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# European Journal of Breast Health

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Turkish Federation of Breast Diseases Societies

European Journal of Breast Health is the official journal of the **Turkish Federation of Breast Diseases Societies**

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# European Journal of Breast Health



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



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European Journal of Breast Health

European Journal of Breast Health

# Aims and Scope

The 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 journal. It is the official publication of the Turkish Federation of Breast Diseases Societies, and the Senologic International Society (SIS) is the official supporter of the journal.

The 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 a 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 articlesreviews, 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, and very original case reports that are prepared and presented according to the ethical guidelines.

TOPICS within the SCOPE of EJBH concerning 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 surgery, oncology, breast health 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 conforms with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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**Editor in Chief: Prof. Vahit ÖZMEN**

Address: Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, Çapa, İstanbul

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E-mail : editor@eurjbreasthealth.com

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| 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 |

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

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

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# Contents

## REVIEW



## ORIGINAL ARTICLES

European Journal of Breast Health

# Contents

Review

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# The Role of Primary Surgery in *De Novo* Metastatic Breast Carcinoma

Berkay Demirors[1], Berk Goktepe[2], Hannah Medeck[3], Serdar Ozbas[4], Atilla Soran[5]

[1]Department of General Surgery, Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Turkey
[2]Department of General Surgery, Ege University School of Medicine, Izmir, Turkey
[3]General Surgery Resident PGY-3, UPMC Mercy Hospital, Pittsburgh PA, USA
[4]Private Practice, Ankara, Turkey
[5]Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA USA

**ABSTRACT**

Approximately 6-10% of all breast carcinoma is metastatic at diagnosis, termed *de novo* metastatic breast carcinoma (dnMBC). Systemic therapy remains the first line of treatment in dnMBC, but there is growing evidence that adjuvant locoregional treatment (LRT) of the primary tumor increases progression-free and overall survival (OS). Although selection bias may exist, real-world data from nearly half a million patients show that patients are undergoing primary tumor removal because of the survival benefit. The main question for the advocates for LRT in this patient population is not whether primary surgery is beneficial in dnMBC patients, but rather who is a good candidate for it. Oligometastatic disease (OMD) is a distinct subset of dnMBC that affects a limited number of organs. A better OS can be achieved with LRT in breast cancer patients, especially in those with OMD, bone only, or favorable subtypes. Though there is currently no consensus among breast care specialists on how to treat dnMBC patients, primary surgery for dnMBC should be taken into consideration for a subset of patients following an extensive multidisciplinary discussion.

**Keywords:** Locoregional treatment; metastatic breast carcinoma; oligometastatic disease; survival; systemic therapy

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**Key Points**

- There are currently no specific guidelines for the treatment of *de novo* metastatic breast cancer (dnMBC) patients.
- Locoregional treatment in stage IV breast cancer may have a potential role in a subgroup of patients with dnMBC.
- Patient age, metastatic burden, and molecular subtypes are important parameters for patient selection.
- With more aggressive treatment, complete clinical and pathological remission can be achieved, especially in oligometastatic patients.
- Primary surgery for dnMBC should be considered for a subset of patients following a thorough multidisciplinary discussion.

## Introduction

The incidence of new-onset primary breast carcinoma (BC) with synchronous metastases at diagnosis is commonly known as *de novo* metastatic breast carcinoma (dnMBC). The incidence of dnMBC is approximately 6-10% (1, 2). With improved imaging modalities, the number of patients diagnosed with dnMBC has increased. As the mechanisms of tumor biology are better understood and with the advent of new systemic treatment (ST) agents, survival has increased in patients with dnMBC. Although the first choice of therapy in patients with stage IV breast cancer (BC) is still ST, there is currently data that suggests that some subgroups of patients with dnMBC may benefit from primary locoregional treatment (LRT). Surgical removal of a primary tumor may improve survival by reducing tumor burden, decreasing immunomodulatory effects, removing the risk of new-onset metastatic illnesses, and reducing the likelihood of resistance (3, 4).

In 2002, Khan et al. (5) conducted a retrospective study indicating that primary surgery may have a role in the treatment of dnMBC. This study generated much interest and numerous retrospective studies and meta-analyses were then published (6-17). Many of these trials indicate that LRT is beneficial against local progression and improves disease-free survival (DFS) and overall survival (OS). However, these trials had inherent patient selection bias because of their retrospective design, rendering the data unreliable. Patients were younger, had less metastatic burden, and usually had favorable molecular subtypes in

**Corresponding Author:**
**Atilla Soran; asoran@upmc.edu**

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the LRT arms. Meta-analysis also showed that LRT improved survival (18-21). Consequently, randomized studies were designed to verify this hypothesis.

## Prospective Randomized Clinical Trials

At the time of writing, the results of four prospective studies with differing methodologies have been published. However, it is important to review and discuss the available data in order to identify subgroups of dnMBC patients that could benefit the most from LRT of the primary tumor (22).

In 2015, Badwe et al. (23) published an Indian study with a total of 350 patients who had ST first and patients who did not progress were later randomly assigned to LRT or continued ST. The findings of this study demonstrated that LRT is ineffective in terms of OS [19.2 months for the LRT group vs 20.5 months in the ST group; hazard ratio (HR) 1.04, 95% confidence interval (CI) 0·81-1·34; $p$ = 0.79]. Furthermore, the site of metastasis (bone, visceral organ, and visceral organ with bone) did not correlate with OS. Individuals in the LRT group had significantly improved locoregional progression-free survival, but distant metastases were associated with poorer results (median 11.3 and 19.8 months for LRT and ST, respectively). The most controversial part of the study was that 26% of LRT patients and 35% of ST patients who were HER2-positive did not receive anti-HER2 medication.

The MF07-01 protocol, supported by the Turkish Federation of Breast Disease Societies, was the second study, published in 2018 (24). Patients were randomised to either upfront surgery followed by ST or ST alone. The early results of this trial were first presented at the San Antonio Breast Symposium in 2015 with a median 3-year follow up and there was no statistically significant difference between groups in terms of OS. However, at a median of 40 months of follow-up, the LRT group (n = 138) had a 34% reduced death risk (HoD), significantly lower than the ST group (n = 136) (HR 0.66, 95% CI 0.49 to 0.88, $p$ = 0.005). The LRT and ST groups had respective OS rates of 41.6% and 24.4%. In the subgroup analysis, estrogen receptor (ER) positive (HR 0.64, 95% CI 0.46-0.91, $p$ = 0.01), HER2 receptor negative (HR 0.64, 95% CI 0.45- 0.91, $p$ = 0.01), patients under 55 years of age (HR 0.57, 95% CI 0.38-0.86, $p$ = 0.007) and patients with solitary bone metastases (HR 0.47, 95% CI 0.23-0.98, $p$ = 0.04) had lower risk of death in the LRT group. In 2021, 10-year follow-up of this study was published (25). The median OS for the LRT group (n = 134) was 46 months compared to 35 months for the ST group (n = 131). The LRT group had a 29% decreased mortality rate (HR 0.71, 95% CI 0.59 to 0.86, $p$ = 0.00003). The OS rates for the LRT and ST groups at 10-years of follow-up were 19% (95% CI 13-28) and 5% (95% CI 2-12), respectively. Using the most recent follow-up information and additional classification criteria, HER2-positive patients in the LRT group had a higher OS rate. The ST group had a 14-fold higher locoregional progression than the LRT group at 10-year follow-up (14% in the ST group versus 1% in the LRT group).

The third prospective trial published in 2019 was the ABCSG-28 POSITIVE study by Fitzal et al. (26). The methodology and design were comparable to the MF07-01 study. Although a sample size of around 254 was intended, only 95 patients were enrolled. This study was stopped early due to poor recruitment that possibly decreased the statistical power. The LRT and ST groups showed comparable OS rates (HR 0.69, 95% CI 0.36-1.33, $p$ = 0.27) and time to distant metastases (HR 0.60, 95% CI 0.34-1.04, $p$ = 0.07). Similar rates of locoregional progression were found in both groups (HR 0.933, 0.375-2.322, p = 0.882), while the LRT group had significantly fewer cases (17.8% vs. 8.9%, $p$ = 0.2148). Surgical margin positivity was observed in 21% of the LRT group. Of note, cT3 and cN2 tumors were more prevalent in the LRT arm (22.2% vs. 6.7% and 15.6% vs. 4.4%, respectively).

The most recent study on this topic was the E2108 trial by Khan et al. (27) published in 2022 after the data was initially presented at ASCO in 2020. The protocol of this study was similar to the Indian study. The initial endpoint was based on OS, while the secondary endpoints were locoregional recurrence and quality of life (QoL). A total of 256 patients with dnMBC who didn't progress after 4-8 months of ST were then randomized to LRT plus ST (n = 125) or ST only groups (n = 131). Three-year OS rates were similar between groups (68.4% vs. 67.9%; HR, 1.11; 90% CI, 0.82–1.52; p = 0.57). No progression-free survival difference was observed between the groups. However, locoregional progression was reduced in the LRT group ($p$<0.001). It was found that hormone receptor (HR) and HER2 status had no statistically significant influence on overall survival with LRT. Of the patients randomly assigned to the LRT group, 14.4% did not receive primary breast surgery and 7.2% had no axillary surgery at all. Furthermore, 8.4% of patients had positive margins in the final histopathological examination. In addition, adjuvant RT, which is inevitable after breast conserving surgery (BCS), was not performed in 12.9% of the patients. Alternatively, 18.8% (5 of 22) had mastectomies or BCS in the ST group. Sentinel lymph node biopsy/axillary lymph node dissection were performed together in 77% of the patients (17 of 22) who were randomly assigned to the ST group, and RT was also completed in 45% of patients (10 of 22) who underwent surgery. There were no palliative axillary procedures performed in the non-operative arm of the published comparable randomized studies. The curative intent of surgery and RT in the ST arm may statistically mask the cumulative effect of LRT on OS. The E2108 study included only 16% of oligometastatic patients, the vast majority of whom had multiple organ metastasis (84%). As such, the study does not reflect the data from the group that was most expected to respond to LRT.

It is important to note that LRT does not contribute to improved OS, even in the MF07-01 study at 3-year follow-up. However, the long-term results of the MF07-01 study in the peer-reviewed publication showed that local control provides a significant survival advantage in all subgroups except for the patients with triple negative (TN) BC in both 5-year and 10-year OS.

## Oligometastatic Disease

The majority of randomized studies did not show a survival benefit of LRT in dnMBC, but these trials are heterogeneous in design and there are subgroups of patients that deserve detailed analysis. When addressing primary surgery for dnMBC patients, detailed information about oligometastatic disease (OMD) is important. Though this term has no formal definition, OMD often refers to less than five metastases (28).

Unfortunately, literature regarding the survival impact of surgical resection of the primary tumor in oligometastatic BC patients is lacking. In the E2108 and Indian studies, no survival difference was reported for oligometastatic patients, which represented 16.3% and 25% of the study population, respectively (23, 27, 29). It is also important to address metastases-directed treatment when assessing

the impact of local treatment of the primary tumor in oligometastatic BC. The combination of LRT of the primary tumor and metastasis-directed therapy, aimed at complete eradication of detectable disease, should be investigated. Metastasis-directed interventions have reduced the risk of death for patients with limited lung/liver metastases who are amenable to interventions after completion of primary cancer treatment.

The IMET study published in 2022 enrolled 200 patients with luminal A/B and/or human HER2-positive patients with operable lung and/or liver metastases in the follow-up assessment after completion of primary BC treatment. The median follow-up time was 77 months in the intervention (IT) group (n = 119; 59.5%) and 57 months (range 39–84) in the ST-only group (n = 81; 40.5%). The median (range) metastasis detection-free interval (MDFI) was 40 (23–70) months in the IT group, and 35 (13–61) months in the ST-only group (p = 0.47). The groups had similar surgeries for the primary tumor and axilla. Nearly half of the patients had liver metastases (49.5%, n = 99), and 42% (n = 84) of the patients had lung metastases. Both lung and liver metastases were found in 8.5% (n=17) of the patients. The primary tumor was HR positive in 75% (n = 150) of the patients, and 32% (n = 64) of the patients had HER2 positive tumors. Metastatic-site resection was performed for 32% (n = 64) of the patients, and 27.5% (n = 55) of the patients underwent metastatic ablative interventions. In the Kaplan-Meier survival analysis, the HoD was 56% lower in the IT group than in the ST-only group (hazard ratio HR 0.44; 95% CI 0.26–0.72; $p$ = 0.001). The HoD was lower in the IT group than in the ST-only group for the patients younger than 55 years (HR, 0.32; 95% CI 0.17–0.62; $p$ = 0.0007). In the multivariable Cox regression model, HoD was significantly lower for the patients who underwent intervention for metastases and had an MDFI longer than 24 months, but their liver metastases doubled the risk of death compared with lung metastases (28).

## Bone-only Disease

The dnMBC patients with bone-only disease usually have a better prognosis. BOMET MF14-01 is a prospective, multicenter registry study that evaluated the role of LRT of the primary tumor in addition to ST in dnMBC patients with bone-only disease. This study included 505 patients and concluded a better survival in the median 3-year follow-up in favor of LRT (HR 0.40, $p$<0.0001) (30).

In a large cohort retrospective study including 3956 BC patients with bone metastases, surgery of the primary tumor in addition to ST significantly improved OS with a median survival of 50 months versus 31 months in ST-only patients ($p$<0.001) (31).

Regarding randomized trials, in the MF07-01 study, 51% and 40% of patients presented with bone-only metastases in the LRT group and ST group respectively. Notably, 23% and 15% of patients had a solitary bone metastasis in the LRT and ST groups, respectively. In unplanned subgroup analysis, solitary bone metastasis was associated with a lower risk of death if treated with LRT in addition to ST (24). Conversely, in the E2108 trial, patients with bone-only disease (37.7%) were under-represented (27).

### Molecular Subtypes

HR-positive tumors have the best prognosis among the subtypes of breast cancer (32). According to retrospective studies, HR-positive dnMBC patients benefit the most from LRT (33-35). In the subgroup analysis of the MF07-01 study, HR-positive status was also a relevant factor for surgical decision making (25). One of the pitfalls of this study was that HR-positive patients are over-represented in the LRT arm, which results in uncertainty regarding the results of this trial. In the ABCSG-28 POSYTIVE study, luminal B subtype did not show a statistically significant benefit from primary tumor surgery. In contrast, surgery adversely affected survival in the luminal A subgroup (26). The E2108 trial showed that the TN immunohistochemical subtype was associated with poor prognosis in dnMBC patients undergoing surgery. Similar findings were seen in the MF07-01 trial. Some retrospective evidence also seems to support the use of LRT in the HER2-positive subtype. Even if HER2 expression results in a more aggressive disease with a poor prognosis, the use of HER2-targeted therapy led to outstanding survival benefit in these patients. According to retrospective observational studies, 13–32% of patients with HER 2 positive dnMBC who received LRT and had no evidence of disease lived for more than ten years (36, 37).

## Quality of Life

While primary surgery in dnMBC patients appears to improve OS, the impact on quality of life (QoL) must also be explored. In their MF07-01Q study, Soran et al. concluded that LRT had no detrimental effect on QoL compared to ST only in a cohort of patients who lived longer than three years, but the toxic effects of continued ST might be the cause of lower physical QoL scores compared to those of the general population and stage I-III BC patients (38). In the E2108 trial, Khan et al. (27) assessed health-related quality of life (HRQoL) using the FACT-B study assessment (Trial Outcome Index), which encompasses depression, anxiety, and well-being. Although HRQoL outcomes in the LRT group worsened at 18-month follow-up, results were comparable at the 6 and 30-month follow-ups. In conclusion, the EA2108 study found neither an improvement in OS nor a change in the QoL scale in patients who underwent LRT.

Although modified radical mastectomy (MRM) is associated with higher morbidity than BCS, retrospective studies of primary surgery in *de novo* metastatic inflammatory BC (IBC) found that MRM was an independent factor associated with OS in patients with dnMBC metastatic IBC (39). Chen et al. (40) Also noted that MRM may improve disease specific survival in a subset of dnIBC patients. A randomized clinical study, JCOG 1017, is currently underway and this study will add more valuable evidence to this cohort of patients' survival and QoL (41).

## Conclusion

Survival in dnMBC patients is currently higher than in the past decade. Typically, patients with dnMBC have more favorable disease characteristics and longer OS compared to metachronous patients (42). Stage IV BC is an extremely heterogenous disease and prognosis for these patients may vary according to the treatment choice. ST for dnMBC patients has dramatically evolved over the last two decades for every molecular subtype. LRT of the primary tumor and modern ST seem to be the perfect partners for better DFS and OS. Current guidelines offer LRT in selected cases due to the lack of clear evidence. However, there may be a subgroup of patients that may benefit more from LRT, including younger age, less tumor burden (oligometastatic disease, bone-only disease) and favorable molecular subtype (HR positive patients). Meanwhile, LRT of the primary tumor should be discussed in a multidisciplinary context for every patient with dnMBC.

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### Authorship Contributions

Surgical and Medical Practices: S.O., A.S.; Concept: B.D., B.G., H.M., S.O., A.S.; Design: B.D., B.G., H.M., S.O., A.S.; Data Collection and/ or Processing: B.D., B.G., H.M., S.O., A.S.; Analysis and/or Interpretation: B.D., B.G., H.M., S.O., A.S.; Literature Search: B.D., B.G., S.O., A.S.; Writing: B.D., B.G., H.M., S.O., A.S.

