present investigation, we don't know how many patients selected mastectomy without considering physician's recommendation for BCS.

Many studies have found that tumors with more proliferating activity, benefit more from chemotherapy and Ki-67% can be used as a predictor factor for a higher rate of pCR (18). Hormone positive receptor breast cancer subtypes often have low Ki-67 expression, resulting in lower response to chemotherapy (19, 20). In accordance with the other studies (21, 22), our study confirmed the Ki-67 proliferation index is a predictor of pCR to NAC in ER+/HER2- patients. Therefore, Ki-67 score should be considered as a biomarker for predicting pCR after NAC. In order to assess the potential value of Ki-67 in predicting response to NAC in breast cancer patients and suggest a cut-off value, several studies have recommended different values from 12% to 25% (23-26). Some of them adopted cutoff value without any valid explanation or based on the median value. Our result was near to another study with Kim and colleagues that suggested a 25% level of Ki-67 is a reasonable value for predicting response to chemotherapy. We found 22.5% of Ki-67 expression as a cutoff value; can predict the pCR in HR+/HER2- breast cancer patients.

As well as, the impact of PR expression on the response of NAC was seen in our analysis which was consistent with other studies that reported significantly higher pCR in PR negative than PR positive (16, 17). Of course, the number of patients with progesterone receptor negative in our study is very low (n=26) and a wide confidence interval indicates that further studies with more sample size in this category are needed.

This study was the first evaluation of this context in Iranian women with breast cancer and it was our advantage. The other advantage was the high sample size. This study had some limitations. Since the study was extracted the data from medical records, missing data of some variables were high and as a major limitation, it may cause inaccurate results. The second limitation was due to the incomplete record of NAC regimen. Therefore, the evaluation of the effect of different regimens on pCR was not possible. Since our study was a retrospective study, we couldn't calculate the down-staging rate to BCS and it was third limitation of our study. One hundred forty- two patients with locally advance disease (T4 and N2) received NAC without considering the breast conserve is possible or not. The rest of patients were treated by NAC to decrease the tumor size. As we mentioned before, we don't know who were candidate for mastectomy before NAC and down staged to BCS after NAC and how many patients selected mastectomy without considering physician's recommendation for BCS due to fear of disease recurrence, and also we don't know how many patients were eligible for breast conserving at the time of diagnosis but they received NAC in order to achieve better cosmetic. Therefore, the frequency of patients who treated with BCS after NAC was reported.

In conclusion, considering the results of the present study and other investigations, the pathologic complete response rate after NAC in ER+/HER2- subtypes of breast cancer is low. Therefore, the optimal therapy for these patients should be further investigated. Meanwhile, Ki67 expression with cutoff point 22.5% could predict the pCR after NAC in ER+/HER2- as a biomarker. Although the decision to refrain from NAC in ER+/HER2– breast tumors should not be based on only one predictive marker, other variables such as age and progesterone receptor expression should be considered carefully.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.609).

Informed Consent: The institutional review board of has approved this study and patients' consent was available in hospital medical file for research projects considering ethical issues.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.O., R.J.; Design - R.O., R.J., B.E.; Supervision - R.O., B.E.; Resources - R.O., A.Y., A.A., M.M.; Data Collection and/or Processing - R.J., A.Y., A.A., M.M.; Analysis and/or Interpretation - B.E.; Literature Search - R.O., B.E.; Writing Manuscript - R.O., B.E.; Critical Review - R.J., A.Y., A.A., M.M.

Acknowledgements: The authors would like to thank Dr. Azadeh Joolaii, Dr. Parisa Azimnejadian, Dr. Farhad Shahi, and Dr. Feresteh Ensani for their assistance.

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

Financial Disclosure: This study (no # 38580) was financially supported by the Vice-Chancellor of Research affairs, Tehran University of Medical Sciences.

References

1. Cunningham JD, Weiss SE, Ahmed S, Bratton JM, Bleiweiss IJ, Tartter PI, Brower ST. The efficacy of neoadjuvant chemotherapy compared to postoperative therapy in the treatment of locally advanced breast cancer. Cancer Invest 1998; 16: 80-86. (PMID: 9512673) [Crossref]
2. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz Jr AB, Hoehn JL, Lees AW, Dimitrov NV, Bear HD. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16: 2672-2685. (PMID: 9704717) [Crossref]
3. Boughey JC, McCall LM, Ballman KV, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Leitch AM, Flippo-Morton T, Hunt KK. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. Ann Surg 2014; 260: 608-614. (PMID: 25203877) [Crossref]
4. King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. Nat Rev Clin Oncol 2015; 12: 335-343. (PMID: 25850554) [Crossref]
5. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005; 23: 3676-3685. (PMID: 15738535) [Crossref]
6. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer Jr CE, Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164-172. (PMID: 24529560) [Crossref]
7. Haque W, Verma V, Hatch S, Klimberg VS, Butler EB, Teh BS. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. Breast Cancer Res Treat 2018; 170: 559-567. (PMID: 29693228) [Crossref]
8. Meyers MO, Klauber-DeMore N, Ollila DW, Amos KD, Moore DT, Drobish AA, Burrows EM, Dees EC, Carey LA. Impact of breast cancer molecular subtypes on locoregional recurrence in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. Ann Surg Oncol 2011; 18: 2851-2857. (PMID: 21442348) [Crossref]
9. Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, Hess KR, Stec J, Ayers M, Wagner P, Morandi P, Fan C, Rabiul I, Ross JS, Hortobagyi GN, Pusztai L. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 2005; 11: 5678-5685. (PMID: 16115903) [Crossref]
10. Von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekljudova V, Mehta K, Loibl S. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30: 1796-1804. (PMID: 22508812) [Crossref]
11. Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, Kau SW, Fornage B, Sahin A, Broglio K, Singletary SE, Valero V. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol 2005; 23: 9304-9311. (PMID: 16361629) [Crossref]
12. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26: 1275-1281. (PMID: 18250347) [Crossref]
13. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, Ebrahimi M. Breast cancer in Iran: an epidemiological review. Breast J 2007; 13: 383-391. (PMID: 17593043) [Crossref]
14. Esserman LJ, Berry DA, Cheang MC, Yau C, Perou CM, Carey L, DeMichele A, Gray JW, Conway-Dorsey K, Lenburg ME, Buxton MB, Davis SE, van't Veer LJ, Hudis C, Chin K, Wolf D, Krontiras H, Montgomery L, Tripathy D, Lehman C, Liu MC, Olopade OI, Rugo HS, Carpenter JT, Livasy C, Dressler L, Chhieng D, Singh B, Mies C, Rabban J, Chen YY, Giri D, Au A, Hylton N, I-SPY 1 TRIAL Investigators. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res Treat 2012; 132: 1049-1062. (PMID: 22198468) [Crossref]
15. Caudle AS, Yu TK, Tucker SL, Bedrosian I, Litton JK, Gonzalez-Angulo AM, Hoffman K, Meric-Bernstam F, Hunt KK, Buchholz TA, Mittendorf EA. Local-regional control according to surrogate markers of breast cancer subtypes and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast conserving therapy. Breast Cancer Res 2012; 14: R83. (PMID: 22621334) [Crossref]
16. Petruolo OA, Pilewskie M, Patil S, Barrio AV, Stempel M, Wen HY, Morrow M. Standard pathologic features can be used to identify a subset of estrogen receptor-positive, HER2 negative patients likely to benefit from neoadjuvant chemotherapy. Ann Surg Oncol 2017; 24: 2556-2562. (PMID: 28560596) [Crossref]
17. Lips E, Mulder L, De Ronde J, Mandjes I, Vincent A, Peeters MV, Nederlof PM, Wesseling J, Rodenhuis S. Neoadjuvant chemotherapy in ER+ HER2– breast cancer: response prediction based on immunohistochemical and molecular characteristics. Breast Cancer Res Treat 2012; 131: 827-836. (PMID: 21472434) [Crossref]

18. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol 2010; 11: 174-183. (PMID: 20152769) [Crossref]
19. Colleoni M, Bagnardi V, Rotmensz N, Viale G, Mastropasqua M, Veronesi P, Cardillo A, Torrisi R, Luini A, Goldhirsch A. A nomogram based on the expression of Ki-67, steroid hormone receptors status and number of chemotherapy courses to predict pathological complete remission after preoperative chemotherapy for breast cancer. Eur J Cancer 2010; 46: 2216-2224. (PMID: 20471822) [Crossref]
20. Faneyte IF, Schrama JG, Peterse JL, Remijnse PL, Rodenhuis S, Van de Vijver M. Breast cancer response to neoadjuvant chemotherapy: predictive markers and relation with outcome. Br J Cancer 2003; 88: 406-412. (PMID: 12569384) [Crossref]
21. Ellis MJ, Suman VJ, Hoog J, Goncalves R, Sanati S, Creighton CJ, DeSchryver K, Crouch E, Brink A, Watson M, Luo J, Tao Y, Barnes M, Dowsett M, Budd GT, Winer E, Silverman P, Esserman L, Carey L, Ma CX, Unzeitig G, Pluard T, Whitworth P, Babiera G, Guenther JM, Dayao Z, Ota D, Leitch M, Olson Jr JA, Allred DC, Hunt K. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol 2017; 35: 1061-1069. (PMID: 28045625) [Crossref]
22. Li X, Krishnamurti U, Bhattarai S, Klimov S, Reid MD, O'Regan R, Aneja R. Biomarkers predicting pathologic complete response to neoadjuvant chemotherapy in breast cancer. Am J Clin Path 2016; 145: 871-878. (PMID: 27298399) [Crossref]
23. Nishimura R, Osako T, Okumura Y, Hayashi M, Arima N. Clinical significance of Ki-67 in neoadjuvant chemotherapy for primary breast cancer as a predictor for chemosensitivity and for prognosis. Breast Cancer 2010; 17: 269-275. (PMID: 19730975) [Crossref]
24. Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, Rauh C, Schulz-Wendtland R, Bani MR, Schrauder M, Kahmann L, Lux MP, Strehl JD, Hartmann A, Dimmler A, Beckmann MW, Wachter DL. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 2011; 11: 486. (PMID: 22081974) [Crossref]
25. Li XR, Liu M, Zhang YJ, Wang JD, Zheng YQ, Li J, Ma B, Song X. Evaluation of ER, PgR, HER-2, Ki-67, cyclin D1, and nm23-H1 as predictors of pathological complete response to neoadjuvant chemotherapy for locally advanced breast cancer. Med Oncol 2011; 28: 31-38. (PMID: 20844986) [Crossref]
26. Kim KI, Lee KH, Kim TR, Chun YS, Lee TH, Park HK. Ki-67 as a predictor of response to neoadjuvant chemotherapy in breast cancer patients. J Breast Cancer 2014; 17: 40-46. (PMID: 24744796) [Crossref]

Original Article

Eur J Breast Health 2020; 16(3): 219-225
DOI: 10.5152/ejbh.2020.5259

Pre-Treatment and Post-Treatment Anxiety, Depression, Sleep and Sexual Function Levels in Patients with Breast Cancer

Filiz İzci[1], Gözdem Özdem[2], Ahmet Serkan İlgün[3], Filiz Ağaçayak[2], Tomris Duymaz[4], Zeynep Erdoğan[2], Gül Alço[5], Filiz Elbüken[5], Alper Öztürk[6], Çetin Ordu[5], Kübra Ceren Ateşal[1], Özge İpek Doğan[1], Fatma Aktepe[5], Vahit Özmen[7]

[1]Department of Psychiatry, İstanbul Erenköy Training and Research Hospital, İstanbul, Turkey
[2]İstanbul Florence Nightangale Hospital, Breast Health Center, İstanbul, Turkey
[3]Department of General Surgery, İstanbul Taksim Training and Research Hospital, İstanbul, Turkey
[4]Department of Physiotherapy and Rehabilitation, İstanbul Bilgi University Faculty of Health Sciences, İstanbul, Turkey
[5]Gayrettepe Florence Nightingale Hospital, Breast Health Center, İstanbul, Turkey
[6]Department of General Surgery, Biruni University School of Medicine, İstanbul, Turkey
[7]Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Objective: In the phase of diagnosis and treatment of breast cancer cases, patients can usually experience sexual dysfunctions, sleep disorders and psychiatric disorders such as anxiety and depression. The main objective of our research is to study of the pre-treatment and post-treatment anxiety, depression, sleep and sexual function levels in the patients with breast cancer.

Materials and Methods: Fifty-six patients with breast cancer and 52 healthy women have participated in our study. In order to determine the anxiety, depression, sleep and sexual function levels, Sociodemographic and Clinical Data Form, Hospital Anxiety Depression Scale (HADS), Pittsburgh Sleep Quality Scale (PSQI) and Arizona Sexual Experiences Scale (ASEX) scores are utilized at pre-treatment and post-treatment phases for patients with breast cancer and our control group.

Results: According to scale scores applied to patients and control group, it has been determined that patients with breast cancer HADS sexual and sleep disorders, that their HADS and PSQI scores were higher and that ASEX scores decreased significantly ($p<0.05$). According to the scale scores calculated before and after treatment, there was a significant decrease in HADS and PSQI scores, whereas SEX scores have been increased significantly ($p<0.05$).