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## References


1. Gnerlich J, Jeffe DB, Deshpande AD, Beers C, Zander C, Margenthaler JA. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. Ann Surg Oncol 2007; 14: 2187-2194. (PMID: 17522944) [Crossref]
2. Blanchard DK, Shetty PB, Hilsenbeck SG, Elledge RM. Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg 2008; 247: 732-738. (PMID: 18438108) [Crossref]
3. Danna EA, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 2004; 64: 2205-2211. (PMID: 15026364) [Crossref]
4. Norton L, Massagué J. Is cancer a disease of self-seeding? Nat Med 2006; 12: 875-878. (PMID: 16892025) [Crossref]
5. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 2002; 132: 620-626; discussion 626-627. (PMID: 12407345) [Crossref]
6. Khan SA. Primary tumor resection in stage IV breast cancer: consistent benefit, or consistent bias? Ann Surg Oncol 2007; 14: 3285-3287. (PMID: 17891444) [Crossref]
7. Babiera GV, Rao R, Feng L, Meric-Bernstam F, Kuerer HM, Singletary SE, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 2006; 13: 776-782. (PMID: 16614878) [Crossref]
8. Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006; 24: 2743-2749. (PMID: 16702580) [Crossref]
9. Fields RC, Jeffe DB, Trinkaus K, Zhang Q, Arthur C, Aft R, et al. Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. Ann Surg Oncol 2007; 14: 3345-3351. (PMID: 17687611) [Crossref]
10. Arriagada R, Rutqvist LE, Mattsson A, Kramar A, Rotstein S. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. J Clin Oncol 1995; 13: 2869-2878. (PMID: 8523049) [Crossref]
11. Hazard HW, Gorla SR, Scholtens D, Kiel K, Gradishar WJ, Khan SA. Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. Cancer 2008; 113: 2011-2019. (PMID: 18780312) [Crossref]
12. Nieto Y, Nawaz S, Jones RB, Shpall EJ, Cagnoni PJ, McSweeney PA, et al. Prognostic model for relapse after high-dose chemotherapy with autologous stem-cell transplantation for stage IV oligometastatic breast cancer. J Clin Oncol 2002; 20: 707-718. (PMID: 11821452) [Crossref]
13. Bafford AC, Burstein HJ, Barkley CR, Smith BL, Lipsitz S, Iglehart JD, et al. Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. Breast Cancer Res Treat 2009; 115: 7-12. (PMID: 18581232) [Crossref]
14. Ruiterkamp J, Ernst MF, van de Poll-Franse LV, Bosscha K, Tjan-Heijnen VC, Voogd AC. Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. Eur J Surg Oncol 2009; 35: 1146-1151. (PMID: 19398188) [Crossref]
15. Shien T, Kinoshita T, Shimizu C, Hojo T, Taira N, Doihara H, et al. Primary tumor resection improves the survival of younger patients with metastatic breast cancer. Oncol Rep 2009; 21: 827-832. (PMID: 19212646) [Crossref]
16. Harris E, Barry M, Kell MR. Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 2013; 20: 2828-2834. (PMID: 23653043) [Crossref]
17. Petrelli F, Barni S. Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. Med Oncol 2012; 29: 3282-3290. (PMID: 22843291) [Crossref]
18. Xiao W, Zou Y, Zheng S, Hu X, Liu P, Xie X, et al. Primary tumor resection in stage IV breast cancer: A systematic review and meta-analysis. Eur J Surg Oncol 2018; 44: 1504-1512. (PMID: 30146252) [Crossref]
19. Gera R, Chehade HELH, Wazir U, Tayeh S, Kasem A, Mokbel K. Locoregional therapy of the primary tumour in *de novo* stage IV breast cancer in 216 066 patients: A meta-analysis. Sci Rep 2020; 10: 2952. (PMID: 32076063) [Crossref]
20. Kim KN, Qureshi MM, Huang D, Ko NY, Cassidy M, Oshry L, et al. The Impact of Locoregional Treatment on Survival in Patients With Metastatic Breast Cancer: A National Cancer Database Analysis. Clin Breast Cancer 2020; 20: e200-e213. (PMID: 32089454) [Crossref]
21. Lane WO, Thomas SM, Blitzblau RC, Plichta JK, Rosenberger LH, Fayanju OM, et al. Surgical Resection of the Primary Tumor in Women With De Novo Stage IV Breast Cancer: Contemporary Practice Patterns and Survival Analysis. Ann Surg 2019; 269: 537-544. (PMID: 29227346) [Crossref]
22. Merloni F, Palleschi M, Gianni C, Casadei C, Curcio A, Romeo A, et al. Locoregional treatment of de novo stage IV breast cancer in the era of modern oncology. Front Oncol 2023; 13: 1083297. (PMID: 3679360) [Crossref]
23. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 2015; 16: 1380-1388. (PMID: 26363985) [Crossref]
24. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Ann Surg Oncol 2018; 25: 3141-3149. (PMID: 29777404) [Crossref]
25. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, et al. MF07-01 Study Group. Primary Surgery with Systemic Therapy in Patients with de Novo Stage IV Breast Cancer: 10-year Follow-up; Protocol MF07-01 Randomized Clinical Trial. J Am Coll Surg 2021; 233: 742-751.e5. (PMID: 34530124) [Crossref]
26. Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M, Balic M, et al. ABCSG. Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE Trial. Ann Surg 2019; 269: 1163-1169. (PMID: 31082916) [Crossref]
27. Khan SA, Zhao F, Goldstein LJ, Cella D, Basik M, Golshan M, et al. Early Local Therapy for the Primary Site in De Novo Stage IV Breast Cancer: Results of a Randomized Clinical Trial (EA2108). J Clin Oncol 2022; 40: 978-987. Erratum in: J Clin Oncol. 2022; 40: 1392. (PMID: 34995128) [Crossref]
28. Soran A, Ozbas S, Ozcinar B, Isik A, Dogan L, Senol K, et al. Breast Health Working Group International. Intervention for Hepatic and

Pulmonary Metastases in Breast Cancer Patients: Prospective, Multi-institutional Registry Study-IMET, Protocol MF 14-02. Ann Surg Oncol 2022; 29: 6327-6336. Erratum in: Ann Surg Oncol 2023; 30: 1074. (PMID: 35876920) [Crossref]

29. Soran A, Özbaş S, Doğan L, Sezgin E, Özmen V, Beriwal S, et al. 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: 158-159. (PMID: 32656512) [Crossref]
30. Soran A, Dogan L, Isik A, Ozbas S, Trabulus DC, Demirci U, et al. The Effect of Primary Surgery in Patients with De Novo Stage IV Breast Cancer with Bone Metastasis Only (Protocol BOMET MF 14-01): A Multi-Center, Prospective Registry Study. Ann Surg Oncol 2021; 28: 5048-5057. (PMID: 33532878) [Crossref]
31. Huang Z, Zhou X, Tong Y, Zhu L, Zhao R, Huang X. Surgery for primary tumor benefits survival for breast cancer patients with bone metastases: a large cohort retrospective study. BMC Cancer 2021; 21: 222. (PMID: 33663462) [Crossref]
32. McAndrew NP, Finn RS. Clinical Review on the Management of Hormone Receptor-Positive Metastatic Breast Cancer. JCO Oncol Pract 2022; 18: 319-327. (PMID: 34637323) [Crossref]
33. Tan Y, Li X, Chen H, Hu Y, Jiang M, Fu J, et al. Hormone receptor status may impact the survival benefit of surgery in stage iv breast cancer: a population-based study. Oncotarget 2016; 7: 70991-71000. (PMID: 27542240) [Crossref]
34. Neuman HB, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? Cancer 2010; 116: 1226-1233. (PMID: 20101736) [Crossref]
35. Thomas A, Khan SA, Chrischilles EA, Schroeder MC. Initial Surgery and Survival in Stage IV Breast Cancer in the United States, 1988-2011. JAMA Surg 2016; 151: 424-431. (PMID: 26629881) [Crossref]
36. Smith CEP, Marcom PK, Mitri Z, Ko NY. Predictors of long-term durable response in de novo HER2-positive metastatic breast cancer and the real-world treatment experience at two institutions. Breast Cancer Res Treat 2022; 196: 215-220. (PMID: 36087190) [Crossref]
37. Wong Y, Raghavendra AS, Hatzis C, Irizarry JP, Vega T, Horowitz N, et al. Long-Term Survival of De Novo Stage IV Human Epidermal Growth Receptor 2 (HER2) Positive Breast Cancers Treated with HER2-Targeted Therapy. Oncologist 2019; 24: 313-318. (PMID: 30139836) [Crossref]
38. Soran A, Soyder A, Ozbas S, Ozmen V, Karanlik H, Igci A, et al. Breast Health Working Group International (supported by the Turkish Federation of Breast Disease Societies). The role of loco-regional treatment in long-term quality of life in de novo stage IV breast cancer patients: protocol MF07-01Q. Support Care Cancer 2021; 29: 3823-3830. (PMID: 33242163) [Crossref]
39. Partain N, Postlewait LM, Teshome M, Rosso K, Hall C, Song J, et al. The Role of Mastectomy in De Novo Stage IV Inflammatory Breast Cancer. Ann Surg Oncol 2021; 28: 4265-4274. (PMID: 33403525) [Crossref]
40. Chen JC, Li Y, Fisher JL, Bhattacharyya O, Tsung A, Bazan JG, et al. Modified Radical Mastectomy in De Novo Stage IV Inflammatory Breast Cancer. Ann Surg Oncol 2022; 29: 6681-6688. (PMID: 35676605) [Crossref]
41. Shien T, Nakamura K, Shibata T, Kinoshita T, Aogi K, Fujisawa T, et al. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. Jpn J Clin Oncol 2012; 42: 970-973. (PMID: 22833684) [Crossref]
42. de Maar JS, Luyendijk M, Suelmann BBM, van der Kruijssen DEW, Elias SG, Siesling S, et al. Comparison between de novo and metachronous metastatic breast cancer: the presence of a primary tumour is not the only difference-a Dutch population-based study from 2008 to 2018. Breast Cancer Res Treat 2023; 198: 253-264. (PMID: 36648694) [Crossref]

**Original Article**

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# Pure Tubular Breast Carcinoma: Clinicopathological Characteristics and Clinical Outcomes

Selman Emiroglu[1], Asmaa Mahmoud Abuaisha[2], Mustafa Tukenmez[1], Neslihan Cabioglu[1], Aysel Bayram[3], Vahit Ozmen[4], Mahmut Muslumanoglu[1]

[1]Breast Surgery Unit, Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[2]Department of Genetics, Institute of Health Sciences, Istanbul University, Istanbul, Turkey
[3]Department of Pathology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[4]Breast Surgery Unit, Department of General Surgery, Grup Florence Nightingale Hospital, Istanbul, Turkey

**ABSTRACT**

**Objective:** Tubular breast carcinoma (TBC) is a rare subtype of breast carcinoma (BC) with a good prognosis. In this study, we aimed to assess the clinicopathological characteristics of pure TBC (PTBC), analyze factors that may influence long-term prognosis, examine the frequency of axillary lymph node metastasis (ALNM), and discuss the need for axillary surgery in PTBC.

**Materials and Methods:** Fifty-four Patients diagnosed with PTBC between January 2003 and December 2020 at Istanbul Faculty of Medicine were included. Clinicopathological, surgical, treatment, and overall survival (OS) data were analyzed.

**Results:** A total of 54 patients with a mean age of 52.2 years were assessed. The mean size of the tumor was 10.6 mm. Four (7.4%) patients had not undergone axillary surgery, while thirty-eight (70.4%) had undergone sentinel lymph node biopsy and twelve (22.2%) had undergone axillary lymph node dissection (ALND). Significantly, four (33.3%) of those who had undergone ALND had tumor grade 2 ($p$ = 0.020) and eight of them (66.7%) had ALNM. Fifty percent (50%) of patients who were treated with chemotherapy had grade 2 and multifocal tumors and ALNM. Moreover, the frequency of ALNM was higher in patients with tumor diameters greater than 10 mm. Median follow-up time was 80 months (12–220). None of the patients had locoregional recurrence, but one patient had systemic metastasis. Furthermore, five-year OS was 97.9%, while ten-year OS was 93.6%.

**Conclusion:** PTBC is associated with favorable prognosis, good clinical outcomes and high survival rate, with rare recurrences and metastases.

**Keywords:** Pure tubular breast carcinoma, clinicopathologic characteristics, axillary lymph node metastasis, and clinical outcomes

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**Key Points**

- Pure tubular breast carcinoma (PTBC) is associated with favorable prognosis and clinical outcomes.
- Fifty percent (50%) of PTBC patients who were treated with chemotherapy had grade 2 and multifocal tumors, and axillary lymph node metastasis (ALNM).
- The frequency of ALNM was higher in PTBC patients with tumor diameters greater than 10 mm.

## Introduction

Tubular breast carcinoma (TBC) is a rare subtype, accounting for 1–2% of all breast carcinomas (BC) (1). TBC is a variant of invasive ductal carcinoma (IDC), characterized by well-formed tubular or glandular structures that are similar to structures seen in non-neoplastic mammary parenchyma (2). TBC is generally positive for estrogen receptors (ER) and usually positive for progesterone receptors (PR) and negative for human epidermal growth factor receptor-2 (HER2) overexpression (1). Histologically, TBC is classified into pure and mixed. Pure TBC (PTBC) contains a minimum of 90% tubular elements, and rare to no mitotic figures with low nuclear grade (G1) (3, 4). Generally, TBC has good biologic behavior and prognosis (3), with an incidence of metastasis of 8–20% compared with 50–60% for BC (5, 6). Even if metastasis occurs, TBC 15-year overall survival (OS) was as high as 100% for PTBC (6).

At the genetic level, genetic alterations in TBC are uncommon (7), and it's similar to that in low-grade luminal subtypes of BC (8). Genetic abnormalities mainly include chromosomal abnormalities, such as 16q loss (78–86%) and 1q gain (50–62%). In addition, other genetic abnormalities have been reported, including the loss of 17p, 8p and 3p and the gain of 16p and 11q (7). Based on gene expression profiling studies, it has been demonstrated that TBC belongs to the

**Corresponding Author:**
**Selman Emiroğlu; selman.emirikci.82@istanbul.edu.tr**

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luminal A subtype of BC. Moreover, no association was reported between *BRCA1* and *BRCA2* mutation carriers and non-carriers in TBC patients' families (9).

According to the National Comprehensive Cancer Network guidelines, TBC treatment is determined by the positivity of PR, ER, and HER2. The treatment protocol for patients with PR and ER negative or HER2 positive will be the same as in IDC. Adjuvant treatments for patients with PR and ER positive and HER2-negative tumors are determined by tumor size and axillary lymph node (ALN) status. Adjuvant endocrine therapy is considered the treatment protocol for tumors of less than 3 cm and is recommended for tumors greater than 3 cm or node positive tumors. For patients with node-positive tumors, adjuvant chemotherapy is an option (10).

Breast cancer surgery has evolved to become more conservative for both the breast and axilla. ALND is typically reserved for patients with significant axillary disease, since it is associated with significant morbidity (11). Therefore, patient selection must be carefully considered. In particular, if there is one or two lymph node positivity, there is no need for complete axillary dissection in axillary surgery, as suggested in the ACOSOG Z0011 study (11). Additionally, many studies have postulated that axillary staging may be unnecessary in TBC patients (12, 13).

## Materials and Methods

### Patients Selection

This study is based on our analysis of a large, mono-institutional series of PTBC patients treated in a high-volume reference center with widely standardized treatment and management. A multidisciplinary team had discussed each case individually after surgery, and all decisions about adjuvant treatment had been made. The study population was made up of patients diagnosed with PTBC between January 2003 and December 2020 at the Department of General Surgery, Breast Surgery Unit. The histological types of all cases were carefully evaluated. Multiple clinical and pathological factors were investigated.

### Pathological Investigation

The pathological tumor stage was assessed according to the American Joint Committee on Cancer's 7$^{th}$ Staging System (14). Clinical features, demographic data and primary tumor characteristics were gathered from the institution digital records and pathology reports. Paraffin-embedded tissue obtained from excision specimen was microcut and stained with hematoxylin and eosin (H&E). ER (clone SP1, 1:100 dilution; Biocare Concord, CA, USA) and PR (clone SP2, 1:400 dilution; Spring Pleasanton, CA, USA), HER2 (clone SP3, 1:200 dilution; Thermo Waltham, MA, USA) and Ki67 (clone SP6, 1:100 dilution; Biocare Concord, CA, USA) were assessed by reviewing the archived glass slides. Either sentinel lymph nodes (SLNs) or lymph nodes cleared during axillary dissection were embedded in paraffin. The block of each lymph node was cut into 2 mm-thick sections and stained with H&E. Each slide was histopathologically reviewed under a light microscope for the presence of any metastatic cancer clusters (Figure 1).

### Patient Follow-up and Treatment

Follow-up of patients was carried out at Istanbul Faculty of Medicine, Breast Surgery Unit. Patients came for follow-up every three months for the first two years, then every six months for the next two years, and later once a year. OS was defined as the number of months from the operation to the date of death. Patients were treated with either mastectomy or lumpectomy and ALND or sentinel lymph node biopsy (SLNB) with local radiotherapy. Hormone (PR/ER) receptor-positive patients received endocrine therapy.

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. Shapiro-Wilk test was used to test the normality of the data distribution of continuous variables with the statistical method. For data analysis, descriptive statistical methods (number, percentage, mean, standard deviation) were used, and for qualitative comparisons between groups, chi-square tests (Pearson chi-square, Continuity Correction, Fisher's Exact test) were used. Survival calculations were made using the Kaplan-Meier analysis method. A *p*-value less than 0.05 was considered to indicate statistically significant differences with a 95% confidence interval.

## Results

### Patients and Tumors Characteristics

During the study period, 6.849 patients were diagnosed with BC, and 0.7% (n = 54) were PTBC. The mean age of the PTBC patients was 52.2 years. Forty-four (81.5%) had undergone breast-conserving surgery (BCS), and ten (18.5%) patients had undergone mastectomy. Four (7.4%) patients had not undergone axillary surgery, while 38 (70.4%) had undergone SLNB and 12 (22.2%) had undergone ALND due to positive results. The mean size of tumors was 10.6 mm. Forty-eight (88.9%) of the tumors were unifocal and six (11.1%) were multifocal. There was no lymphatic vascular invasion (LVI) or necrosis in any of the patients. Forty-eight (88.9%) patients had grade 1 tumor and six (11.1%) patients had grade 2 (Table 1).