Conclusion: According to the findings of our study, anxiety, depression, sexual dysfunction and sleep disorders in patients with breast cancer are far more explicit in the pre-treatment phase than post-treatment phase. Therefore, it is crucial to psycho-socially support patients with breast cancer in the early periods before starting the treatment after diagnosis.

Keywords: Anxiety, breast cancer, depression, sexual function, sleep quality

Cite this articles as: İzci F, Özdem G, İlgün AS, Ağaçayak F, Duymaz T, Erdoğan Z, et al. Pre-Treatment and Post-Treatment Anxiety, Depression, Sleep and Sexual Function Levels in Patients with Breast Cancer. Eur J Breast Health 2020; 16(3): 219-225.

Introduction

Breast cancer is the most common cancer type in women around the world, with 1 of 8 women being diagnosed with breast cancer during their lives (1). Most of the patients who receive diagnosis of breast cancer experience psychological reactions such as denial, anger or fear against the breast cancer after the start of treatment as well as during the treatment (2). Following the diagnosis of breast cancer, most of the patients with breast cancer face fatigue, depression, anxiety, mood disorders, sleep disorders and sexual problems (3). Depression prevalence is high in the first year following the diagnosis of breast cancer, and three studies having the highest depression prevalence in a systematic compilation contain the patients who are in the first year of the diagnosis (4). Another study illustrated that depression prevalence was around 32.8% among the breast cancer cases in a large sample of breast cancer. Moreover, it has been reported that 40% of the patients who Hospital Anxiety Depression Scale (HADS) recurrence have HADS high anxiety and depression scores (5). It has been determined that 42% of the patients with advanced breast cancer HADS psychiatric disorder; and 35.7% of them HADS depression or anxiety or both (6).

Insomnia is one of the most common cancer symptoms, which is even more common in breast cancer cases and affect 42-69% of the patients with breast cancer (7). While insomnia may increase the risk of depressive symptoms and anxiety symptoms, sometimes depressive symptoms and anxiety symptoms may contribute to the progress of insomnia (8).

Corresponding Author :
Filiz İzci; filizizci@yahoo.com

Received: 24.10.2019
Accepted: 05.03.2020
Available Online Date: 17.04.2020

Sexual life in cancer patients may be affected by unexpected cancer diagnosis, changes in age-related sexual functions (such as menopausal changes in women), changes in body image caused by cancer treatments, infertility, fatigue, pain, and communication problems with the partner before diagnosis. Sexual dysfunction in patients with breast cancer is usually caused by many factors rather than a single factor (9). Mastectomy operation due to cancerous breast tissue presents a threat to the sexuality, motherhood, charm and body image of women, since woman breast is one of the most prominent symbols of femininity and sexuality in the female body and also it is a very important organ for the woman. It is stated that surgical, radiotherapy, chemotherapy or hormonal treatment for breast cancer affect the physical health of patients including their sexual life (10).

In our study, we aimed to examine the pre-treatment and post-treatment anxiety, depression, sleep and sexual function levels in patients with breast cancer.

Materials and Methods

After having obtained the approval from The Demiroğlu Bilim University Ethics Committee , literate patients with early breast cancer, who applied to The Breast Health Center between August 2017-Februrary 2018, aged between 18-65, who has no chronical disease and who accepted to take part in the study, were prospectively included in our study. The patients, who HADS alcohol abuse/substance use or who HADS psychiatric disorder such as schizophrenia or who HADS mental retardation, were excluded from the study. Control group consisted of volunteers who accepted to take part in our study, normalized in terms of age, were literate, were healthy in body and mind, who have not taken medicine, alcohol and psychoactive substance and who were not smokers. Written informed consent was obtained from all participants.

Data collection tools

In our study, Sociodemographic and Clinical Data Collection Form, Clinical Interview Scale – Clinical Version configured for DSM-IV Axis Diagnosis (SCID-I/CV), HADS, Pittsburgh Sleep Quality Scale (PSQI), Arizona Sexual Life Scale (ASEX) scores have been calculated for patients with breast cancer and for individuals in our control group. The evaluation based on the scores have been studied before the treatment (after establishing the diagnosis) and after the completion of the treatment.

Sociodemographic and clinical information

This form consists of questions such as age of the patient, marital status of the patient, educational background of the patient, regular partner status, sex frequency, insomnia problem and sexual problem existence which is filled out by the researcher physician.

SCID-I/CV

SCID-I is a clinical interview for DSM-IV Axis I disorders structured by First et al. (11) in 1997. Its acceptability and reliability studies for Turkey have been already done (12).

Key Points

- Sleep and sex is a necessity for patients with breast cancer.
- Mental health quality is essential for cancer treatment.
- Cancer treatment may affect sleep and sex levels.
- Cancer treatment can affect the level of anxiety and depression.

ASEX

ASEX is a scale developed by McGahuey et al. (13) in order to measure changes and disorders in sexual functions of patients using psychotropic drugs. This scale is a Likert type self-assessment test consisting of five questions, and multiple forms to be filled by both men and women. In our study, the form for women has been used. This scale aims to evaluate sexual functions excluding the sexual orientation and the relationship with the spouse. In the form for women used in this study, there are questions addressing the sexual drive (ASEX1), psychological excitation (ASEX2), physiological excitation (vaginal lubrication) (ASEX3), capacity to reach orgasm (ASEX4) and satisfaction level after orgasm (ASEX5) respectively. Each question is scored ranging from 1 to 6, and the total score varies from 5 to 30. Low scores show that sexual respond is strong, easy and satisfactory, whereas high scores refer to the existence of sexual dysfunction. The higher the scores are, the more sexual dysfunction exist. Turkish acceptability and reliability works have been applied to the patients with end-stage renal failure (14).

PSQI

The Pittsburgh Sleep Quality Index was developed by Buysse et al. (15), and is a screening and evaluation test based on self-feedback. This index provides detailed information regarding sleep quality, type and severity of sleep disorder within the last one month. Consisting of 24 questions, the Pittsburgh Sleep Quality Index measures scores related to seven components. These are subjective sleep quality (PSQI1), sleep latency (PSQI2), sleep duration (PSQI3), habitual sleep efficiency (PSQI4), sleep disturbances (PSQI5), use of sleeping medication (PSQI6), and daytime dysfunction (PSQI7). In this index, there are five questions to be answered by the partner of the patients. However, these five questions are not used for scoring. Each item is weighted on a 0–3 interval scale. The total score of seven components is equal to the total PSQI score. Total PSQII score may range from 0 to 21. Scores that are equal to or less than 5 refer to "good" sleep quality, whereas scores more than 5 refer to "bad" sleep quality. Having a PSQI score higher than 5 means that the relevant person has serious difficulties at least in two components or has mild to moderate difficulties in more than three components. This Index's acceptability and reliability works in Turkish have been performed by Agargun et al. (16).