All the tumors were ER positive and HER2 negative, but forty-nine (90.7%) were PR positive and five (9.3%) were PR negative (Table 1). All patients received adjuvant endocrine therapy. Eight patients (14.8%) who had ALNM received both chemotherapy and radiotherapy. Radiotherapy was administered to all patients who underwent BCS (38/54; 70.4%) (Table 1).

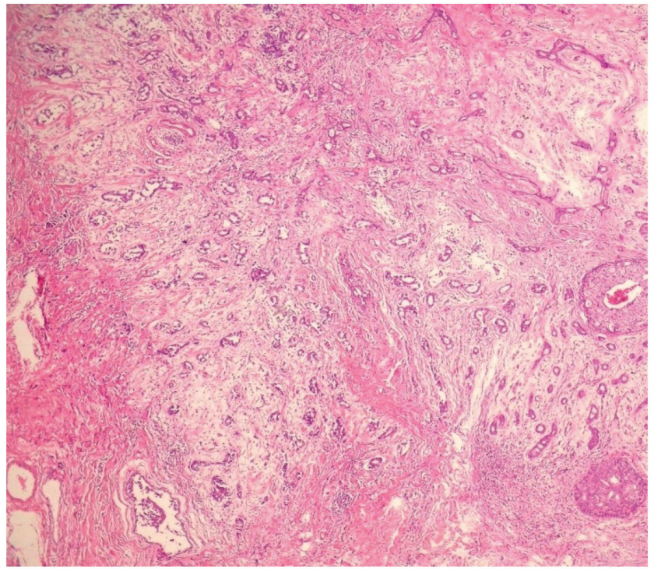

**Figure 1.** Well-defined glands with round, oval or angular contours, open lumina, and absence of myoepithelial cell layer in PTBC

*PTBC: Pure tubular breast carcinoma*

**Comparison of the Different Characteristics of Patients and Tumors**

Twelve patients had undergone ALND due to ALNM, and significantly, four of them (33.3%) had tumor grade 2 ($p$ = 0.020) and eight (66.7%) had ALNM ($p$ = 0.001). Moreover, fifty percent (50%) of patients who were treated with chemotherapy had grade 2, ALNM and multifocal tumors ($p$ = 0.001, $p$ = 0.007 and $p$ = 0.031, respectively). Furthermore, the frequency of ALNM was higher in patients with tumor diameters greater than 10 mm (Table 2).

**Patients Follow-up and Overall Survival**

Median follow-up time was 80 (12–220) months. None of patients exhibited loco-regional recurrence, but one patient had systemic metastasis. Five-year OS was 97.9%, while ten-year OS was 93.6% (Figure 2).

Table 1. Patient and tumor characteristics

| Characteristics (n = 54) | Category | n (%) |
|---|---|---|
| Age, mean (SD) | All | 52.2 (10.7) |
| Age group | <50 years | 23 (42.6) |
| | ≥50 years | 31 (57.4) |
| pT stage | pT1 | 53 (98.1) |
| | pT2 | 1 (1.9) |
| pN stage | pN0 | 46 (85.2) |
| | pN1-N2 | 8 (14.8) |
| Tumor focality | Unifocal | 48 (88.9) |
| | Multifocal | 6 (11.1) |
| Tumor diameter (mm), mean (SD) | All | 10.6 (4.7) |
| | ≤10 mm | 32 (59.3) |
| | >10 mm | 22 (40.7) |
| Breast surgery | BCS | 44 (81.5) |
| | Mastectomy | 10 (18.5) |
| | Not done | 4 (7.4) |
| Axillary surgery | SLNB | 38 (70.4) |
| | ALND | 12 (22.2) |
| Grade | 1 | 48 (88.9) |
| | 2 | 6 (11.1) |
| LVI | Negative | 54 (100) |
| Necrosis | Negative | 54 (100) |
| ER | Positive | 54 (100) |
| PR | Positive | 49 (90.7) |
| | Negative | 5 (9.3) |
| HER2 | Negative | 54 (100) |
| Adjuvant therapy | None* | 8 (14.8) |
| | RT | 38 (70.4) |
| | CT+RT | 8 (14.8) |
| Median follow-up (months) | All | 80 (4–220) |
| Type of recurrence | Locoregional | 0 (0.0) |
| | Systemic | 1 (1.9) |
| | No | 53 (98.1) |
| Cause of death | Metastatic breast cancer | 1 (1.9) |
| | Other | 2 (3.7) |
| | No death | 51 (94.4) |

pT: pathologic tumor; pN: pathologic node; ER: estrogen receptor; PR: progesterone receptor; CT: chemotherapy; RT: radiotherapy; LVI: lymph vascular invasion; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; *: patients received only adjuvant endocrine therapy

## Discussion and Conclusion

TBC is well known to be one of the less aggressive BCs, and histologically it is distinguished by tubule formation. In this study, cases were reported using the The American Joint Committee on Cancer criteria, and only cases of PTBC were included. These results showed that PTBC has a favorable prognosis, with good clinical outcomes and high survival rate. Furthermore, recurrences and metastases are rare.

Pathological tumor size is accepted as an independent factor in determining the frequency of lymph node involvement frequency. The presence of a small tumor diameter has been identified as a favorable prognostic factor for TBC. Lea et al. (15) investigated 146 cases of PTBC and the median tumor size was 10 mm (range 1-52 mm), with 93 of them being less than or equal to 20 mm. In addition, using a histological criterion of more than 90% tubule formation to define PTC, Papadatos et al. (16) showed that the median size of PTBC was small at about 10 mm. Dejode et al. (17) also reported a similar result, with a median tumor size of 9.59 (1–22) mm. Additionally, in line with the literature (18, 19), Metovic at al. (20) confirmed the small size (generally less than 10 mm) of PTBC tumors and the excellent outcomes. Moreover, there were no local or distant recurrences observed in the PTBC. Our findings are in keeping with

Table 2. Comparison of patients stratified by tumor grade, patient age, lymph node involvement and tumor focus (multifocal versus unifocal)

| | All | Middle grade (II) | | Young age (≤50) | | LN (+) | | Multifocal (Yes) | |
|---|---|---|---|---|---|---|---|---|---|
| Patients (n = 54) | n | n (%) | p | n (%) | p | n (%) | p | n (%) | p |
| Age | | | 0.384[a] | | NA | | 0.999[a] | | 0.073[a] |
| <50 | 23 | 4 (17.4) | | NA | | 3 (13) | | 5 (21.7) | |
| ≥50 | 31 | 2 (6.5) | | NA | | 5 (16.1) | | 1 (3.2) | |
| Tumor diameter | | | 0.211[a] | | 0.233[c] | | 0.051[a] | | 0.678[a] |
| ≤10 mm | 32 | 2 (6.3) | | 11 (34.4) | | 2 (6.3) | | 3 (9.4) | |
| >10 mm | 22 | 4 (18.2) | | 12 (54.5) | | 6 (27.3) | | 3 (13.6) | |
| ALNM | | | 0.213[a] | | 0.999[a] | | NA | | 0.999[a] |
| No | 46 | 4 (8.7) | | 20 (43.5) | | NA | | 5 (10.9) | |
| Yes | 8 | 2 (25) | | 3 (37.5) | | NA | | 1 (12.5) | |
| Tumor focus | | | 0.127[a] | | 0.073[a] | | 0.999[a] | | NA |
| Unifocal | 48 | 4 (8.3) | | 18 (37.5) | | 7 (14.6) | | NA | |
| Multifocal | 6 | 3 (33.3) | | 5 (83.3) | | 1 (16.7) | | NA | |
| Breast surgery | | | 0.070[a] | | 0.294[a] | | 0.632[a] | | 0.070[a] |
| BCS | 44 | 3 (6.8) | | 17 (38.6) | | 6 (13.6) | | 3 (6.8) | |
| Mastectomy | 10 | 3 (30) | | 6 (60) | | 2 (20) | | 3 (30) | |
| Axillary surgery | | | 0.020[b*] | | 0.677[b] | | <0.001[b*] | | 0.641[b] |
| Not done | 4 | 0 (0) | | 1 (25) | | 0 (0) | | 0 (0) | |
| SLNB | 38 | 2 (5.3) | | 16 (42.1) | | 0 (0) | | 4 (10.5) | |
| ALND | 12 | 4 (33.3) | | 6 (50) | | 8 (66.7) | | 2 (16.7) | |
| Grade | | | NA | | 0.384[a] | | 0.213[a] | | 0.127[a] |
| 1 | 48 | NA | | 19 (39.6) | | 6 (12.5) | | 4 (8.3) | |
| 2 | 6 | NA | | 5 (66.7) | | 2 (33.3) | | 2 (33.3) | |
| PR | | | 0.999[a] | | 0.380[a] | | 0.999[a] | | 0.999[a] |
| Positive | 49 | 6 (12.2) | | 22 (44.9) | | 8 (16.3) | | 6 (12.2) | |
| Negative | 5 | 0 (0) | | 1 (20) | | 0 (0) | | 0 (0) | |
| Adjuvant therapy | | | 0.001[b*] | | 0.370[b] | | 0.007[b*] | | 0.031[b*] |
| Didn't receive* | 8 | 1 (12.5) | | 5 (62.5) | | 0 (0) | | 1 (12.5) | |
| RT | 38 | 1 (2.6) | | 14 (36.8) | | 4 (10.5) | | 2 (5.3) | |
| CT + RT | 8 | 4 (50.0) | | 4 (50) | | 4 (50) | | 3 (37.5) | |

*: p<0.05; [a]: Fisher's Exact testi; [b]: Pearson chi-square; [c]: continuity correction; NA: not available; LN: lymph node; ER: estrogen receptor; PR: progesterone receptor; CT: chemotherapy; RT: radiotherapy; BCS: breast conserving surgery; ALNM: axillary lymph node metastasis; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; *: They received only adjuvant endocrine therapy

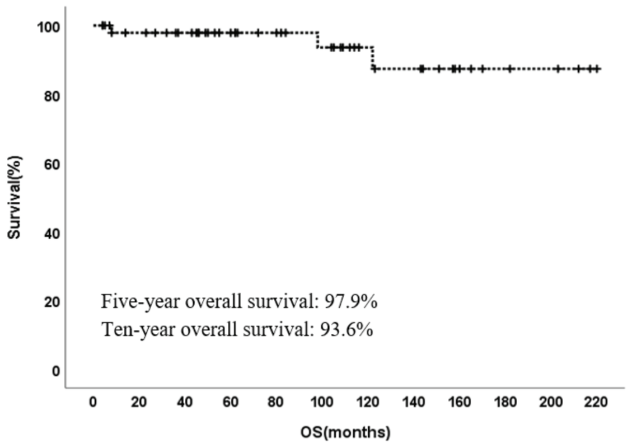


**Figure 2.** Overall survival in all PTBC patients (n = 54) in the present study

*PTBC: Pure tubular breast carcinoma*

these earlier studies; the mean tumor size was 10.6 mm, there was an absence of LVI and necrosis in the PTBC cases, and this result agrees with the findings of Rakha et al. (7). All of these findings suggest good prognosis and outcomes in PTBC.

ALNM is one of the most important prognostic factors in the staging and clinical management of BC. Many authors have found that PTBC patients have a lower incidence of ALNM and a better prognosis than patients with more poorly differentiated carcinomas (21, 22). Several studies have reported the association between tumor size and ALNM in TBC, especially in the pure subtype (12, 13, 16, 23). Nevertheless, there is a suggestion to perform SLNB on tumors larger than 10 mm, but this remains debatable (13, 18). Papadatos et al. (16) reported ALNM in only one of 22 cases, and they found no ALNM in PTBC when the tumor diameter was 10 mm or less (zero of 16). Furthermore, Cabral et al. (12) reported no ALNM in tumors less than or equal to 15 mm (zero of 20). Moreover, Winchester et al. (23) found no association between ALNM and tumor diameter in tumors smaller than 10 mm or tumors 10–20 mm. In the present study, ALNM occurrence was more likely in PTBC patients with tumor diameters greater than 10 mm.

Similar to our results, PTBCs in general are ER positive with a low-grade tumor (15, 24, 25). These characteristics result in a more favorable response to adjuvant endocrine treatment, leading to better prognosis and survival rate. None of the patients in the present study had a loco-regional recurrence, except for one patient who had multiple systemic metastasis (1.9%). The five-year OS was 97.9%, and the ten-year OS was 93.6%. In comparison to other study findings, Huang et al. (26) investigated the outcomes of TBC in 2.735 patients and showed that five-year OS was 97.2% and ten-year OS was 90.7%. In another study by Poirier et al. (27), it was reported that the 13-year OS of 223 PTBC patients was 95.8% for N0 PTBC patients, compared to 90.0% for N1-3 PTBC. Also, 13-year OS of PTBC was similar to that of grade 1 IDC (27). In the study of Lea et al. (15), 146 PTBC patients were investigated, and ALNM was uncommon. Eight (5%) patients had recurrent disease, and three of them died as a result. However, ten-year OS was 97%.

Peters et al. (21) found that as the non-tubular component increased, so did the tumor's biological aggressiveness. As we found no locoregional or systemic recurrence, with the exception of one patient in this study, we also suggest that PTBC tumors are less aggressive. As a result of our findings and those of others, it appears that PTBC patients may expect favorable prognosis, good clinical outcome and high survival rate, which may in part be due to the fact that PTBC are often ER positive and low grade, which leads to a good response to therapy. Surgical axillary investigation may not be warranted in PTBC patients who have a good initial prognosis.

Pure TBC is associated with favorable prognosis, good clinical outcomes and high survival rate and recurrences and shows rare recurrences and metastases.

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**Ethics Committee Approval:** Ethics committee approval is not required as it is a retrospective study.

**Informed Consent:** Retrospective study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: S.E., A.M.A., M.T., N.C., M.M.; Concept: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.; Design: S.E., A.M.A., M.T., N.C., M.M.; Data Collection or Processing: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.; Analysis or Interpretation: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.; Literature Search: S.E., A.M.A., M.T., N.C.; Writing: S.E., A.M.A., M.T., N.C., A.B., V.O., M.M.

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

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## References

1. Van Duerzen CHM, Denkert C, Purdie CA. Tubular carcinoma. In: WHO Classification of Tumors Editorial Board, eds. Breast Tumors: WHO Classification of Tumors series, 5th edition, volume 2. Lyon, France: International Agency for Research on Cancer; 2019.p.119-20. [Crossref]
2. Rosen PP. Tubular carcinoma. In: Rosen's Breast Pathology. Lippincott-Raven, PA, USA; 1996.p.325-6. [Crossref]
3. Kempson R. Stanford school of medicine surgical pathology criteria: tubular carcinoma of the breast; 2008. http://surgpathcriteria.stanford.edu/breast/tubularcabr [Crossref]
4. Tavassoli F, Devilee P. Pathology and genetics tumours of breast and female genital organs. IARC Press, Lyon, France; 2003. [Crossref]
5. Carstens PHB. Tubular carcinoma of the breast. A study of frequency. Am J Clin Pathol 1978; 70: 204-210. (PMID: 696679) [Crossref]
6. Cooper HS, Patchefsky AS, Krall RA. Tubular carcinoma of the breast. Cancer 1978; 42: 2334-2342. [Crossref]
7. Rakha EA, Lee AH, Evans AJ, Menon S, Assad NY, Hodi Z, et al. Tubular carcinoma of the breast: further evidence to support its excellent prognosis. J Clin Oncol 2010; 28: 99-104. (PMID: 19917872) [Crossref]
8. Abdel-Fatah TM, Powe DG, Hodi Z, Reis-Filho JS, Lee AH, Ellis IO. Morphologic and molecular evolutionary pathways of low nuclear grade invasive breast cancers and their putative precursor lesions: further evidence to support the concept of low nuclear grade breast neoplasia family. Am J Surg Pathol 2008; 32: 513-523. (PMID: 18223478) [Crossref]

9. Limaiem F, Mlika M. Tubular Breast Carc noma. [Updated 2022 Apr 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publ sh ng; 2022. [Crossref]
10. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022; 20: 691-722. (PMID: 35714673) [Crossref]
11. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017; 318: 918-926. (PMID: 28898379) [Crossref]
12. Cabral AH, Recine M, Paramo JC, McPhee MM, Poppiti R, Mesko TW. Tubular carcinoma of the breast: an institutional experience and review of the literature. Breast J 2003; 9: 298-301. (PMID: 12846864) [Crossref]
13. Javid SH, Smith BL, Mayer E, Bellon J, Murphy CD, Lipsitz S, et al. Tubular carcinoma of the breast: results of a large contemporary series. Am J Surg 2009; 197: 674-677. (PMID: 18789411) [Crossref]
14. American Joint Committee on Cancer. AJCC cancer staging handbook. 7th edn. New York: Springer; 2010. [Crossref]
15. Lea V, Gluch L, Kennedy CW, Carmalt H, Gillett D. Tubular carcinoma of the breast: axillary involvement and prognostic factors. ANZ J Surg 2015; 85: 448-451. (PMID: 25060384) [Crossref]
16. Papadatos G, Rangan AM, Psarianos T, Ung O, Taylor R, Boyages J. Probability of axillary node involvement in patients with tubular carcinoma of the breast. Br J Surg 2001; 88: 860-864. (PMID: 11412259) [Crossref]
17. Dejode M, Sagan C, Campion L, Houvenaeghel G, Giard S, Rodier JF, et al. Pure tubular carcinoma of the breast and sentinel lymph node biopsy: a retrospective multi-institutional study of 234 cases. Eur J Surg Oncol 2013; 39: 248-254. (PMID: 23273874) [Crossref]
18. Diab SG, Clark GM, Osborne CK, Libby A, Allred DC, Elledge RM. Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas. J Clin Oncol 1999; 17: 1442-1448. (PMID: 10334529) [Crossref]
19. McDivitt RW, Boyce W, Gersell D. Tubular carcinoma of the breast. Clinical and pathological observations concerning 135 cases. Am J Surg Pathol 1982; 6: 401-411. (PMID: 6289683) [Crossref]
20. Metovic J, Bragoni A, Osella-Abate S, Borella F, Benedetto C, Gualano MR, et al. Clinical Relevance of Tubular Breast Carcinoma: Large Retrospective Study and Meta-Analysis. Front Oncol 2021; 11: 653388. (PMID: 33996576) [Crossref]
21. Peters GN, Wolff M, Haagensen CD. Tubular carcinoma of the breast. Clinical pathologic correlations based on 100 cases. Ann Surg 1981; 193: 138-149. (PMID: 7469549) [Crossref]
22. Deos PH, Norris HJ. Well-differentiated (tubular) carcinoma of the breast. A clinicopathologic study of 145 pure and mixed cases. Am J Clin Pathol 1982; 78: 1-7. (PMID: 6285690) [Crossref]
23. Winchester DJ, Sahin AA, Tucker SL, Singletary SE. Tubular carcinoma of the breast. Predicting axillary nodal metastases and recurrence. Ann Surg 1996; 223: 342-347. (PMID: 8604915) [Crossref]
24. Kitchen PR, Smith TH, Henderson MA, Goldhirsch A, Castiglione-Gertsch M, Coates AS, et al. Tubular carcinoma of the breast: prognosis and response to adjuvant systemic therapy. ANZ J Surg 2001; 71: 27-31. (PMID: 11167594) [Crossref]
25. Fasano M, Vamvakas E, Delgado Y, Inghirami G, Mitnick J, Roses D, et al. Tubular Carcinoma of the Breast: Immunohistochemical and DNA Flow Cytometric Profile. Breast J 1999; 5: 252-255. (PMID: 11348296) [Crossref]
26. Huang K, Misra S, Bagaria SP, Gabriel EM. Outcomes of patients with invasive mucinous and tubular carcinomas of the breast. Breast J 2021; 27: 691-699. (PMID: 34173285) [Crossref]
27. Poirier É, Desbiens C, Poirier B, Boudreau D, Jacob S, Lemieux J, et al. Characteristics and long-term survival of patients diagnosed with pure tubular carcinoma of the breast. J Surg Oncol 2018; 117: 1137-1143. (PMID: 29205352) [Crossref]

Original Article

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# The Influence of the Surgical Treatment Method on the Quality of Life of Women With Breast Cancer

Magdalena Konieczny[1], Andrzej Fal[2]

[1]Medical Institute, The Jan Grodek State University in Sanok, Sanok, Poland
[2]Collegium Medicum, Warsaw Faculty of Medicine, Cardinal Stefan Wyszyński University, Warsaw, Poland

**ABSTRACT**

**Objective:** Breast cancer is the most common malignant neoplasm among women in Poland. The primary treatment for breast cancer is surgery. The choice of surgical treatment method can significantly affect the quality of life of women with breast cancer.

**Materials and Methods:** Women treated surgically because of breast cancer were included. The quality of life was assessed by survey using the quality of live questionnaire (QLQ)-C30 and QLQ-BR23 (European Organization for the Research and Treatment of Cancer) questionnaires, taking into account the following factors: The method of surgery performed and comparing breast conserving therapy (BCT) with mastectomy, and breast reconstruction or the lack of it.

**Results:** The study included 243 subjects. Women had a reduced overall quality of life (53.88 points out of 100), in particular emotional (59.77) and sexual (17.49) functioning, and a poor body image assessment (61.57). Patients after BCT functioned better in physical ($p$ = 0.001) and sexual ($p$ = 0.007) terms, and also experienced lower pain intensity ($p$ = 0.003) and shoulder discomfort ($p$ = 0.024). The quality of life was significantly higher ($p$ = 0.003) in the opinion of women who underwent breast reconstructive surgery.

**Conclusion:** The quality of life of women depends on the surgical treatment method used when treating breast cancer. For this reason, the choice of method, whenever possible, should promote breast protection or its postoperative reconstruction.

**Keywords:** Breast cancer; quality of life; mastectomy; conserving therapy; reconstruction

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**Key Points**

- Generally, women surgically treated for breast cancer had a reduced overall quality of life.
- A relatively higher declared quality of life was found in the group who underwent breast conserving therapy (BCT) as compared to patients who underwent mastectomy.
- After BCT, patients functioned better physically and sexually.
- A higher declared quality of life was also reported by patients who underwent breast reconstruction compared to the group who did not undergo reconstruction.
- In order to ensure the highest possible quality of life for women with breast cancer, the surgical method, whenever possible, should include breast protection or the possibility of reconstruction.

## Introduction

Breast cancer is the most often diagnosed malignant neoplasm in women. Globally, there are over 2.2 million new cases diagnosed annually and almost 700 thousand deaths from this cancer (1, 2). In Poland, the number of new diagnoses of breast cancer increases year by year and currently it is the most frequently diagnosed cancer among women. This cancer is also the second most common cause of death in the female population. In 2020, 24,644 new cases of breast cancer were confirmed, which accounted for 24.2% of all cancer diagnoses in women (2, 3). Despite significant progress in the diagnosis and treatment of breast cancer, it has a marked negative impact on the quality of life of affected women (4). Due to the increase in the number of cancer cases, as well as higher 5-year survival rates, which together result in an increasing number of women completing treatment, it is important to ensure the highest quality of life for these patients. Quality of life largely depends on clinical practice, for example the

**Corresponding Author:**
Magdalena Konieczny; magdalenakonieczny@wp.pl

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choice of therapy, and is increasingly important in the objective and subjective assessment of treatment outcomes (5, 6).

Surgery, the main task of which is to completely excise the tumour with a reserve of healthy tissues, is central in the treatment of breast cancer. It should be remembered that the methods of surgical treatment have evolved over time. With the development of biological and genetic laboratory techniques and imaging methods, there has been a shift from the use of extensive but tolerated surgery to minimally invasive surgery that is equally effective (7). Surgical treatment of the breast is considered to be very aggressive, causing fear and anxiety, mainly in terms of the aesthetic effects of the treatment, but also the uncertainty of effects in the context of the underlying disease. Patients fear disability, death, and also fear the breaking up of their family (8). Patients who have undergone radical surgical treatment may suffer from the "half woman/body complex" which can cause lowered self-esteem. They feel defective, have lowered self-esteem in terms of femininity and shaky self-esteem in the social dimension. Moreover, among women who have undergone surgical treatment, depression, problems in the sexual sphere and financial difficulties are observed as a consequence of the disease (9, 10).

Conducting research on the assessment of the quality of life after surgical treatment of breast cancer is particularly important because the results of such research may clearly indicate the need for individual adjustment of the therapeutic process, especially psychotherapy, to the real needs of women.

The objective of the study was to assess the influence of the surgical treatment used on the quality of life of women with breast cancer. The assessment takes into account the method of surgery, specifically mastectomy vs breast conserving therapy (BCT) and the performance or non-performance of breast reconstruction.

## Materials and Methods

### Data Collection Process

Studies to assess the quality of life were carried out among women diagnosed with breast cancer who had undergone surgery. All women were treated at the Podkarpackie Oncology Centre in Brzozów, Poland. The quality of life was assessed, taking into account surgical method (BCT *vs.* mastectomy) and whether or not breast reconstruction had been performed. Characteristics of the respondents taking into account the surgical treatment method is presented in Figure 1.

The inclusion criteria for the study were: Diagnosis of breast cancer; undergoing a stage of surgical treatment; and giving informed consent to participate in the study. The exclusion criteria were: non-breast cancer in the last 5 years; bilateral breast cancer; life expectancy less than half a year; age under 18 or over 75 years; and immediate breast reconstruction. All patients participating in the study were informed about the purpose of the research, guaranteed confidentiality and anonymity, and the voluntary nature of participation, as well as the possibility to withdraw from the study at any stage.

### Methods

The research used a diagnostic survey method, and the research tools were a standardized questionnaire to measure the quality of life of women treated for breast cancer. These were the quality of live questionnaire (QLQ)-C30 and the QLQ-BR23 (breast cancer) module in the Polish version (11, 12). In order to obtain socio-demographic and medical data, an original questionnaire was used. In Poland, the accuracy and reliability of the QLQ-C30 questionnaire and its version BR-23 were assessed, which confirmed the legitimacy of their use in assessing the quality of life of patients with breast cancer (12).

The QLQ-C30 questionnaire consists of five scales that assess the quality of life in terms of physical functioning, performing social roles, emotional, and cognitive and social functioning, as well as general assessment of health and quality of life. The QLQ-C30 questionnaire also includes scales assessing disease symptoms, such as fatigue, nausea and vomiting, and pain. In addition, this questionnaire contains six individual items (questions) also determining the intensity of symptoms - dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, and financial problems resulting from the disease.

The European Organization for the Research and Treatment of Cancer (EORTC) QLQ-BR23 scale is a complementary module to QLQ-C30 and is dedicated to women with breast cancer. In the case of QLQ-BR23, body image, sexual functioning, sexual pleasure, perspective of the future and the following symptom scales are assessed: side effects of systemic treatment; breast-related ailments; shoulder-related ailments; and sadness/stress related to hair loss.

The research was approved by the Society for Quality of Life Research at the European Commission, based in Brussels, and the director of the Fr. B. Markiewicz's Podkarpackie Oncological Centre in Brzozów. The project also received a positive opinion from the Bioethics Committee and was in line with the recommendations of the Helsinki Declaration.

### Statistical Analysis

The results were statistically processed according to the EORTC guidelines. For each patient, the raw coefficient was calculated, and then a linear transformation was performed to obtain the value of the score. All scales range from 0 to 100. In the case of functional scales, the higher coefficient corresponds to a better (higher) level of functioning, while the higher the score for symptom scales and individual symptoms, the greater the symptom severity and the worse the patient feels.

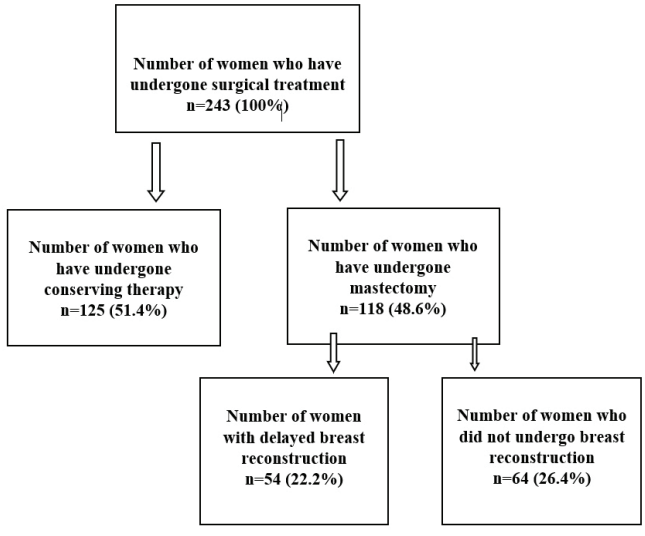


**Figure 1.** Characteristics of the respondents in the field of the surgical treatment method

The Statistica 10.0 program (StatSoft Inc., 2011) was used for statistical analysis (13). The consistency of the distribution of quantitative variables with the normal distribution was tested using the Shapiro–Wilk test. In the event of failure to meet the assumptions regarding the use of parametric methods, non-parametric methods were used to verify statistical hypotheses. The following non-parametric tests were used: Mann–Whitney U test, Kruskal–Wallis test (including Dunn's Post–hoc test). The significance level was assumed to be $\alpha = 0.05$. The results were considered statistically significant when the calculated test probability p met the inequality $p<0.05$.

## Results

### Study Participants

The mean ± standard deviation (SD) age of the patients participating in the studies was 55.4±13.7 years. The largest group consisted of patients aged over 60 to 75 (n = 79; 32.4%), while the smallest group were patients in the age group 20–30 (n = 11; 4.4%). Moreover, the proportion of patients in the age groups 31–40, 41–50, 51–60 was, respectively, 22.5% (n = 54), 24.6% (n = 60), and 16.1% (n = 39). The majority of the respondents lived in cities - 56.3% (n = 137), with the greatest number of women living in cities with up to 10,000 inhabitants (29.1%; n = 71) and cities with up to 50,000 inhabitants (16.6%; n = 40), and the smallest percentage were women living in cities with more than 50,000 inhabitants (10.6%, n = 26). Most of the women were married or in a partner relationship (68.1%, n = 165). The largest group of respondents had secondary education (38.2%; n = 93), slightly less women had higher education (35.3%; n = 86), and just over a quarter had basic vocational education (26.5%; n = 64). Information on socio-demographic data is presented in Table 1.

Table 1. Socio-demographic characteristics of the whole study group

| Variable | n | % |
|---|---|---|
| Age group (years) | | |
| 20–30 | 11 | 4.4 |
| 31–40 | 54 | 22.5 |
| 41–50 | 60 | 24.6 |
| 51–60 | 39 | 16.1 |
| 61–75 | 79 | 32.4 |
| Place of residence | | |
| Village | 106 | 43.7 |
| City up to 10.000 inhabitants | 71 | 29.1 |
| City of more than 10.000 and less than 50.000 inhabitants | 40 | 16.6 |
| City with more than 50.000 inhabitants | 26 | 10.6 |
| Marital status | | |
| In relationship | 165 | 68.1 |
| Single | 78 | 31.9 |
| Education | | |
| Primary/vocational | 64 | 26.5 |
| Secondary | 93 | 38.2 |
| Tertiary | 86 | 35.3 |

The number of women who underwent BCT was 125 (51.4%), while the remaining women (48.6%; n = 118) underwent mastectomy. The study group was balanced in terms of systemic treatment - chemotherapy, radiotherapy and hormone therapy. All patients underwent the same type of axillary surgery, i.e. dissection of the axillary lymph nodes (Table 2).

### General Quality of Life

The evaluation of individual functional scales QLQ-C30 showed that the participants had a reduced overall quality of life and health (mean = 53.88, median = 50.00, SD = 19.72). Physical functioning (mean = 74.86, median = 80.00, SD = 18.07), performing social roles (mean = 73.87, median = 66.67, SD = 22.89), cognitive (mean = 70.32, median = 66.67, SD = 25.52) and social (mean = 69.86, median = 66.67, SD = 28.69) functioning were rated the highest, and emotional functioning (mean = 59.77, median = 66.67, SD = 24.99) was rated the lowest. The women included in the study were significantly concerned about their futures (mean = 30.97, median = 33.33, SD = 33.86). It should be highlighted that in functional assessment, women rated sexual functioning the lowest (mean = 17.49, median = 0.00, SD = 23.56). The mean sexual satisfaction score of sexually active patients was 46.41 (median = 33.33, SD = 33.86). The mean value of the scale assessing patients' body image was 61.57 (median = 66.67, SD = 32.95) (Figures 2, 3).

### Quality of Life and Surgical Method

Significant differences were observed between patients who underwent BCT and mastectomy in terms of health and quality of life ($p = 0.002$) and physical functioning ($p = 0.001$). Patients who underwent BCT had a higher quality of life in these domains compared to women who underwent mastectomy. The majority of the women did not differ in terms of the intensity of symptoms resulting from the disease. The values of symptom scales in patients who underwent BCT were similar to the results achieved by women after mastectomy, with the exception of intensity of pain, which was reported to be higher in women after mastectomy (Table 3).

Significant differences were reported between the following subscales of the functional scales of the QLQ-BR23 questionnaire: Body image ($p = 0.003$), sexual functioning ($p = 0.007$) and sexual satisfaction ($p = 0.005$), and in the case of symptom scales, the differences concerned shoulder-related ailments ($p = 0.024$). Sexual functioning, sexual satisfaction and body image were rated higher by women who underwent BCT and lower by respondents who underwent mastectomy. Women who underwent mastectomy indicated a greater severity of shoulder-related ailments compared to the respondents after conserving therapy (means of 31.56 *vs.* 26.56, respectively). Detailed data is included in Table 4.

### Quality of Life and Breast Reconstructive Surgery

The quality of life was higher in the opinion of women who underwent breast reconstruction compared to the group of respondents who did not undergo such surgery. A higher assessment of the quality of life was expressed by higher values of functional scales and symptom scales QLQ-C30 and BR23 (Tables 5 and 6). Women with breast cancer who did not undergo breast reconstruction assessed their health and quality of life lower, as well as their physical functioning, performing social roles, emotional functioning and social functioning. The decrease in the quality of life was influenced by the intensification of symptoms in the group of women who did not undergo breast reconstruction.