HADS

This is a scale developed to determine the anxiety and depression risk in patients with physical injuries and in those applied to primary care medical service and to measure its level and severity change (17). It has been translated into Turkish, and its acceptability and reliability tests have been carried out (18). It has sub-scales as Anxiety (HADS-A) and Depression (HADS-D). It contains 14 questions in total. Seven of them (odd numbers) measure the anxiety and other seven questions (even numbers) measure the depression level. It ensures quart Likert type measurement. In studies conducted in Turkey, anxiety sub-scale cut-off score was found 10/11, and depression sub-scale score was found 7/8. Based on this result, patients who have more than X are considered as part of the risk group. The patients can get a minimum score of 0 and maximum score of 21 from the mentioned sub-scales. HADS is preferred due to the fact that it does not contain any substance related to physical symptoms.

Statistical analysis

Statistical analyses have been carried out by using IBM Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) version 20. Conformity of variables to the normal distribution has been examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov test).

Sociodemographic data, sex frequency, sleep disorders and existence of sexual problem have been given by using cross tables. by using Chi-Square or Fisher tests, it has been decided if there was a difference between the groups in terms of the reported frequencies or not.

Descriptive analyses have been given by using median, 25 percent, 75 percent and interquartile range for non-normal distributed variables. Since age, PSQI, ASEX and HADS values did not show normal distribution, groups have been compared by using Mann-Whitney U test.

Correlation coefficients and statistical significances for the relation between variables of which at least one was non-normal or ordinal have been calculated by using Spearman test. Type 1 error level for statistical significance has been considered as 5%.

Table 1. Sociodemographic characteristics of patient and control group

		Patient group n (%)	Control group n (%)	p
Age		53±33 (mean±SD)	52.5±33 (mean±SD)	0.26
Education level	Primary/ High School	40 (37)	47 (43.5)	0.013
	University	16 (14.8)	5 (4.6)	
Working status	Not working	33 (30.6)	42 (38.9)	0.014
	Working	23 (21.3)	10 (9.3)	
Marital status	Married	43 (39.8)	45 (41.7)	0.192
	Single/ Divorced	13 (12)	7 (6.5)	
Psychiatric disease	Yes	6 (5.6)	3 (2.8)	0.49
	No	50 (46.3)	49 (45.4)	
Use of cigarette	Yes	4 (3.7)	17 (15.7)	0.001
	No	52 (48.1)	35 (32.4)	
Use of alcohol	Yes	1 (0.9)	6 (5.6)	0.051
	No	55 (50.9)	46 (42.6)	
Regular partner status	Yes	39 (36.1)	28 (25.9)	0.091
	No	17 (15.7)	24 (22.2)	
Sex problems	Yes	15 (13.9)	3 (2.8)	0.003
	No	41 (38)	49 (45.4)	
Sex frequency	1>at one month	8 (7.4)	26 (24.1)	0.000
	1<at one month	48 (44.4)	26 (24.1)	
Sleep problems	Yes	23 (21.3)	5 (4.6)	0.000
	No	33 (30.6)	47 (43.5)	

p<0.05

Results

Fifty-six patients with breast cancer meeting the criteria of study and 52 healthy women as the control group were included in this study. The average age of patient groups was 53±33, and average age of control group was 52.5±33 (p>0.05). When sociodemographic differences between the patient group and the control group were examined, it was seen that university graduates were significantly more in the patient group (p=0.013). In addition to this, it was determined that number of working women in the patient group was significantly higher (p=0.014). Sleep disorder and sexual problems were also significantly seen more frequently in the patient group (p=0.000, p=0.003). When these two groups are compared in terms of sex frequency (4 times or more vs less than 4 times in a month), there was a significant difference between the groups. It was determined that sex frequency in the patient group was significantly decreased (p=0.000) (p<0.05) (Table 1).

Average of ASEX 1, ASEX 3, ASEX Total, PSQI1, PSQI2, PSQI3, PSQI4, PSQI5, PSQI6, HADS–A, HADS-D, HADS-T scale scores applied to the patient and control group were found statistically different in the patient group compared to the control group (p<0.05) (Table 2).

Based on the scale scores applied in pre-treatment period and post-treatment period; a significant difference has been observed between PSQI1, PSQI2, PSQI5, PSQI6, ASEX1, ASEX2, ASEX3, ASEX4, ASEX5, ASEX Total, HADS-D, HADS-A and HADS-T levels (p<0.05) (Table 3).

In the correlation analysis performed among the pre-treatment PSQI, ASEX, HADS scale values, there was a negative correlation between PSQI and ASEX scores, and a positive correlation between PSQI and HADS scores (respectively: r: –0.22, p:0.02; r=0.61, p=0.000) (p<0.05). In the correlation analysis performed among the post-treatment PSQI, ASEX and HADS scale scores, a positive relation between PSQI, ASEX scores and PSQI, HADS scores was determined (respectively: r=0.27, p=0.04; r=0.46, p=0.000) (p<0.05) (Table 4).

Discussion and Conclusion

In patients with breast cancer, some serious psychological problems occur because of multiple reasons such as uncertainty about the treatment, physical symptoms, fear of recurrence and death, changes in female identity, body image perception and sexual functions, difficulties in daily life activities, lack of social and emotional support (19). Surgery, radiotherapy, chemotherapy or hormonal treatments for breast cancer treatment affect the physical and mental health of patients. As a result of this, symptoms such as depression, mood disorders, deterioration in body image perception, trauma in female identity and sexual dysfunction are seen (20). It has been observed that women with breast cancer, who HADS chemotherapy, HADS more physical problems and sexual dysfunctions than those who did not get chemotherapy, and that symptoms related to ovarian failure negatively affected the quality of life of the woman and their sexual relations with their partners (21).

When patients with breast cancer are compared to age-controlled healthy women, Meyerowitz et al. (22) found similar impacts of diagnosis and treatments on sexuality, and sexual function and satisfaction, however they also reported that sexual lives of approximately one-third of women with breast cancer were affected negatively and that those women HADS problems with their partners and lubrication disorder.