Table 2. Characteristics of the study group taking into account medical factors

| Treatment group | Breast-conserving surgery | | Total mastectomy without reconstruction | | Total mastectomy with reconstruction | |
|---|---|---|---|---|---|---|
| **Variable** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| Systemic treatment | | | | | | |
| Chemiotherapy | 125 | 51.4 | 64 | 26.4 | 54 | 22.2 |
| Radiotherapy | 122 | 50.2 | 62 | 25.5 | 54 | 22.2 |
| Hormotherapy | 118 | 48.6 | 60 | 24.7 | 52 | 21.4 |
| Type of axillary surgery - axillary lymph node dissection | 125 | 51.4 | 64 | 26.4 | 54 | 22.2 |

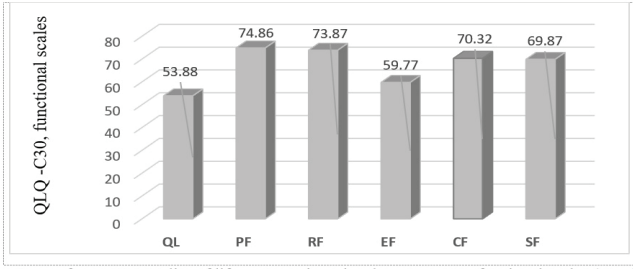


**Figure 2.** Assessment of women's quality of life-categories related to QLQ-C30, functional scales 5QL – health status and quality of life

*PF: physical functioning; RF: performing social roles; EF: emotinal functioning; CF: cognitive functioning; SF: social functioning*

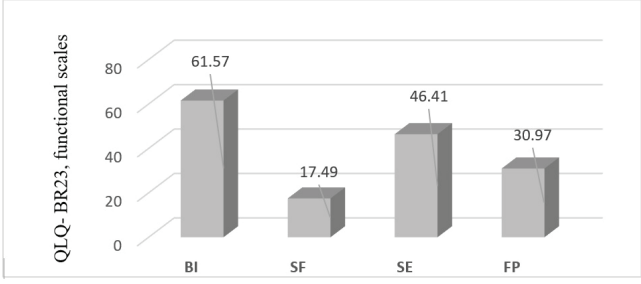


**Figure 3.** Assessment of women's quality of life – categories related to QLQ-BR23, functional scales

*(An image of your own body. SF: sexual function; SE: sexual satisfaction; FP: the prospect of the future)*

These patients indicated a greater severity of symptoms, including fatigue, pain and loss of appetite. At the same time, the respondents emphasized the emergence of financial problems as a result of the disease. These differences were so large that they were statistically significant (Table 5).

The values of the functional and symptom scales of the QLQ-BR23 questionnaire also indicated a reduced assessment of the quality of life in the group of women not undergoing breast reconstructive surgery (Table 6). The respondents who underwent breast reconstructive surgery had a statistically significantly higher assessment of their body image compared to women who did not undergo breast reconstruction. Moreover, patients after reconstructive surgery rated their quality of sex life higher and, to a lesser extent, indicated side effects of systemic treatment, shoulder-related ailments and breast-related ailments were less severe.

## Discussion and Conclusion

Surgery is of fundamental importance in the treatment of women diagnosed with breast cancer. The choice of the method, which may include BCT, mastectomy, mastectomy with simultaneous or delayed reconstruction, and removal of lymph nodes significantly determines the quality of life of patients. Breast cancer is a disease that particularly affects the emotional functioning of patients. On the one hand, it is a life-threatening disease, and on the other hand, it interferes with the psyche of women who are afraid of losing their femininity and sexuality (14). Therefore, the reasons for making decisions about breast reconstructive surgery primarily include the desire to maintain the current appearance and physical activity (15).

This study assessed the quality of life of women depending on the surgical method (conserving therapy *vs.* mastectomy). The results suggest that a significant problem for women after mastectomy is the low quality of life in the sexual sphere, and therefore the need for support for affected women, especially in this area. The results of the research conducted by Kowalczyk et al. (16) show greater disorders of sexual functions in women after mastectomy compared to patients after BCT, and our results are in agreement with this. According to Kowalczyk et al. (16) in this situation, the partner's support and proper relationships are of particular importance, as they reduce the risk of deteriorating sexual functioning and low body image assessment. Similar studies were also conducted by Alicikus et al. (17) among Turkish women comparing selected aspects of women's quality of life divided into patients after mastectomy and after conserving therapy. The group of women who underwent mastectomy more often reported a decrease in libido, which resulted in a reduction in their quality of life. Although in these studies, 80% of patients were satisfied with the overall appearance, only 54% of them accepted their naked body. In contrast, patients included in our study rated sexual functioning the lowest, which implies that both body sexuality and functioning in this area constitute a special problem for women who are surgically treated for breast cancer.

An important issue, physical rather than psychological, to which patients with breast cancer pay attention, involves shoulder-related ailments. We showed that women who underwent mastectomy reported greater ailments compared to the respondents after conserving therapy. Other authors also drew attention to the problem of upper limb ailments (18, 19). However, there is a lack of long-term follow-up, conducted several years after surgery, to assess the severity of these ailments and the possible transiency of the symptom. A small number

Table 3. Mean values of the QLQ-C30 scale and the surgical method

| QLQ | *p* | Surgical method | | | |
|---|---|---|---|---|---|
| | | Conserving therapy | | Mastectomy | |
| | | M | SD | M | SD |
| QLQ-C30 | | | | | |
| Health and quality of life | 0.002 | 56.05 | 18.09 | 54.19 | 18.53 |
| Physical functioning | 0.001 | 77.32 | 16.50 | 74.78 | 16.72 |
| Performing social roles | ns | 71.84 | 23.75 | 72.95 | 20.03 |
| Emotional functioning | ns | 58.72 | 24.00 | 60.63 | 23.99 |
| Cognitive functioning | ns | 69.92 | 25.14 | 75.36 | 20.33 |
| Social functioning | ns | 68.97 | 28.77 | 72.22 | 24.86 |
| Fatigue | ns | 37.42 | 18.42 | 35.27 | 19.15 |
| Nausea/vomiting | ns | 34.48 | 38.11 | 35.99 | 36.89 |
| Pain | 0.003 | 21.46 | 17.22 | 25.91 | 18.19 |
| Dyspnoea | ns | 19.54 | 24.67 | 16.91 | 23.34 |
| Insomnia | ns | 38.70 | 27.32 | 37.20 | 27.73 |
| Loss of appetite | ns | 39.08 | 33.03 | 36.72 | 32.41 |
| Constipation | ns | 10.73 | 19.35 | 15.46 | 23.28 |
| Diarrhoea | ns | 9.58 | 16.00 | 8.69 | 14.75 |
| Financial problems | ns | 32.18 | 34.64 | 32.37 | 28.57 |

M: mean; SD: standard deviation; ns: not significant

Table 4. Mean values of the QLQ-BR23 scale and the surgical method

| QLQ BR-23 | *p* | Surgical method | | | |
|---|---|---|---|---|---|
| | | Conserving therapy | | Mastectomy | |
| | | M | SD | M | SD |
| Body image | 0.003 | 58.97 | 32.22 | 52.70 | 32.85 |
| Sexual functioning | 0.007 | 24.90 | 26.15 | 13.53 | 20.47 |
| Sexual satisfaction | 0.005 | 47.59 | 27.74 | 44.46 | 24.22 |
| Perspective of the future | ns | 31.42 | 33.47 | 26.09 | 30.18 |
| Side effects of treatment | ns | 33.55 | 21.5 | 30.3 | 18.06 |
| Shoulder-related ailments | 0.024 | 26.56 | 20.15 | 31.56 | 18.24 |
| Breast-related ailments | ns | 27.49 | 17.75 | 23.55 | 19.7 |
| Hair loss | ns | 71.53 | 35.05 | 65.79 | 39.88 |

M: mean; SD: standard deviation; ns: not significant

of studies in this field have shown that five years after diagnosis, 38% of patients still experienced shoulder discomfort, significantly affecting their quality of life (20). In particular, these problems involve oedema and the limited range of motion of the upper limb.

In our study, a significantly higher quality of life was demonstrated in the group of women who underwent conserving therapy. This concerned, in particular, the scope of physical functioning, body image assessment, sexual functioning and satisfaction, as well as pain and shoulder-related ailments. Similarly, the studies conducted by Akça et al. (21) showed that BCT has a more beneficial effect on overall health and quality of life, physical, cognitive and social functioning, and the severity of symptoms in women compared to mastectomy. Patients who underwent mastectomy had a lower quality of life compared to women after BCT. Similar results were obtained by Enien et al. (22), who reported that patients after BCT had a higher quality of life in terms of functioning. Moreover, women after mastectomy reported

Table 5. Mean values of the QLQ-C30 scale and breast reconstructive surgery

| QLQ-C30 | *p* | Breast reconstructive surgery | | | |
|---|---|---|---|---|---|
| | | No reconstruction | | Reconstruction | |
| | | Mean | SD | Mean | SD |
| Health and quality of life | 0.003 | 56.31 | 19.21 | 70.25 | 18.35 |
| Physical functioning | 0.007 | 68.56 | 18.26 | 82.36 | 19.04 |
| Performing social roles | 0.002 | 73.26 | 22.25 | 79.85 | 22.56 |
| Emotional functioning | 0.005 | 57.46 | 20.58 | 63.45 | 20.14 |
| Cognitive functioning | ns | 68.59 | 22.45 | 77.55 | 21.35 |
| Social functioning | 0.033 | 73.15 | 22.48 | 83.49 | 19.85 |
| Fatigue | 0.001 | 42.18 | 21.16 | 30.56 | 19.58 |
| Nausea/vomiting | ns | 42.38 | 22.58 | 38.59 | 19.65 |
| Pain | 0.002 | 31.25 | 2081 | 21.55 | 19.55 |
| Dyspnoea | ns | 21.58 | 25.85 | 17.95 | 15.89 |
| Insomnia | ns | 42.59 | 22.77 | 38.66 | 25.18 |
| Loss of appetite | 0.00 | 45.89 | 25.48 | 31.24 | 22.48 |
| Constipation | ns | 15.89 | 22.15 | 14.58 | 20.38 |
| Diarrhoea | ns | 17.45 | 19.25 | 15.25 | 18.25 |
| Financial problems | 0.01 | 44.15 | 18.45 | 35.25 | 17.25 |

SD: standard deviation; ns: not significant

Table 6. Mean values of the QLQ-BR23 scale and breast reconstructive surgery

| QLQ-BR23 | *p* | Breast reconstructive surgery | | | |
|---|---|---|---|---|---|
| | | No reconstruction | | Reconstruction | |
| | | Mean | SD | Mean | SD |
| Body image | 0.002 | 58.73 | 31.16 | 68.64 | 36.23 |
| Sexual functioning | 0.003 | 16.58 | 20.31 | 25.46 | 19.65 |
| Sexual satisfaction | ns | 42.86 | 20.15 | 45.13 | 21.3 |
| Perspective of the future | ns | 35.42 | 32.33 | 30.15 | 21.28 |
| Side effects of the treatment | 0.001 | 34.72 | 20.91 | 25.69 | 20.46 |
| Shoulder-related ailments | 0.002 | 26.52 | 15.23 | 20.51 | 18.48 |
| Breast-related ailments | 0.004 | 28.12 | 18.18 | 18.12 | 17.23 |
| Hair loss | ns | 65.24 | 36.48 | 68.18 | 35.25 |

SD: standard deviation; ns: not significant

more shoulder-related ailments. Similar conclusions can also be drawn from the study conducted by Arora et al. (23). These authors showed that patients who underwent mastectomy had worse social functioning compared to patients after tumorectomy and had a lower assessment of their own body image. It should be noted that in recent years there has been an increase in the number of mastectomies performed, and at the same time, as a result of increased awareness of women and the development of surgical and oncoplastic techniques, an increase in breast reconstructive procedures is also evident (24-26).

Women treated for breast cancer had a reduced overall quality of life. A relatively higher declared quality of life was observed in the group of patients who underwent BCT compared to patients who underwent mastectomy. Patients after BCT functioned better physically and sexually. Higher declared quality of life was also observed in the group of patients who underwent breast reconstruction compared to the group who did not undergo reconstruction. In order to ensure the highest possible quality of life for women with breast cancer, the surgical method, whenever possible, should include breast protection or the possibility of its reconstruction.

**Ethics Committee Approval:** The project also received a positive opinion from the Bioethics Committee and was in line with the recommendations of the Helsinki Declaration (approval number: 47/2016, date: 09.12.2016 - Wyszyński University Bioethics Committee).

**Informed Consent:** All patients gave informed consent before enrolment in this study.

**Peer-review:** externally peer-reviewed.

**Authorship Contributions**

Concept: M.K., A.F.; Design: M.K., A.F.; Data Collection or Processing: M.K., A.F.; Analysis or Interpretation: M.K., A.F.; Literature Search: M.K., A.F.; Writing: M.K., A.F.

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

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## References


1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249. (PMID: 33538338) [Crossref]
2. The Global Caner Observatory. https://gco.iarc.fr/. Accessed 5.01.2022. [Crossref]
3. Gliniewicz A, Zielińska A, Kwiatkowska K, Dudek-Godeau D, Bielska–Lasota M. Survival in women diagnosed with breast and cervical cancer in Poland – compared to European countries, based on CONCORD - 3 Programme. Przegl Epidemiol 2018; 72: 499-508. (PMID: 30810005) [Crossref]
4. Xiao C, Miller AH, Felger J, Mister D, Liu T, Torres MA. A prospective study of quality of life in breast cancer patients undergoing radiation therapy. Adv Radiat Oncol 2016; 1: 10-16. (PMID: 27453954) [Crossref]
5. Yan B, Yang LM, Hao LP, Yang C, Quan L, Wang LH, et al. Determinants of Quality of Life for Breast Cancer Patients in Shanghai, China. PLoS One 2016; 11: e0153714. (PMID: 27082440) [Crossref]
6. Imran M, Al-Wassia R, Alkhayyat SS, Baig M, Al-Saati BA. Assessment of quality of life (QoL) in breast cancer patients by using EORTC QLQ-C30 and BR-23 questionnaires: A tertiary care center survey in the western region of Saudi Arabia. PLoS One 2019; 14: e0219093. (PMID: 31291302) [Crossref]
7. Kim MK, Kim T, Moon HG, Jin US, Kim K, Kim J, et al. Effect of cosmetic outcome on quality of life after breast cancer surgery. Eur J Surg Oncol 2015; 41: 426-432. (PMID: 25578249) [Crossref]
8. Kyranou M, Paul SM, Dunn LB, Puntillo K, Aouizerat BE, Abrams G, et al. Differences in depression, anxiety, and quality of life between women with and without breast pain prior to breast cancer surgery. Eur J Oncol Nurs 2013; 17: 190-195. (PMID: 22892272) [Crossref]
9. Jagsi R, Li Y, Morrow M, Janz N, Alderman A, Graff J, et al. Patient-reported Quality of Life and Satisfaction With Cosmetic Outcomes After Breast Conservation and Mastectomy With and Without Reconstruction: Results of a Survey of Breast Cancer Survivors. Ann Surg 2015; 261: 1198-1206. (PMID: 25654742) [Crossref]
10. Meneses K, Azuero A, Hassey L, McNees P, Pisu M. Does economic burden influence quality of life in breast cancer survivors? Gynecol Oncol 2012; 124: 437-443. (PMID: 22138013) [Crossref]
11. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376. [Crossref]
12. Zawisza K, Tobiasz-Adamczyk B, Nowak W, Kulig J, Jedrys J. Trafność i rzetelność kwestionariusza oceny jakości zycia EORTC QLQ C30 oraz jego modułu dotyczacego pacjentek z nowotworami piersi (EORTC QLQ BR23) [Validity and reliability of the quality of life questionnaire (EORTC QLQ C30) and its breast cancer module (EORTC QLQ BR23)]. Ginekol Pol 2010; 81: 262-267. (PMID: 20476597) [Crossref]
13. StatSoft, Inc. (2011), data analysis software system, version 11, www.statsoft.com [Crossref]
14. Guyomard V, Leinster S, Wilkinson M. Systematic review of studies of patients' satisfaction with breast reconstruction after mastectomy. Breast 2007; 16: 547-567. (PMID: 18024116) [Crossref]
15. Flitcroft K, Brennan M, Spillane A. Women's expectations of breast reconstruction following mastectomy for breast cancer: a systematic review. Support Care Cancer 2017; 25: 2631-2661. (PMID: 28474240) [Crossref]
16. Kowalczyk R, Nowosielski K, Cedrych I, Krzystanek M, Glogowska I, Streb J, et al. Factors Affecting Sexual Function and Body Image of Early-Stage Breast Cancer Survivors in Poland: A Short-Term Observation. Clin Breast Cancer 2019; 19: e30-e39. (PMID: 30385228) [Crossref]
17. Alicikus ZA, Gorken IB, Sen RC, Kentli S, Kinay M, Alanyali H, et al. Psychosexual and body image aspects of quality of life in Turkish breast cancer patients: a comparison of breast conserving treatment and mastectomy. Tumori 2009; 95: 212-218. (PMID: 19579868) [Crossref]
18. Albert US, Koller M, Kopp I, Lorenz W, Schulz KD, Wagner U. Early self-reported impairments in arm functioning of primary breast cancer patients predict late side effects of axillary lymph node dissection: results from a population-based cohort study. Breast Cancer Res Treat 2006; 100: 285-292. (PMID: 16710790) [Crossref]
19. Lopez Penha TR, van Bodegraven J, Winkens B, Heuts EM, Voogd AC, von Meyenfeldt MF. The quality of life in long-term breast cancer survivors with breast cancer related lymphedema. Acta Chir Belg 2014; 114: 239-244. (PMID: 26021418) [Crossref]
20. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Hölzel D. Axilla surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. Breast Cancer Res Treat 2003; 79: 47-57. (PMID: 12779081) [Crossref]
21. Akça M, Ata A, Nayır E, Erdoğdu S, Arıcan A. Impact of Surgery Type on Quality of Life in Breast Cancer Patients. J Breast Health 2014; 10: 222-228. (PMID: 28331675) [Crossref]
22. Enien MA, Ibrahim N, Makar W, Darwish D, Gaber M. Health-related quality of life: Impact of surgery and treatment modality in breast cancer. J Cancer Res Ther 2018; 14: 957-963. (PMID: 30197331) [Crossref]
23. Arora NK, Gustafson DH, Hawkins RP, McTavish F, Cella DF, Pingree S, et al. Impact of surgery and chemotherapy on the quality of life of younger women with breast carcinoma: a prospective study. Cancer 2001; 92: 1288-1298. (PMID: 11571745) [Crossref]
24. Throckmorton AD, Esserman LJ. When informed, all women do not prefer breast conservation. J Clin Oncol 2009; 27: 484-486. (PMID: 19114690) [Crossref]
25. Critchley AC, Thompson AM, Chan HY, Reed MW. Current controversies in breast cancer surgery. Clin Oncol (R Coll Radiol) 2013; 25: 101-108. (PMID: 23183307) [Crossref]
26. Jagsi R, Jiang J, Momoh AO, Alderman A, Giordano SH, Buchholz TA, et al. Trends and variation in use of breast reconstruction in patients with breast cancer undergoing mastectomy in the United States. J Clin Oncol 2014; 32: 919-926. (PMID: 24550418) [Crossref]

**Original Article**

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# Prognostic Factors Influencing Progression-Free Survival in HER2-Positive Metastatic Breast Cancer Patients Who Were Treated With A Combination of Lapatinib and Capecitabine

İzzet Doğan, Nail Paksoy, Naziye Ak, Sezai Vatansever, Pınar Saip, Adnan Aydıner
Department of Medical Oncology, İstanbul University Institute of Oncology, İstanbul, Turkey

**ABSTRACT**

**Objective:** The aim was to assess the prognostic variables in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer patients receiving lapatinib plus capecitabine.