Table 2. Comparison of ASEX, PUA, HADS scales of patient and control group

		N	25 per	50 per (median)	75 per	IQR	Mean±SD	p
PSQI1	Patient	56	1	1	2	1	1.39±0.65	0.000
	Control	52	0	1	1	1	0.56±0.50	
	Total	108						
PSQI2	Patient	56	2	2	3	1	2.41±1.05	0.000
	Control	52	0	0	0.75	1	0.25±0.43	
	Total	108						
PSQI3	Patient	56	0	0	1	1	0.73±0.86	0.000
	Control	52	0	0	0	0	0.1±0.29	
	Total	108						
PSQI4	Patient	56	0	0	0	0	0.2±0.51	0.058
	Control	52	0	0	0	0	0.04±0.19	
	Total	108						
PSQI5	Patient	56	1	2	2	1	1.63±0.62	0.000
	Control	52	1	1	1	0	1.06±0.46	
	Total	108						
PSQI6	Patient	56	0	0	0	0	0.29±0.75	0.001
	Control	52	0	0	1	1	0.48±0.50	
	Total	108						
PSQI7	Patient	56	0	0	0	0	0.29±0.65	0.85
	Control	52	0	0	0	0	0.27±0.52	
	Total	108						
PSQI-T	Patient	56	5	7	8	3	6.95±3.1	0.000
	Control	52	2	3	4	2	2.75±1.2	
	Total	108						
ASEX 1	Patient	56	4	5	5	1	4.36±1.13	0.000
	Control	52	5	5	6	1	5.06±1.22	
	Total	108						
ASEX 2	Patient	56	4	4	5	1	4.18±1.11	0.067
	Control	52	4	5	6	2	4.62±1.28	
	Total	108						
ASEX 3	Patient	56	4	4	5	1	4.38±1.03	0.004
	Control	52	4	5	6	2	4.88±1.21	
	Total	108						
ASEX 4	Patient	56	4	4	5	1	4.29±0.98	0.099
	Control	52	4	5	6	2	4.58±1.46	
	Total	108						
ASEX 5	Patient	56	3	4	5	2	4.20±1.19	0.123
	Control	52	4	5	6	2	4.52±1.4	
	Total	108						
ASEX-T	Patient	56	18.25	21.5	25	6.75	21.39±5	0.011
	Control	52	20	24	30	10	23.96±6.27	
	Total	108						

Table 2. Comparison of ASEX, PUA, HADS scales of patient and control group (continued)

		N	25 per	50 per (median)	75 per	IQR	Mean±SD	p
HADS-D	Patient	56	13.25	16	17		14.73±3.96	0.000
	Control	52	8	9	10		8.73±1.99	
	Total	108						
HADS-A	Patient	56	14	16.5	19		15.98±3.59	0.000
	Control	52	9	11	12		10.46±2.07	
	Total	108						
HADS-T	Patient	56	26.5	32	36		30.71±7.14	0.000
	Control	52	17.25	20	21		19.19±3.19	
	Total	108						

p<0.05. HADS: Hospital Anxiety Depression Scale; HADS-A: Anxiety subscale; HADS-D: Depression subscale; HADS-T: Total scale; PSQI: Pittsburgh Sleep Quality Scale; PSQI1: Sleep latency; PSQI2: Subjective sleep quality; PSQI3: Sleep duration; PSQI4: Habitual sleep efficiency; PSQI5: Sleep disturbances; PSQI6: Use of sleeping medication; PSQI7: Daytime dysfunction; PSQI-T: Total scale; ASEX: Arizona Sexual Life Scale; ASEX1: Sexual drive; ASEX2: Psychological excitation; ASEX3: Vaginal lubrication; ASEX4: Capacity to reach orgasm; ASEX5: Satisfaction level after orgasm; ASEX-T: Total scale per: percentile; IQR: Inter quartile range

Table 3. Comparison of patients' scores before and after treatment

	Before treatment				After treatment				
	25 per	50 per	75 per	Mean±SD	25 per	50 per	75 per	Mean±SD	p
PSQI1	1	1	2	1.39±0.65	0	1	1	0.79±0.75	0.000
PSQI2	2	2	3	2.41±1.05	1	1	2	1.54±1	0.000
PSQI3	0	0	1	0.73±0.86	0	0	1	0.68±0.87	0.47
PSQI4	0	0	0	0.2±0.51	0	0	0	0.23±0.66	0.79
PSQI5	1	2	2	1.63±0.62	1	1	1	1.16±0.41	0.000
PSQI6	0	0	0	0.29±0.75	0	0	0	0.16±0.53	0.053
PSQI7	0	0	0	0.29±0.65	0	0	0	0.18±0.43	0.32
PSQI-T	5	7	8	6.95±3.15	3	4	5.75	4.75±2.57	0.000
ASEX 1	4	5	5	4.69± 1.22	4.25	5	6	5.13±1	0.000
ASEX 2	4	4	5	4.39±1.21	4	5	6	4.95±1	0.000
ASEX 3	4	4	5	4.62±1.15	4	5	6	4.93±1	0.009
ASEX 4	4	4	5	4.43±1.24	4	5	6	4.86±1	0.014
ASEX 5	3	4	5	4.35±1.3	4	5	6	4.86±1.2	0.014
ASEX-T	18.25	21.5	25	22.63±5.77	22.25	25	29	25.02±5.2	0.001
HADS-D	13.25	16	17	11.84±4.36	5	8	10	7.95±4.22	0.000
HADS-A	14	16.5	19	13.32±4.04	6.25	8	12.75	9.07±4.18	0.000
HADS-T	26.5	32	36	25.17±8.03	11.25	16	22.75	17.02±7.84	0.000

p<0.05. HADS: Hospital Anxiety Depression Scale; HADS-A:Anxiety subscale; HADS-D: Depression subscale; HADS-T: Total scale; PSQI: Pittsburgh Sleep Quality Scale; (PSQI1); Sleep latency PSQI2: Subjective sleep quality; PSQI3: Sleep duration; PSQI4: Habitual sleep efficiency; PSQI5: Sleep disturbances; PSQI6: Use of sleeping medication; PSQI7: Daytime dysfunction; PSQI-T: Total scale; ASEX: Arizona Sexual Life Scale; ASEX1: Sexual drive; ASEX2: Psychological excitation; ASEX3: Vaginal lubrication; ASEX4: Capacity to reach orgasm; ASEX5: Satisfaction level after orgasm; ASEX-T: Total scale; per: percentile

In another study, there was no significant difference in sexual dysfunctions between Patients who received medical treatment after the surgical intervention and those who did not. More than half of the women stated that they HADS sexual problems before breast cancer, and about half of the Patients stated that their sexual problems started after breast cancer treatment. They said that chemotherapy HADS negative effects on their sexual life. In approximately half of women, it was observed that breast cancer and its treatments HADS a negative effect on both their relationships with their partners and sexual lives. More than half of the women with breast cancer HADS sexual dysfunction

Table 4. Correlation analysis of PSQI, ASEX, HADS total scores before and after treatment

		PSQI	ASEX	HADS
PSQI	Before treatment	-	r:–0.22	r=0.61
			p:0.02	p=0.000
	After treatment	-	r=0.27	r=0.46
			p=0.04	p=0.000
ASEX	Before treatment	r:–0.22	-	r=–0.08
		p:0.02		p=0.36
	After treatment	r=0.27	-	r=0.26
		p=0.04		p=0.051
HADS	Before treatment	r=0.61	r=–0.08	-
		p=0.000	p=0.36	
	After treatment	r=0.46	r=0.26	-
		p=0.000	p=0.051	

p<0.05. HADS: Hospital Anxiety Depression Scale; PSQI: Pittsburgh Sleep Quality Scale; ASEX: Arizona Sexual Life Scale

(23). In our study, it was seen that the Patients HADS decreased sexual function compared to the control group. However, in our before and after treatment comparisons; we have found that sexual functions have increased significantly in the post-treatment period, compared to the pre-treatment levels despite the treatment process and the side effects that might be secondary to the treatment.