**Materials and Methods:** Retrospective data on HER2-positive metastatic breast cancer patients who received lapatinib and capecitabine were analyzed. Survival outcome was obtained with Cox regression analysis and the Kaplan–Meier method.

**Results:** The study included 102 patients. Forty-four (43.1%) patients had *de novo* metastatic disease. The most frequent metastatic sites were, in order, bone (61.8%), brain (57.8%), liver (35.3%), and lung (34.3%). All of the patients had previously received chemotherapy based on trastuzumab. With combined lapatinib and capecitabine, complete response was observed in 7.8%, partial response in 30.4%, and stable disease in 24.5%. Progression-free survival was 8 (95% confidence interval, 5.1–10.8) months. In multivariable analysis, endocrine therapy ($p$ = 0.02), de novo metastatic disease ($p$ = 0.02), and age ($p$ = 0.02) were prognostic factors for progression-free survival. However, the number of chemotherapy cycles with trastuzumab, palliative radiotherapy, history of breast surgery, and the number of metastatic sites were not significant in this respect.

**Conclusion:** These results have demonstrated the effectiveness of lapatinib plus capecitabine in metastatic HER2-positive breast cancer patients. Furthermore, unfavorable prognostic factors for progression-free survival were shown to be hormone-negative tumor, *de novo* metastatic disease, and young age.

**Keywords:** Breast cancer; metastasis; HER2/neu receptor; lapatinib; capecitabine

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**Key Points**

- The combination of lapatinib and capecitabine was effective in the treatment of human epidermal growth factor receptor 2 positive metastatic breast cancer.
- Clinical and pathological factors affected the efficacy of the combination of lapatinib and capecitabine.
- The combination of lapatinib and capecitabine was well tolerated in patients and side effects are generally easily managed.

## Introduction

Breast cancer is the most common malignancy in women globally and the second most frequent cause of cancer-related death (1). Breast cancer is divided into subtypes with biologically different characteristics. Human epidermal growth factor receptor 2 (HER2) oncogene receptor can be detected in approximately 15–25% of breast cancer patients (2, 3). The HER2 receptor is a transmembrane protein with intracellular tyrosine kinase activity from the epidermal growth factor receptor family (4). It has functions in cell growth and differentiation. HER2 receptor positivity is detected by *in situ* hybridization and immunohistochemistry (IHC) methods. Many therapeutic agents target the HER2 receptor, such as trastuzumab, pertuzumab, lapatinib, trastuzumab emtansine, and trastuzumab deruxtecan, and have been using to treat many HER2-positive solid tumors, especially breast and gastric cancer.

Trastuzumab is the first agent to used as a targeted therapy in the treatment of HER2-positive metastatic breast cancer patients. In patients whose disease progressed after trastuzumab-based therapy,

**Corresponding Author:**
**İzzet Doğan; dr.izzetdogan@gmail.com**

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tumor progression was delayed, and a trend towards an improvement in overall survival (OS) was achieved, although not statistically significant, with the combination of lapatinib plus capecitabine (LC) compared to only capecitabine (5, 6). In another study, the combination of LC was found to be superior in terms of progression-free survival (PFS) compared to capecitabine alone in patients who had previously received multiple treatments (anthracycline, taxane, and trastuzumab) (7). There is a limited number of studies examining the factors affecting the time to progression with the combination of LC in HER2-positive metastatic breast cancer patients who have received previous treatment. The aim of this study was to examine the factors affecting the efficacy of the combination of LC.

## Materials and Methods

### Patient Inclusion and Data

This study was designed as a cross-sectional, retrospective study. Ethics committee approval was obtained before the study, and our study was conducted according to good clinical practices guidelines. Patients who received treatment in a single oncology center between 2009 and 2020 were included in the study. The patients in the study were identified through the information processing system. All patients included in the study had metastatic breast cancer with HER2-positive features and had previously received at least one series of cancer chemotherapy. Patients who received other treatments, such as pertuzumab and trastuzumab emtansine targeting the HER2 receptor, other than trastuzumab-based treatment, before LC treatment, and patients who did not have sufficient data were excluded from the study. Demographic and clinicopathological features of the study cohort were extracted from hospital files. All treatments (surgery, radiotherapy, systemic cancer treatments) given to the patients were also noted. Progesterone receptor and estrogen receptor (ER) positivity were determined by IHC. HER2 receptor positivity was diagnosed by IHC (score 3) or *in situ* hybridization methods.

The patients used capecitabine 1000 mg/m$^2$ twice a day (1–14 days every three weeks) and lapatinib 1250 mg/day. Treatment-related response assessments were performed radiologically (computed tomography or magnetic resonance imaging) every three months. LC combination-related response assessment was performed using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. In addition, treatment-related adverse events were graded. Records of patient deaths were extracted from the death information system of the Ministry of Health. OS was calculated as the duration from the onset of LC to death from any cause. PFS was determined as the duration from the beginning of LC to disease progression. Univariate and multivariate analyzes were performed for clinical and pathological parameters affecting PFS.

### Statistical Analysis

Statistical analyzes were conducted with SPSS, version 25 (IBM Inc., Armonk, NY, USA). Continuous variables are shown as median values (minimum-maximum), while categorical variables are shown as numbers and percentages. Univariate analysis was performed for parameters affecting PFS. Multivariate analysis was done using the Cox regression method, using the parameters that were significant in the univariate analysis and the factors that were reported to have significance in the literature. Overlapping parameters were not included in the analysis. Survival curves were plotted with the Kaplan–Meier analysis. Statistical significance was assumed when $p<0.05$.

## Results

### Patients Characteristic and Treatment Modality

One hundred and nineteen HER2-positive metastatic breast cancer patients who had received LC were identified. Seventeen patients were excluded from the study because they had received trastuzumab emtansine or pertuzumab prior to LC treatment, and thus the data of 102 patients were analyzed. The median age of the patients included in the study was 47 (range 24–87) years, and three (2.9%) patients were male. The major histopathological subtype was invasive ductal carcinoma (76.5%), and ER positivity was present in 42.2% of the patients. At the time of diagnosis, 44 (43.2%) patients had *de novo* metastatic disease. The median number of metastatic sites was 4 (1–5). The most common site of metastasis was bone (61.8%), and 57.8% of patients had brain metastases. Table 1 presents the clinical and pathological features of the patients.

Mastectomy was performed in 61 (59.8%) patients. All of the patients received trastuzumab-based treatment before LC treatment. Before LC treatment, 54 (52.9%) of the patients had received one cycle of chemotherapy, and 48 (47.1%) had received two or more cycles chemotherapy regimens. The patients used chemotherapy regimens containing anthracycline, taxane, platinum, and fluoropyrimidine in different combinations as chemotherapy. Palliative metastasectomy for brain metastasis was performed in 11 (10.8%) patients. The number of patients who received palliative radiotherapy before treatment was 79 (77.5%), and 55 (53.9%) of these patients received brain radiotherapy. Fifty-five (53.9%) patients were given bisphosphonate therapy for bone metastases. The treatment features of the patients are presented in Table 2.

With LC chemotherapy, the overall response rate was 38.2%, and the disease control rate was 62.7% (Table 3). LC-related grade 1–2 adverse events were observed in 55 (57.3%) patients, and grade 3–4 adverse events were observed in 22 (22.9%) patients. The most common toxicities were non-hematological (fatigue, diarrhea, hand-foot syndrome, and others) and were observed in 57.8% of the patients. LC had to be discontinued in four (3.9%) patients due to toxicity. The most important toxicity leading to drug discontinuation was hand-foot syndrome. After LC treatment, 45 (44.1%) patients received palliative chemotherapy, and 19 (18.6%) patients received palliative radiotherapy.

### Survival Outcomes and Prognosis

The median follow-up time after initiation of LC was 16.9 (1–149) months. During the study period, 91 (89.1%) patients died. The median PFS duration was 8 [95% confidence interval (CI), 5.1–10.8] months (Figure 1). Median OS was 17.8 (95% CI, 13.1–22.4) months (Figure 2). In the multivariate analysis for parameters affecting PFS, age ($p$ = 0.02), *de novo* metastatic disease ($p$ = 0.02), and use of palliative endocrine therapy ($p$ = 0.02) were significant factors affecting PFS (Table 4). Primary tumor site, primary tumor surgery, histopathological type, number of metastasis sites, metastasis sites, number of palliative chemotherapy, and palliative radiotherapy were not found to be prognostic.

## Discussion and Conclusion

These results suggest that LC was effective and safe for HER2-positive metastatic breast cancer patients who were previously treated. The combination of tyrosine kinase inhibitors such as lapatinib, pyrotinib,

Table 1. Clinical and pathological characteristics of the patients

| | Number of patients (n = 102) | (%) |
|---|---|---|
| **Age at diagnosis, years** | | |
| <50 | 55 | 53.9 |
| ≥50 | 47 | 46.1 |
| **Gender** | | |
| Female | 99 | 97.1 |
| Male | 3 | 2.9 |
| **Number of metastatic sites** | | |
| 1-2 | 55 | 53.9 |
| ≥3 | 46 | 45.1 |
| Unknown | 1 | 1 |
| **Metastatic sites** | | |
| Bone | 63 | 61.8 |
| Brain | 59 | 57.8 |
| Liver | 36 | 35.3 |
| Lung | 35 | 34.3 |
| Other sites | | |
| **Stage at diagnosis** | | |
| Stage 1 | 4 | 3.9 |
| Stage 2 | 5 | 4.9 |
| Stage 3 | 49 | 48 |
| Stage 4 | 44 | 43.2 |
| **Primary tumor locations** | | |
| Left sides | 49 | 48 |
| Right sides | 47 | 46.1 |
| Bilateral | 1 | 1 |
| Unknown | 5 | 4.9 |
| **Histological type** | | |
| Invasive ductal carcinoma | 78 | 76.5 |
| Other types | 9 | 8.8 |
| Unknown | 15 | 24.7 |
| **ER status** | | |
| Positive | 43 | 42.2 |
| Negative | 59 | 57.8 |
| **PR status** | | |
| Positive | 33 | 32.4 |
| Negative | 69 | 67.6 |

ER: estrogen receptor; PR: progesterone receptor

Table 2. Treatment features of the patients

| | Number of patients | % |
|---|---|---|
| **Surgery** | | |
| Mastectomy | 61 | 59.8 |
| Lumpectomy | 12 | 11.8 |
| No | 29 | 28.4 |
| **Radiotherapy before metastatic disease** | | |
| Adjuvant | 38 | 37.3 |
| Neoadjuvant | 3 | 2.9 |
| No | 61 | 59.8 |
| **Chemotherapy before metastatic disease** | | |
| Adjuvant | 41 | 40.2 |
| Neoadjuvant | 14 | 13.7 |
| No | 47 | 46.1 |
| **Endocrine therapy before metastatic disease** | | |
| Tamoxifen | 20 | 19.6 |
| Aromatase inhibitors | 3 | 2.9 |
| No | 79 | 77.5 |
| **Palliative chemotherapy before LC** | | |
| 1 series | 54 | 52.9 |
| ≥2 series | 48 | 47.1 |
| **Palliative endocrine therapy before LC** | | |
| Aromatase inhibitors | 28 | 27.5 |
| Tamoxifen | 17 | 16.6 |
| No | 57 | 55.9 |
| **Palliative radiotherapy before LC** | | |
| Yes | 79 | 77.5 |
| No | 23 | 22.5 |
| **Metastasectomy** | | |
| Yes | 12 | 11.8 |
| No | 90 | 80.2 |

LC: lapatinib plus capecitabine

and neratinib with capecitabine is used in the treatment of HER2-positive metastatic breast cancer patients. Lapatinib selectively inhibits epidermal growth factor receptor and HER-2 tyrosine kinases and inhibits cell proliferation by restricting HER-2, AKT, Raf, and ERK phosphorylation, especially in breast cancer cells with high HER2 expression (8). In the study performed by Geyer et al. (7), the median time to progression with LC was 8.4 months in HER2-positive metastatic breast cancer patients who were previously treated, and it was superior to patients who received only capecitabine. In another study, inluding brain metastatic patients with HER2 positive breast cancer, conducted by Metro et al. (9), the disease control rate was 59%, and brain-specific progression survival was 5.6 months with LC combination. Similarly, in a meta-analysis that included 12 studies, the objective response with LC was 29%, while the median PFS was 4.1 months and the median OS 11.2 months (10). In a study comparing the combinations of lapatinib with capecitabine, vinorelbine, and gemcitabine, although it was not statistically significant, PFS was nine months with capecitabine and seven months with other agents, and the toxicity profiles of different agents were similar (11). It has been shown that the combination of LC passes into brain tissue in HER2-positive brain metastatic breast cancer patients who have not

Table 3. Responses to LC in the patients

| | Number of patients (n = 102) | % | Actual-% |
|---|---|---|---|
| **Response rates** | | | |
| Complete response | 8 | 7.8 | 8.3 |
| Partial response | 31 | 30.4 | 31.9 |
| Stable disease | 25 | 24.5 | 25.7 |
| Progression | 33 | 32.4 | 34.1 |
| Overall response rate | 39 | 38.2 | 40.2 |
| Disease control rate | 64 | 62.7 | 65.9 |
| Unknown | 5 | 4.9 | |

LC: lapatinib plus capecitabine

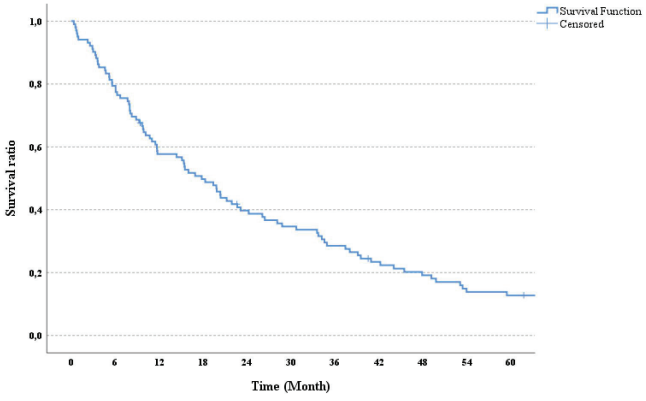


**Figure 1.** Kaplan–Meier Curve for PFS in the patients who were treated with LC

*PFS: progression-free survival; LC: lapatinib plus capecitabine*

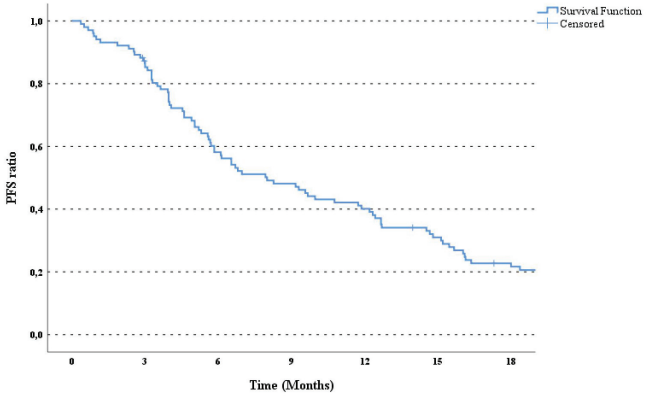


**Figure 2.** Kaplan–Meier curve for OS in the patients who were treated with LC

*OS: overall survival; LC: lapatinib plus capecitabine*

received brain radiotherapy (12). Therefore, LC treatment can be considered as an option to delay whole brain irradiation and its side effects in brain metastatic patients with HER2-positive breast cancer (13). In addition, in a case report, the combination of LC was shown to have efficacy in a breast cancer patient with leptomeningeal metastasis (14). Real-world data published by Gui et al. (15) showed that early initiation with lapatinib-based therapy was more beneficial in terms of PFS and OS. In this study, when lapatinib-based therapy was used in the first series, PFS was 10.4 months and OS 32.9 months, while in the third series, PFS was 5.8 months and OS 13 months. In the present study, half of the patients had brain metastases, and the results of LC-related survival results were consistent with the literature. In a study evaluating tucatinib, a new generation tyrosine kinase inhibitor, the addition of tucatinib to trastuzumab and capecitabine improved survival compared to placebo in patients with previously treated HER2-positive metastatic breast cancer (16). In addition, in patients with HER2 positive brain metastatic breast cancer, tucatinib provided better HER2 inhibition in both impaired and intact blood-brain barrier than neratinib and lapatinib (17). A meta-analysis showed that tucatinib in combination with trastuzumab + capecitabine or TDM-1 had better survival outcomes than lapatinib

Table 4. Univariate and multivariate analysis for PFS in the patients who were treated with LC

| | Univariate analysis | Multivariate analysis | |
|---|---|---|---|
| | *p* | *p* | Odds ratio CI 95% |
| **Age** (<50 *vs.* ≥50) | 0.06 | 0.02 | 0.57 (0.36–0.91) |
| ***De novo* metastasis** (No *vs.* yes) | 0.36 | 0.02 | 1.91 (1.07–3.40) |
| **Primary tumor sites** (Left *vs.* right) | 0.34 | | |
| **Primary surgery** (No *vs.* Yes) | 0.6 | 0.06 | 1.95 (0.97–3.94) |
| **Histopathologival type** (IDC *vs.* other type) | 0.54 | | |
| **ER status** (Positive vs. negative) | 0.36 | | |
| **Number of metastatic sites** (1-2 *vs.* ≥3) | 0.53 | 0.24 | |
| **Brain metastasis** (Yes *vs.* No) | 0.99 | | |
| **Liver metastasis** (Yes *vs.* No) | 0.28 | | |
| **Lung metastasis** (Yes *vs.* No) | 0.72 | | |
| **Number of palliative chemotherapy** (1 *vs.* ≥2) | 0.69 | 0.33 | |
| **Palliative hormonotheray** (No *vs.* Yes) | 0.15 | 0.02 | 0.58 (0.37–0.91) |
| **Palliative radiotherapy** (No *vs.* Yes) | 0.91 | 0.39 | |

Hosmer and Lemeshow test model *p* value = 0.5, PFS: progression-free survival; LC: lapatinib plus capecitabine; CI: confidence interval; IDC: invasive ductal carcinomas; ER: estrogen receptor

+ capecitabine or other treatments in patients with metastatic breast cancer who received HER2-based therapy (18).

We observed that LC treatment response appeared to have different efficacy in different patients and different effects on PFS. There are limited studies in the literature predicting LC response. We found that patients under 50 years of age, *de novo* metastatic disease, and patients who do not receive palliative hormone therapy due to having hormone receptor-negative tumors had a worse prognosis in terms of PFS. In a study evaluating 52 HER2-positive metastatic breast cancer patients who received LC, time to progression was evaluated and those over 50 years of age, with hormone-positive disease, and with tumors with high HER2 and HER3 expression had better outcomes. Also, in this study, it was also determined that the absence of previous use of capecitabine and the high expression of HER2 and HER3 affected OS positively (19). In another study published by Ang et al. (20), it was reported that OS was significantly improved in patients who developed dermatitis and hand-foot syndrome within 42 days of the start of LC. This study also showed that nausea and vomiting as early side effects were associated with worse OS. In the analysis performed by Gui et al. (15), it was shown that liver metastasis, brain metastasis, number of metastatic sites, and hormone receptor status did not affect median PFS, but the use of LC combined and in early cycles significantly affected PFS in the patients receiving LC. The patient group included in this study was extremely heterogeneous, the 102 patients involved in the study were divided into three different groups, and many patients had previously used capecitabine as a single agent. In addition, some of the patients used different chemotherapy agents other than capecitabine together with lapatinib. In an open-label study published by Ro et al. (21), it was found that the presence of non-visceral metastatic disease and history of longer use of trastuzumab were associated with prolonged PFS in patients receiving LC combination. In this study, it was also detected that hormone receptor positivity and clinical benefit rate significantly increased for brain PFS.

### Study Limitations

Our study had some limitations due to its retrospective nature. The patient group involved in the study was heterogeneous, and the number of patients was relatively limited. Some data of a small number of patients could not be collected.

In this study, we showed that LC was effective and safe in HER2-positive metastatic breast cancer patients who were previously treated. The LC-related prognostic factors were found to be associated with age, using endocrine therapy, and *de novo* metastatic disease. There is very limited research into the parameters that affect LC-related response. Our study contributes to the literature in this respect. In the future, there is a need for molecular and genetic studies that investigate factors affecting HER2-based treatment response in the treatment of breast cancer patients.

**Ethics Committee Approval:** The local ethics committee approved this study at the Istanbul University Faculty of Medicine (date/approval number: 28.06.2021/265629).

**Informed Consent:** Retrospective study.

**Peer-review:** Internally and externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: İ.D., N.P., N.A., S.V., P.S., A.A.; Concept: İ.D., N.P., N.A., S.V., P.S., A.A.; Design: İ.D., N.P., N.A., S.V., P.S., A.A.; Data Collection or Processing: İ.D., N.P., N.A., A.A.; Analysis or Interpretation: İ.D., N.P., N.A., A.A.; Literature Search: İ.D., N.P., N.A., A.A.; Writing: İ.D., N.P., N.A., A.A.

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## References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021; 71: 7-33. (PMID: 33433946) [Crossref]
2. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J, et al. Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res 2015; 5: 2929-2943. (PMID: 26693050) [Crossref]
3. Noone AM, Cronin KA, Altekruse SF, Howlader N, Lewis DR, Petkov VI, et al. Cancer Incidence and Survival Trends by Subtype Using Data from the Surveillance Epidemiology and End Results Program, 1992-2013. Cancer Epidemiol Biomarkers Prev 2017; 26: 632-641. (PMID: 27956436) [Crossref]
4. Iqbal N, Iqbal N. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. Mol Biol Int 2014; 2014: 852748. (PMID: 25276427) [Crossref]
5. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008; 112: 533-543. (PMID: 18188694) [Crossref]
6. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist 2010; 15: 924-934. (PMID: 20736298) [Crossref]
7. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733-2743. (PMID: 17192538) [Crossref]
8. Konecny GE, Pegram MD, Venkatesan N, Finn R, Yang G, Rahmeh M, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. Cancer Res 2006; 66: 1630-1639. (PMID: 16452222) [Crossref]
9. Metro G, Foglietta J, Russillo M, Stocchi L, Vidiri A, Giannarelli D, et al. Clinical outcome of patients with brain metastases from HER2-positive breast cancer treated with lapatinib and capecitabine. Ann Oncol 2011; 22: 625-630. (PMID: 20724575) [Crossref]
10. Petrelli F, Ghidini M, Lonati V, Tomasello G, Borgonovo K, Ghilardi M, et al. The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis. Eur J Cancer 2017; 84: 141-148. (PMID: 28810186) [Crossref]
11. Gómez HL, Neciosup S, Tosello C, Mano M, Bines J, Ismael G, et al. A Phase II Randomized Study of Lapatinib Combined With Capecitabine, Vinorelbine, or Gemcitabine in Patients With HER2-Positive Metastatic Breast Cancer With Progression After a Taxane (Latin American Cooperative Oncology Group 0801 Study). Clin Breast Cancer 2016; 16: 38-44. (PMID: 26642810) [Crossref]
12. Morikawa A, Peereboom DM, Thorsheim HR, Samala R, Balyan R, Murphy CG, et al. Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a

prospective study. Neuro Oncol 2015; 17: 289-295. (PMID: 25015089) [Crossref]

13. Bachelot T, Romieu G, Campone M, Dieras V, Cropet C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 2013; 14: 64-71. (PMID: 23122784) [Crossref]
14. Nakao T, Okuda T, Fujita M, Kato A. A case of leptomeningeal metastases of human epidermal growth factor receptor 2-positive breast cancer that responded well to lapatinib plus capecitabine. Surg Neurol Int 2019; 10: 131. (PMID: 31528467) [Crossref]
15. Gui X, Li H, Yan Y, Zhang R. Efficacy of lapatinib combined with capecitabine in patients with HER2-positive metastatic breast cancer in a real-world study. Oncol Lett 2020; 20: 378. (PMID: 33154776) [Crossref]
16. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med 2020; 382: 597-609. (PMID: 31825569) [Crossref]
17. Li J, Jiang J, Bao X, Kumar V, Alley SC, Peterson S, et al. Mechanistic Modeling of Central Nervous System Pharmacokinetics and Target Engagement of HER2 Tyrosine Kinase Inhibitors to Inform Treatment of Breast Cancer Brain Metastases. Clin Cancer Res 2022; 28: 3329-3341. (PMID: 35727144) [Crossref]
18. DeBusk K, Abeysinghe S, Vickers A, Nangia A, Bell J, Ike C, et al. Efficacy of tucatinib for HER2-positive metastatic breast cancer after HER2-targeted therapy: a network meta-analysis. Future Oncol 2021; 17: 4635-4647. (PMID: 34463120) [Crossref]
19. Han SW, Cha Y, Paquet A, Huang W, Weidler J, Lie Y, et al. Correlation of HER2, p95HER2 and HER3 expression and treatment outcome of lapatinib plus capecitabine in her2-positive metastatic breast cancer. PLoS One 2012; 7: e39943. (PMID: 22848366) [Crossref]
20. Ang FLI, Rowland A, Modi ND, McKinnon RA, Sorich MJ, Hopkins AM. Early Adverse Events predict Survival Outcomes in HER2-positive Advanced Breast Cancer Patients treated with Lapatinib plus Capecitabine. J Cancer 2020; 11: 3327-3333. (PMID: 32231738) [Crossref]
21. Ro J, Park S, Kim S, Kim TY, Im YH, Rha SY, et al. Clinical outcomes of HER2-positive metastatic breast cancer patients with brain metastasis treated with lapatinib and capecitabine: an open-label expanded access study in Korea. BMC Cancer 2012; 12: 322. (PMID: 22839200) [Crossref]

Original Article

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# Evaluation of Topical Sclerosant Agents for Minimization of Postmastectomy Seroma: A Placebo-Controlled, Double-Blind, Randomized Trial

Ashraf Khater, Ahmed Hassan, Omar Farouk, Ahmed Sinbel, Saleh Saleh, Mahmoud Abdelaziz, Osama Eldamshety

Department of Surgery, Oncology Center, Faculty of Medicine, Mansoura University, Mansoura, Egypt

**ABSTRACT**

**Objective:** Seroma after mastectomy is a bothersome problem. Topical sclerosants are one method used to reduce seroma. The aim of this study was to evaluate if spraying flaps before closure with doxycycline or bleomycin after total mastectomy can prevent seroma.

**Materials and Methods:** After institutional review board approval, using a computer-based randomization program, a prospective, double-blind, placebo-controlled randomized, superiority study was conducted during the period from the first of August 2017 to the first of August 2018. IRB proposal code was MS/17.08.66 and the trial was approved at 15/8/2017. The trial is available publicly at http://www.eulc.edu.eg/eulc_v5/Libraries/Thesis/BrowseThesisPages.aspx?fn=PublicDrawThesis&BibID=12553049. The primary outcome of the study was to assess the incidence of seroma following total mastectomy after intervention comprising spraying of skin flaps with doxycycline or bleomycin versus placebo. Patients who were candidates for total mastectomy were randomized into control, doxycycline, and bleomycin groups. The postoperative data included length of the hospital stay, pain score among the three groups, post-operative drained fluid volume, post-operative day of drain removal, complication rates including infection, flap necrosis and hematoma, the incidence of seroma and aspirated seroma volume, and total number of postoperative visits.

**Results:** Of 125 patients, 90 were candidates for total mastectomy. Analysis of these 90 showed that the incidence of seroma was similar; 43.4%, 40% and 40% in the control, doxycycline, and bleomycin groups, respectively ($p$ = 0.99). Furthermore, wound complication rates were similar among all groups.

**Conclusion:** Despite improved recognition and management of risk factors, seromas remain a common clinical concern in the postoperative setting of total mastectomy. These results suggest that sclerosant agents, specifically bleomycin and doxycycline, have no utility for prevention of post mastectomy seroma.

**Keywords:** Mastectomy, seroma, sclerosant

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**Key Points**

- Mastectomy.
- Seroma.
- Sclerosant.

## Introduction

Since mastectomy was first described by Halsted in 1894, surgeons have faced several problems, such as necrosis of the skin flaps, breakdown of the wound, hematoma, seroma, and infection (1). Seromas can disrupt the healing process, lengthen the convalescence, be upsetting for the patient, and delay adjuvant therapy (2). The incidence of post-mastectomy seroma has been reported to vary widely from 15% to 81% (1). Various methods have been tried aiming to decrease the occurrence of seroma, with limited success. These include insertion of suction drains, obliteration of mastectomy or the axillary space by sutures, topical application of sclerotherapy with tetracycline, application of fibrin glue, and external application of compressive dressings. Spraying of mastectomy flaps with doxycyclines and bleomycin were previously reported as having a positive effect in seroma prevention (3). The aim of this study was to evaluate if seroma can be prevented after total mastectomy by the spraying of flaps before closure with doxycycline or bleomycin. The primary outcome was to assess the incidence of seroma after total mastectomy when flaps were sprayed with doxycycline or bleomycin versus placebo. The secondary endpoints were the operative outcomes and complication rates, including hematoma, flap necrosis and wound infection.

**Corresponding Author:**
**Ashraf Khater, dr.ashrafkhater@yahoo.com**

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## Materials and Methods

After Institutional Review Board approval, a prospective, double-blind, placebo-controlled randomized, superiority study was conducted during the period from the first of August 2017 to the first of August 2018. After obtaining informed consent, ninety female patients, aged between 25 and 75 years old who were candidates for elective total mastectomy were enrolled. Patients were included if they had operable breast cancer with no distant metastases and consented to participate. Those with incapacitating cardiac disease, uncontrolled diabetes, advanced liver disease, coagulopathy, or collagen vascular disease were excluded. Exclusion criteria also included patients aged less than 25 years, patients using steroids or anticoagulants, patients with ongoing systemic infection at the time of surgery, those with history of chest irradiation or prior axillary surgery, patients with planned immediate breast reconstruction, pregnant and lactating patients, those who were unfit for general anesthesia, patients with locally advanced cancer with no neoadjuvant chemotherapy, patients with metastatic cancer and those unwilling to participate in the trial. After using a computer-based randomization program, patients were assigned to groups by a closed envelope method (Figure 1). Patients were divided into three groups: Doxycycline, bleomycin, and placebo control. Participants in the doxycycline group were sprayed with 500 mg doxycycline [5x100 mg tablets of Doxymycin (EL-NILE CO) diluted in 100 mL saline] onto the undersurface of the skin flaps after the mastectomy and after achieving hemostasis. Patients in the bleomycin group were sprayed with 60 units of bleomycin (2 ampules of Bleomycin 30 IU; Salius Pharma), also diluted in 100 mL saline. Patients in the control group were sprayed with 100 mL of saline. Surgeons were blinded to the three preparations, which were prepared by a third party. Skin was closed routinely in all patients after placing two Nelaton catheters 18French drains, one in the axilla and the second underneath the mastectomy flaps. Drains were clamped for three hours postoperatively to keep solutions in contact with the skin flaps. In all patients, a dry light dressing was placed. Arm exercise was allowed from the first postoperative day but lifting more than 5 kg or lifting the arm above the shoulder was prohibited until two weeks after surgery. All participants were followed up by routine postoperative visits for 1-2 months. Drains were removed when daily output was less than 50 mL in any 24-hour period.

Ultrasonographic evaluation was the main tool for diagnosis of seroma formation. Grading was performed as described by Kuroi et al. (4) in 2005. This grading system was: G1, asymptomatic seroma; G2, symptomatic seroma that resolves with aspiration; and G3, symptomatic seroma that resolves with surgical or radiologic intervention.

The preoperative data included patient age, body mass index (BMI) in kg/m$^2$, is the patient is premenopausal or postmenopausal, medical comorbidities (diabetes, chronic liver disease, hypertension, and heart disease), receipt of neoadjuvant therapy, the affected breast side, size and the tumor size. The operative data included the duration of the procedure, estimated blood loss, the number of retrieved axillary nodes, the number of positive axillary nodes, the final pathologic diagnosis including cancer stage, specimen weight and the removed skin surface area. Postoperative data included length of hospital stay, post-operative drained fluid volume, the day of drain removal, the mean pain score of the groups, reported by visual analogue scale (VAS) measured after 4 and 8 hours after surgery and then every 12 hours until discharge. Rate of complications including infection, flap necrosis and hematoma, the incidence of seroma, aspirated seroma volume, and the total number of postoperative visits were also recorded.

### Statistical Analysis

Analysis of the qualitative and quantitative data was performed using chi-square analysis and analysis of variance, respectively. Analyses of quantitative variables were evaluated by Bartlett's test for equal variances. If this test identified heterogeneity of variance, the data was subjected to log transformation or the Box-Cox transformation procedure and reanalyzed after heterogeneity of variance had been corrected. If transformation procedures were unsuccessful in correcting heterogeneity of variance, treatment differences were compared using the Wilcoxon rank-sum test. A value of $p<0.05$ was considered statistically significant. The calculated sample size with 90% power and $p$-value of 0.05 was 106. Interim analyses of overall events rates during the study provided a guide as to whether the sample size needed to be altered as the study proceeded. Due to limited time and resources, the sample size was modified to be 90 with three equally sized groups to detect a 0.3 effect reduction in the incidence of postmastectomy seroma at 80% power with $p$-value 0.05.