The most common psychiatric illnesses in the Patients with breast cancer are depression and anxiety. Comorbidity of the depression occurring together with breast cancer is 46% which is a high rate; this rate increases within the first year after the diagnosis (18). In a study conducted, a negative correlation has been seen between anxiety scores and body image, future expectation and sexual function (24). When depressive score levels were compared as pre-treatment period and post-treatment period; it has been determined that depressive symptoms increased by 20% between 0 and 6th month, 12.9% between 6th and 12th month (25). In our study; depression and anxiety scores of the Patients were higher than those of the control group, and anxiety and depression were seen in pre-treatment period more often than in post-treatment period. Furthermore, there was a weak positive correlation between depression and anxiety scores and sexual function scores after the treatment.

Sleep disorders are commonly seen in breast cancer patients. Even after multiple years after the initial diagnosis, sleep disorders continue in some Patients (26). When the quality of sleep was examined in two hundred Patients with breast cancer, it was determined that 38% of them HADS poor quality sleep. It was shown that there was no significant correlation between sleepiness in daytime, depression and sleep quality (27). In another study; 43% of Patients with breast cancer HAD sleep disorders. Intrusive thoughts related to breast cancer were found to result in just 12% of the severity of insomnia symptoms. It was reported that these thoughts were an important determinant of insomnia symptoms. It was thought that emotional distress and anxiety that might arise from intrusive thoughts could eventually result in deficiencies in sleep and daytime functioning (28). It was observed that survivors among the sample consisting of the Patients with breast cancer were significantly less active; and sleep quality and physical and mental health of them were worse than those without cancer. It was reported that sleep quality was an important determinant of mental and physical health (29). In a prospective study examining the relationship between sleep times and breast cancer, a relationship was found between short duration of sleep and breast cancer risk. This situation has been explained with the anti-proliferative effect of the melatonin hormone on breast cancer cells and its suppressive feature on gonadal secretion (30). In our study, it was found that Patients group HAD a significant deterioration in the sleep scores compared to the control group. 23% of the Patients HAD sleep problems, and the sleep disturbance continued after the treatment but it is decreased compared to the pre-treatment period. There was a positive correlation between sleep scores and anxiety/depression scores and a negative correlation with sexual function scores. It was observed that sleep disorder was associated with anxiety and depression scores in post-treatment period.

Our study finds that the Patients with breast cancer have higher anxiety, depression, sleep disorder scores than control group, whereas sexual function levels of them are lower than the control group. Moreover, compared to pre-treatment period, an improvement in sleep quality, sexual function, anxiety and depression levels in post-treatment period was revealed. Sleep and sexual function were shown to be associated with anxiety and depression. Similar to studies in the literature, we confirm that treatments such as diagnosis and surgery, chemotherapy and hormone therapy in breast cancer Patients affect the physical and mental health of patients. However, in this study, it was observed that psychological symptoms such as anxiety and depression in post-treatment period as well as changes in the sexual life and sleep, which are both symptoms of physical and mental disorders, improved compared to the pre-treatment period. The results of this study showed that psychosocial support in breast cancer patients during diagnosis and pre-treatment period is more important than the support in post-treatment period. Because anxiety, depression, sleep disorder score levels in the patients with breast cancer are higher in the pre-treatment period, whereas sexual function levels are lower compared to the post-treatment period.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Demiroğlu Bilim University (Date: 02.08.2017 No: 44140529/2017-80).

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.İ., G.Ö.; Design – G.Ö., Ö.İ.D., G.Ö., F.E., F.İ.; Supervision – Z.E., V.Ö., F.A., A.Ö., G.Ö., A.S.İ.; Funding – V.Ö., F.A., Ç.O., F.E., F.İ., A.Ö., T.D.; Materials – F.A., F.E., F.İ., K.C.A., A.S.İ., T.D.; Data Collection and/or Processing – F.İ., F.E., F.A., K.C.A., Ö.İ.D.; Analysis and/or Interpretation - F.İ., A.S.İ., Z.E., Ç.O., A.Ö.; Literature Review – F.İ., F.A., V.Ö., A.Ö., K.C.A.; Writing – F.İ., A.S.İ., Ö.İ.D., T.D., G.A.; Critical Review – V.Ö., F.A., A.S.İ., G.A., Ç.O.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Christensen H, Marck D. The efficacy of mindfulness based stress reduction (MBSR) for decreasing anxiety and depression among breast cancer survivors. Sch Physician Assist Stud 2017; 16: 613.
2. Lueboonthavatchai P. Prevalence and psychosocial factors of anxiety and depression in breast cancer patients. J Med Assoc Thai 2007; 90: 2164-2174. (PMID: 18041438)
3. Rogers LQ, Courneya KS, Anton PM, Verhulst S, Vicari SK, Robbs RS, McAuley E. Effects of a multicomponent physical activity behavior change intervention on fatigue, anxiety, and depressive symptomatology in breast cancer survivors: randomized trial. Psychooncology 2017; 26: 1901-1906. (PMID: 27530961) [Crossref]
4. Maass SWMC, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: A systematic review. Maturitas 2015; 82: 100-108. (PMID: 25998574) [Crossref]
5. Vahdaninia M, Omidvari S, Montazeri A. What do predict anxiety and depression in breast cancer patients? A follow-up study. Soc Psychiatry Psychiatr Epidemiol 2010; 45: 355-361. (PMID: 19458878) [Crossref]
6. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. Breast Cancer Res Treat 2008; 110: 9-17. (PMID: 17674188) [Crossref]
7. Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. J Clin Oncol 2011; 29: 3580-3586. (PMID: 21825267) [Crossref]
8. Chen PJ, Huang CL, Weng SF, Wu MP, Ho CH, Wang JJ, Tsai WC, Hsu YW. Relapse insomnia increases greater risk of anxiety and depression: evidence from a population-based 4-year cohort study. Sleep Med 2017; 38: 122-129. (PMID: 29031746) [Crossref]
9. Can G. Kanserde cinsel sağlık. Androloji Bülteni Hemşire Çalışma Grubu 2004; 19: 355-356.
10. Eti F. Mastektomili hastalara ameliyat öncesi ve sonrası uygulanan hemşirelik bakımının beden imajını algılama ve fiziksel iyileşme üzerine etkisi. İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü Cerrahi Hastalıkları Hemşireliği Anabilim Dalı, Doktora Tezi, İstanbul. 1992
11. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Clinical Version (SCID-I/CV). American Psychiatric Press, Washington D.C 1997.
12. Çorapcıoğlu A, Aydemir Ö, Yıldız M, Esen A, Köroğlu E. DSM-IV Eksen I Bozuklukları (SCID-I)için yapılandırılmış klinik görüşme, klinik versiyon. Hekimler Yayın Birliği Matbaası, Ankara, 1999.
13. Mcgahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): Reliability and Validity. J Sex Marital Ther 2006; 26: 25-40. (PMID: 10693114) [Crossref]
14. Soykan A. The reliability and validity of Arizona sexual experiences scale in Turkish ESRD patients undergoing hemodialysis. Int J Import Res 2004; 16: 531-534. (PMID: 15175639) [Crossref]
15. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatric Res 1989; 28: 193-213. (PMID: 2748771) [Crossref]
16. Agargun MY. Pittsburgh uyku kalitesi indeksinin gecerligi ve guvenirligi. Turk Psikiyatri Dergisi 1996; 7: 107-115.
17. Zigmond AS, Snaith PR. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67: 361-370. [Crossref]
18. Aydemir Ö. Validity and Reliability of Turkish Version of Hospital Anxiety and Depression Scale. Turkish Journal of Psychiatry 1997; 8: 280-287.
19. Schidmit-Buchi S, Halfens RJ, Dassen T, van den Borne B. A review of psychosocial needs of breast-cancer patients and their relatives. J Clin Nurs 2008; 17: 2895-2909. (PMID: 19012759) [Crossref]
20. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. Breast Cancer Res Treat 2007; 110: 9-17. (PMID: 17674188) [Crossref]
21. Wilmoth MC, Coleman EA, Smith SC, Davis C. Fatigue, weight gain, and altered sexuality in patient with breast cancer: Exploration of a symptom cluster. Oncology Nursing Forum 2004; 31: 1069-1075. (PMID: 15547630) [Crossref]
22. Meyerowitz BE, Desmond KA, Rowland JH, Wyatt GE, Ganz PA. Sexuality following breast cancer. J Sex Marital Ther 1999; 25:237-250. (PMID: 10407796) [Crossref]
23. Aygın D, Aslan FE. A Study of Sexual Dysfunction in Women with Breast Cancer. Eur J Breast Health 2008; 4: 105-114.
24. Fatiregun OA, Olagunju AT, Erinfolami AR, Arogunmati OA, Fatiregun OA, Adeyami JD. Relationship between anxiety disorders and domains of health related quality of life among Nigerians with breast cancer. Breast 2017; 31: 150-156. (PMID: 27866090) [Crossref]
25. Jones SM, LaCroix AZ, Li W, Zaslavsky O, Wassertheil-Smoller S, Weit¬lauf J, Brenes GA, Nassir R, Ockene JK, Caire-Juvera G, Danhauer SC. Depression and quality of life before and after breast cancer diagnosis in older women from the Women's Health Initiative. J Cancer Surviv 2015; 9: 620-629. (PMID: 25708515) [Crossref]
26. Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep 2001; 24: 583-590. (PMID: 11480655) [Crossref]
27. Lowery-Allison AE, Passik SD, Cribbet MR, Reinsel RA, O'Sullivan B, Norton L, Kirsh KL, Kavey NB. Sleep problems in breast cancer survivors 1-10 years posttreatment. Palliat Support Care 2018; 16: 325-334. (PMID: 28508735) [Crossref]
28. Taylor TR, Huntley ED, Makambi K, Sween J, Adams-Campbell LL, Frederick W, Mellman TA. Understanding sleep disturbances in African-American breast cancer survivors: a pilot study. Psychooncology 2012; 21: 896-902. (PMID: 21648016) [Crossref]
29. Rafie C, Ning Y, Wang A, Gao X, Houlihan R. Impact of physical activity and sleep quality on quality of life of rural residents with and without a history of cancer: findings of the Day and Night Study. Cancer Manag Res 2018; 10: 5525-5535. (PMID: 30519100) [Crossref]
30. Cao J, Eshak ES, Liu K, Muraki I, Cui R, Iso H, Tamakoshi A, JACC Study Group. Sleep duration and risk of breast cancer: The JACC Study. Breast Cancer Res Treat 2019; 174: 219-225. (PMID: 30460465) [Crossref]

Eur J Breast Health 2020; 16(3): 226-227
DOI: 10.5152/ejbh.2020.5770

The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis

Sami Akbulut, Tevfik Tolga Şahin
Department of Surgery and Liver Transplant Institute, İnönü University School of Medicine, Malatya, Turkey

Cite this articles as: Akbulut S, Şahin TT. The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis. Eur J Breast Health 2020; 16(3): 226-227.

Dear Editor,

We read the recent article ''The predictive value of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in patients with recurrent idiopathic granulomatous mastitis '' published by Cetinkaya et al. (1) with great interest. Authors stated that they investigated the relationship between the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and the prognosis of idiopathic granulomatous mastitis (IGM).

We do not agree with the authors' statement which indicated that although the etiology of IGM was unclear, tuberculosis (TB), sarcoidosis, mycotic, and parasitic infections may play a role in the development of the IGM. It is a common fact that granulomatous mastitis (GM) is classified into two according to the underlying etiology; primary (idiopathic) and secondary (specific) GM. Secondary GM is caused by various specific infectious (bacteria, fungi, parasites) and non-infectious diseases (sarcoidosis, Wegener's granulomatosis, etc.). On the other hand, IGM is characterized by chronic non-caseification (non-necrotizing) granulomatous inflammation which does not have a specific underlying disease. TB should be included in the differential diagnosis in the endemic areas such as Turkey. Besides, TB and other infections have no direct relationship with IGM.

The authors have shown that patients with preoperative NLR ≥5.02 have 9.33 times higher risk of recurrence when compared to patients with NLR<5.02 (p=0.013). We have analyzed this result and calculated the categorical correlation coefficient for this relationship and the Phi coefficient (Ø) was calculated as 0.437 (p=0.005). This shows a positive and strong relationship between the high NLR and the risk of recurrence. The authors have shown that the sensitivity and specificity of high NLR for prediction of recurrences were 62.5% and 84.8%; respectively. The most important part of this analysis is the negative predictive value of high NLR for prediction of recurrence to be 90.3%. In other words, high NLR gives a better idea regarding patients that will not develop recurrence rather than predicting the recurrence of IGM. This theory is supported by the fact that high NLR had a specificity of 84.8% and a positive predictive value of 50.2%.

The authors should have performed a multivariate analysis to determine the independent risk factors for recurrence by using the variables with a p-value <0.1 that was determined in the univariate analysis. However, the authors did not perform any logistic regression analysis. We have used the methodology on the variables expressed in authors' Table-2 and performed a logistic regression analysis. The only variable that fit the criteria was NLR and the multivariate analysis yielded similar results as the univariate analysis. We were able to show that NLR ≥5.02 was an independent risk factor determining the recurrence in patients with IGM (Logistic regression with backward LR; Wald: 6.49, p=0.011, OR=9.33 95% CI=1.67-52.06).

Recently, NLR is used as a surrogate marker for the systemic inflammatory process. During systemic inflammation, neutrophil counts increase, and lymphocyte counts decrease which increases NLR. For this reason. NLR can be used to predict the severity of the disease in various clinical conditions such as various infectious diseases, cancer, and critically ill patients. In literature, there is only one study

Corresponding Author :
Sami Akbulut; akbulutsami@gmail.com

Received: 03.03.2020
Accepted: 20.03.2020

analyzing the role of NLR in IGM. Kargin et al. (2) have compared NLR in patients with (n=7) and without (n=52) recurrence and have found that NLR was significantly higher in patients with a recurrence (p<0.001) but they have not performed a ROC analysis to support their observations.

References

1. Çetinkaya ÖA, Çelik SU, Terzioğlu SG, Eroğlu A. The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis. Eur J Breast Health 2020; 16: 61-65. (PMID: 31912016) [Crossref]
2. Kargin S, Turan E, Esen HH, Kargin NC. Role of Pre-treatment Neutrophil-Lymphocyte Ratio in the Prediction of Recurrences After Granulomatous Mastitis Treatment. Turkiye Klinikleri J Med Sci 2020; 40: 46-51.

Author's Reply

Re: The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis

Ömer Arda Çetinkaya[1], Süleyman Utku Çelik[1,2], Serdar Gökay Terzioğlu[3], Aydan Eroğlu[4]

[1]Department of General Surgery, Ankara University School of Medicine, Ankara, Turkey
[2]Clinic of General Surgery, Gulhane Training and Research Hospital, Ankara, Turkey
[3]Clinic of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey
[4]Surgical Oncology Unit, Department of General Surgery, Ankara University School of Medicine, Ankara, Turkey

Dear Editor,

We read the comment on our article (1), "The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis" with great interest.

We agree with Akbulut and Sahin. Granulomatous mastitis (GM) is a heterogeneous group of diseases of unknown etiology; however, idiopathic granulomatous mastitis (IGM) is a diagnosis of exclusion.

With a cut-off value of 5.02, the preoperative neutrophil-to-lymphocyte ratio had a sensitivity of 62.5% and a specificity of 84.8%, as we reported, as well as a positive predictive value (PPV) of 50.0% and a negative predictive value (NPV) of 90.3% in predicting recurrent IGM. Sensitivity and specificity are independent of the population of interest subjected to the test. They are dependent on the cut-off value above or below which the test is positive. In other words, these diagnostic performance parameters are threshold dependent. However, PPV and NPV are dependent on the prevalence of the disease in the population of interest and is known as changeable parameters according to prevalence (2). In rare cases such as IGM, the recurrence rate may change from region to region as well as according to treatment strategies. Thus, if the prevalence of the disease in a 2 × 2 table is not the same as in the population, interpreting the results according to PPV or NPV may not be the right approach (3).

Multivariate analysis is used to describe analyses of data where there are multiple variables or observations for each unit or individual and is used to further examine the variables indicated by the univariate analysis. Theoretically, every variable collected in the study could be a candidate predictor. However, to reduce the risk of false-positive findings and improve model performance, the events per variable rule of thumb is commonly applied and at a minimum set to 10 for multivariate logistic regression. This rule of thumb recommends that at least 10 individuals need to have developed the outcome of interest for every predictor variable included in the model (4). For logistic regression, the number of events is given by the size of the smallest of the outcome categories. In our study, because of relatively low number of patients and the low recurrence rate (8/33), we could not run multivariate analysis. Interestingly, we are not able to understand how Akbulut and Sahin run a multivariate analysis, without any dataset in their hands. Of course, this is impossible. Because selecting variables for regression analysis using univariate analysis is not the only way; there are multiple methods used for choosing the variables to be included in the final model without introducing bias into the analysis. These variables can be determined by the literature review, the experience in the field, correlation, or maybe risk factors for the disease. We think that to perform a multivariate analysis using the data in table 2 (1) will give a wrong direction.

Corresponding Author: Ömer Arda Çetinkaya
e-mail: omerardacetinkaya@yahoo.com

DOI: 10.5152/ejbh.2020.5786

Received: 15.05.2020
Accepted: 18.05.2020

Cite this article as: Çetinkaya ÖA, Çelik SU, Terzioğlu SG, Eroğlu A. Re: The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis. Eur J Breast Health 2020; 16(3): 227.

References

1. Çetinkaya ÖA, Çelik SU, Terzioğlu SG, Eroğlu A. The Predictive Value of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio in Patients with Recurrent Idiopathic Granulomatous Mastitis. Eur J Breast Health 2020; 16: 61-65. (PMID: 31912016) [Crossref]
2. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. Continuing Education in Anaesthesia Critical Care & Pain 2008; 8: 221-223. [Crossref]
3. Molinaro AM. Diagnostic tests: how to estimate the positive predictive value. Neurooncol Pract 2015; 2: 162-166. (PMID: 31386059) [Crossref]
4. Shipe ME, Deppen SA, Farjah F, Grogan EL. Developing prediction models for clinical use using logistic regression: an overview. J Thorac Dis 2019; 11: 574-584. (PMID: 31032076) [Crossref]

Erratum

Eur J Breast Health 2020; 16(3): 228
DOI: 10.5152/ejbh.2020.300420

In the article by Soran et al., entitled '"Breast Cancer Diagnosis, Treatment, and Follow-Up During COVID-19 Pandemic" (Eur J Breast Health 2020; 16: 86-88, DOI: 10.5152/ejbh.2020.240320) that was published in the April 2020 issue of European Journal of Breast Health, one of the contributing authors' name was erroneously omitted from the author list and affiliation information of one author was provided incorrectly due to an author error.

These errors have been corrected and the updated version of the article is available on the journal's website.