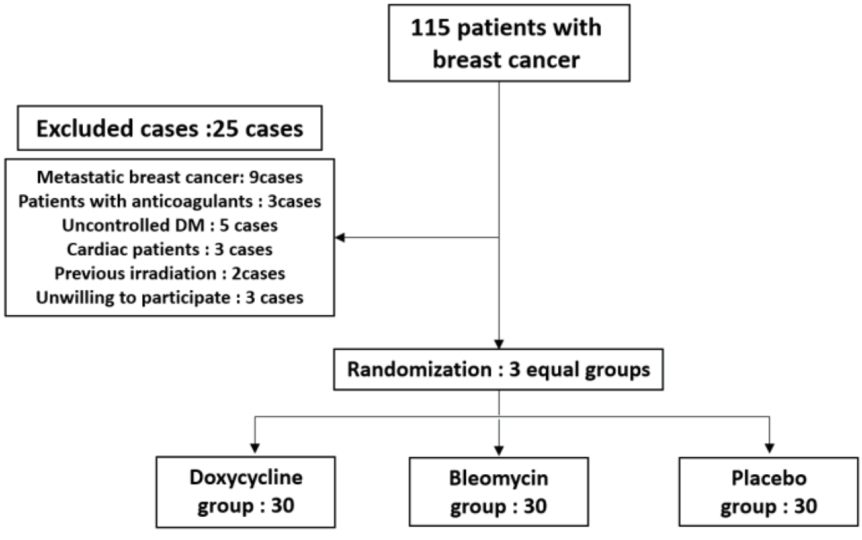


**Figure 1.** Flowchart and randomization of patients

## Results

All patients were biopsied to prove malignancy before planning of treatment. Of 125 patients (Figure 1), 90 patients underwent total mastectomy with axillary surgery. Sentinel lymph node biopsy was performed in five patients in the doxycycline group and three patients in the bleomycin group. Comparison of demographic data and comorbid conditions for control, doxycycline and bleomycin groups showed no difference. The three groups were comparable with regard to age, BMI and comorbidities. Within the bleomycin group, there was a lower incidence of hypertension compared with the other two groups while only patients in the doxycyline had prexeisting heart disease (Table 1). There was a significantly higher number of patients with clinically locally advanced breast cancer in the doxycycline group compared to the other two groups ($p$ = 0.005), but there was no difference in breast size between the groups. There was no difference in mammographic size of the malignant breast mass/masses among the study patients, neither was there any difference in the number of clinically detected axillary lymph nodes during the preoperative examination. There was no significant difference as regards the side of the diseased breast among all groups ($p$ = 0.392). There was a significantly greater number of patients with early breast cancer in the bleomycin group (Table 1). There were no significant differences between number of the cases who underwent neoadjuvant therapy or exhibited tumor downsizing after receiving neoadjuvant therapy. As regards tumor size, there was a significant difference following pathological dissection after surgery with relatively smaller tumor size in the bleomycin group ($p$ = 0.002) with no significant difference as regard the breast size itself or surface area of the excised skin. There was no significant difference in the number of cases who underwent axillary clearance and those who did not among all groups. There was no difference in the total number of excised axillary lymph nodes, nor in the number of the axillary lymph nodes with malignant infiltration. Table 2 shows a comparison of operative outcome and postoperative complications between the three groups. Analysis revealed that all measured parameters were similar between all groups. However, some differences emerged. Using the VAS scoring system, there was a significant difference in the postoperative pain with higher number of cases suffering from pain in the bleomycin group, especially in the early postoperative hours ($p$<0.001). There was also a significantly higher incidence of post mastectomy hematoma in the bleomycin group ($p$ = 0.008). Overall complication rate was similar in all groups as regard the incidence of independent complications, including, infection, flap necrosis and hematoma. The incidence of seroma was comparable among the three groups with no significant difference either as a whole or when stratified by grade of seroma. No seroma occurred in 18/30 in the doxycycline and bleomycin groups and in 17/30 in the placebo group. The incidence of G1, G2 and G3 seroma in the three groups is shown in Table 3. This did not differ between groups. There was no difference in postoperative fluid

Table 1. Comparison of patients and tumor characteristics between the three groups

| | Doxycycline (n = 30) | Placebo (n = 30) | Bleomycin (n = 30) | p |
|---|---|---|---|---|
| Mean age (years) | 55.47±11.74 | 53.30±13.14 | 50.60±11.50 | 0.304 |
| Mean BMI (kg/m$^2$) | 37.79±7.40 | 39.47±7.94 | 36.48±7.64 | 0.322 |
| Incidence of diabetes mellitus | 9 (30.0%) | 8 (26.7%) | 3 (10.0%) | 0.136 |
| Chronic pulmonary disease | 3 (10.0%) | 1 (3.3%) | 0 (0.0%) | 0.160 |
| Hypertension | 10 (33.3%) | 14 (46.7%) | 3 (10.0%) | 0.007* |
| Heart disease | 3 (10.0%) | 0 (0.0%) | 0 (0.0%) | 0.045* |
| Proportion with large breasts (cup C&D) | 24 (80.0%) | 24 (80.0%) | 25 (83.3%) | 0.930 |
| Proportion with positive axillary LNs | 11 (36.7%) | 10 (33.3%) | 12 (40.0%) | 0.866 |
| Mean radiological tumor size (cm) | 3.07±1.83 | 3.20±1.98 | 2.78±1.02 | 0.607 |
| Left sided cases | 13 (43.3%) | 18 (60.0%) | 17 (56.7%) | 0.392 |
| Tumor stage | | | | |
| 0 | 1 (3.3%) | 0 (0.0%) | 3 (10.0%) | <0.001* |
| I | 1 (3.3%) | 5 (16.7%) | 18 (60.0%) | |
| II | 12 (40%) | 11 (36.7%) | 0 (0.0%) | |
| III | 16 (53.3%) | 14 (46.6%) | 9 (30.0%) | |
| Neoadjuvant therapy | 18 (60.0%) | 16 (53.3%) | 18 (60.0%) | 0.833 |
| Response to neoadjuvant therapy | 11 (36.7%) | 8 (26.7%) | 15 (50.0%) | 0.174 |
| Mean largest diameter of tumor (cm) | 3.94±1.99 | 3.81±1.87 | 2.28±2.06 | 0.002* |
| Mean removed skin surface area (cm$^2$) | 17.60±7.04 | 17.83±5.91 | 16.50±5.92 | 0.684 |
| Axillary clearance | 25 (83.3%) | 30 (100.0%) | 27 (90.0%) | 0.074 |
| Mean total number of LNs removed | 13.73±9.15 | 18.10±7.65 | 16.50±9.32 | 0.153 |
| This is to be corrected into: Median number of malignant LN: 4 with a range of 2-7 | 3.67±4.86 | 4.77±7.28 | 5.10±8.07 | 0.700 |

BMI: body mass index; LN: lymph nodes

drainage volume among the three groups. Furthermore, there was no difference in the proportion of patients in each group who underwent seroma aspiration or the volume of aspiration fluid. Finally, there was no difference between groups in terms of the incidence of drain reinsertion in refractory cases for simple aspiration.

## Discussion and Conclusion

The most common sequel after mastectomy is the formation of a post-operative seroma. It should be noted that the clinical definition of seroma differs from the ultrasonographic definition. The clinical definition of seroma is the presence of fluctuant serous collection after drain removal that necessitates aspiration or drain re-insertion. The ultrasonographic definition adds that the subclinical (G1) seroma that may not affect the post-operative recovery (4). Various surgical and medical techniques have been tried with the aim of decreasing the incidence and magnitude of this problem, and currently there is no consensus for preventative therapy (5).

The pathophysiology of post-operative seroma remains unclear. The most widely accepted hypothesis for seroma formation is lymph fluid collection associated with transection of wide areas of lymph bearing tissues resulting in a large dead space after surgery. Therefore it has been recommended to obliterate the dead space to avoid seroma formation (6, 7). Woodworth et al. (8) in a study of 252 patients showed that the rate of seroma was around 25.5%. Porter et al. (9) concluded that the incidence of seroma was around 26% in an analysis of 80 patients (9). The incidence of seroma in the current study was much higher than in these earlier studies at around 41.1%. The use of electrocautery dissection decreases blood loss, but it increases the incidence of seroma (9, 10). In contrast, argon beam coagulation and harmonic scalpel were reported to decrease seroma formation (11, 12). The use of sclerotherapy as a preventive measure for post-operative seroma has been described. This sclerotherapy consists of filling the dead space with an irritating substance to induce a fibrotic reaction with the clinical aim of sealing the space. Commonly used irritating substances included doxycycline, bleomycin, ethanol, and talc (13). To our knowledge, a few published reports have documented the use of sclerotherapy for prevention

Table 2. Comparison of operative outcome and postoperative complications between the three groups

| | Doxycycline (n = 30) | Placebo (n = 30) | Bleomycin (n = 30) | *p* |
|---|---|---|---|---|
| Operation time (minutes) | 83.50±33.04 | 92.83±42.84 | 85.00±31.27 | 0.563 |
| Estimated blood loss (mL) | 45.33±32.35 | 55.00±39.46 | 37.33±26.90 | 0.127 |
| Mean VAS after 4h | 5.27±1.34 | 7.03±0.89 | 6.80±1.10 | <0.001* |
| Mean VAS after 8h | 3.13±0.35 | 4.07±0.87 | 4.90±1.24 | <0.001* |
| Mean VAS after 12h | 3.10±0.31 | 3.70±0.65 | 4.50±1.31 | <0.001* |
| Postoperative hematoma, n (%) | 0 (0.0%) | 1 (3.3%) | 6 (20.0%) | 0.008* |
| Flap ischemia, n (%) | 6 (20.0%) | 5 (16.7%) | 6 (20.0%) | 0.930 |
| Postoperative infection, n (%) | 1 (3.3%) | 2 (6.7%) | 3 (10.0%) | 0.585 |

VAS: visual analog scale

Table 3. Comparison between the three groups in terms of incidence of seroma, clinical features of seroma and its management

| | Doxycycline (n = 30) | Placebo (n = 30) | Bleomycin (n = 30) | *p* |
|---|---|---|---|---|
| **Time of drain removal (days)** | 19.43±5.50 | 19.13±7.13 | 18.20±5.26 | 0.711 |
| **Seroma incidence** | | | | |
| No seroma | 18 (60.0%) | 17 (56.7%) | 18 (60.0%) | 0.992 |
| G1 seroma | 3 (10.0%) | 2 (6.7%) | 3 (10.0%) | |
| G2 seroma | 4 (13.3%) | 4 (13.3%) | 3 (10.0%) | |
| G3 seroma | 5 (16.7%) | 7 (23.3%) | 6 (20.0%) | |
| **Postoperative drainage (mL)** | | | | |
| Amount in the first 3 days | 629.00±451.07 | 601.83±330.71 | 568.00±209.23 | 0.791 |
| Total amount of drained fluid | 2891.17±2048.38 | 3415.33±3788.49 | 3389±1679.82 | 0.694 |
| Amount in the last 3 days | 139.50±20.73 | 141.83±16.69 | 140.50±20.02 | 0.895 |
| Amount on last day | 21.83±13.93 | 23.33±11.55 | 25.00±10.42 | 0.597 |
| Number of patients undergoing aspiration of seroma, n (%) | 10 (33.3%) | 10 (33.3%) | 9 (30.0%) | 0.950 |
| Total aspirated volume (mL) | 66.50±142.09 | 108.67±367.29 | 57.00±119.49 | 0.670 |
| Drain reinsertion, n (%) | 5 (16.7%) | 6 (20.0%) | 6 (20.0%) | 0.930 |

or treatment of seromas. The existing reports suggested that this treatment was effective and well-tolerated. However, a comprehensive comparative analysis of the different possible options was lacking. The hypothesis for the sclerosing action of doxycycline was the destruction of the mesothelial cells lining the pseudocyst, as well as inhibition of fibrinolysis and induction of fibroblast growth factors (14). The concentration of the recommended material in most studies was 500 mg of doxycycline dissolved in 50 to 100 mL of sterile saline. This was prescribed for pleurodesis, but the main disadvantage of doxycycline was the associated pain, so analgesic and/or conscious sedation was usually added (15). Bansal et al. (14) applied doxycycline to trunk, thigh, and gluteal seromas in 16 patients. In this study, 500 mg of doxycycline in 25 mL normal saline was injected into the seroma cavities and compression garments were applied postoperatively. Most seromas resolved within four weeks, whereas seromas of the anterior abdominal wall resolved within eight weeks (14). Our study showed no significant difference in the incidence of post-mastectomy seroma with or without doxycycline administration at the same dose. Our study showed no increased incidence of postoperative complications between doxycycline and the control group as regard postoperative hematoma, flap necrosis, pain, and infection.

For bleomycin, most studies recommended its use in pleurodesis in a dosage of 60 IU mixed with 50 to 100 mL sterile saline. In comparison with tetracycline, similar or higher success rates were reported when bleomycin was used as a sclerosing agent (16-18). A direct trial comparing doxycycline with bleomycin in pleurodesis using a small-bore catheter has demonstrated a similar success rate (79% doxycycline and 72% bleomycin) (15). Our study showed no significant difference as regard to the incidence of postmastectomy seroma between bleomycin, doxycycline, and control group. The main disadvantage of bleomycin as a sclerosing agent was its relatively higher cost when compared to other sclerosing agents, such as doxycycline and talc (18, 19). Our study showed a higher number of cases suffering from pain and postoperative hematoma in the bleomycin group in the early postoperative hours. Our study showed that there was no significant difference among the three groups in the amount of drainage within the first three postoperative days. Kuroi et al. (1) showed that the duration of drainage did not have a significant influence on seroma formation. In contrast, Pogson et al. (6) reported that the *in situ* dwelling time of drains is an important risk factor for seroma formation and early drain removal with a larger amount of wound drainage can participate in postoperative seroma formation (6). Varshney and Goddord (20) found that longer drainage duration is usually associated with a very minimal incidence of postmastectomy seroma formation, but early removal can markedly increase seroma formation. Gupta et at. (21) reported that 8-day drainage after modified radical mastectomy resulted in a lower incidence of seroma than 5-day drainage. In our study, the drains were removed only after the daily drainage output was less than 50 mL in the preceeding 24 hours. There was no significant difference between the three groups in terms of postoperative time of drain removal. In our study, non-suction drainage was used in all cases to eliminate the suspected risk associated with type of drainage on seroma formation.

Despite improved recognition and management of risk factors, seromas remain a common concern after total mastectomy. The use of sclerosing agents, such as bleomycin and doxycycline with non-suction drainage did not decrease the incidence of post-mastectomy seroma when compared to placebo in this population.

**Ethics Committee Approval:** Ethical approval was granted by the Institutional Review Board Mansoura Faculty of Medicine Mansoura University (approval number: MS/17.08.66, date: 15.08.2017).

**Informed Consent:** Written informed consent forms were obtained from all patients.

**Peer-review:** Externally and internally peer-reviewed.

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Surgical and Medical Practices: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Concept: A.K.; Design: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Data Collection or Processing: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Analysis or Interpretation: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Literature Search: A.K., A.H., O.F., A.S., S.S., M.A., O.E.; Writing: A.K., A.H., O.F., A.S., S.S.

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## References

1. Kuroi K, Shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S, et al. Evidence-based risk factors for seroma formation in breast surgery. Jpn J Clin Oncol 2006; 36: 197-206. (PMID: 16684859) [Crossref]
2. Boostrom SY, Throckmorton AD, Boughey JC, Holifield AC, Zakaria S, Hoskin TL, et al. Incidence of clinically significant seroma after breast and axillary surgery. J Am Coll Surg 2009; 208: 148-150. (PMID: 19228516) [Crossref]
3. Soon PS, Clark J, Magarey CJ. Seroma formation after axillary lymphadenectomy with and without the use of drains. Breast 2005; 14: 103-107. (PMID: 15767179) [Crossref]
4. Kuroi K, Shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S, et al. Pathophysiology of seroma in breast cancer. Breast Cancer 2005; 12: 288-293. (PMID: 16286909) [Crossref]
5. Saydam S, Harmancioglu O. Seroma prevention. Eur Surg Res 2001; 33: 8-245. [Crossref]
6. Pogson CJ, Adwani A, Ebbs SR. Seroma following breast cancer surgery. European Journal of Surgical Oncology, Vol. 29, No.9, 2003, pp. 711-717. [Crossref]
7. Khater A, Elnahas W, Roshdy S, Farouk O, Senbel A, Fathi A, et al. Evaluation of the Quilting Technique for Reduction of Postmastectomy Seroma: A Randomized Controlled Study. Int J Breast Cancer 2015; 2015: 287398. (PMID: 26246912) [Crossref]
8 Woodworth PA, McBoyle MF, Helmer SD, Beamer RL. Seroma formation after breast cancer surgery: incidence and predicting factors. Am Surg 2000; 66: 444-450. (PMID: 10824744) [Crossref]
9. Porter KA, O'Connor S, Rimm E, Lopez M. Electrocautery as a factor in seroma formation following mastectomy. Am J Surg 1998; 176: 8-11. (PMID: 9683123) [Crossref]
10. Hoefer RA Jr, DuBois JJ, Ostrow LB, Silver LF. Wound complications following modified radical mastectomy: an analysis of perioperative factors. J Am Osteopath Assoc 1990; 90: 47-53. (PMID: 2312369) [Crossref]
11. Ridings P, Bailey C, Bucknall TE. Argon beam coagulation as an adjunct in breast-conserving surgery. Ann R Coll Surg Engl 1998; 80: 61-62. (PMID: 9579131) [Crossref]
12. Khater A. Harmonic scalpel as a single instrument in modified radical mastectomy. Is it more cost effective than electrocautery and ligature? Egypt J Surg 2010; 29: 59-63. [Crossref]
13. Shermak MA, Rotellini-Coltvet LA, Chang D. Seroma development following body contouring surgery for massive weight loss: patient risk factors and treatment strategies. Plast Reconstr Surg 2008; 122: 280-288. (PMID: 18594418) [Crossref]
14. Bansal A, Bhatia N, Singh A, Singh AK. Doxycycline sclerodesis as a treatment option for persistent Morel-Lavallée lesions. Injury 2013; 44: 66-69. (PMID: 22204771) [Crossref]

15. Patz EF Jr, McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Gilkeson RC, et al. Sclerotherapy for malignant pleural effusions: a prospective randomized trial of bleomycin vs doxycycline with small-bore catheter drainage. Chest 1998; 113: 1305-1311. (PMID: 9596311) [Crossref]
16. Hartman DL, Gaither JM, Kesler KA, Mylet DM, Brown JW, Mathur PN. Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions. J Thorac Cardiovasc Surg 1993; 105: 743-747. (PMID: 7682268) [Crossref]
17. Moffett MJ, Ruckdeschel JC. Bleomycin and tetracycline in malignant pleural effusions: a review. Semin Oncol 1992; 19(2 Suppl 5): 59-62. (PMID: 1384146) [Crossref]
18. Martínez-Moragón E, Aparicio J, Rogado MC, Sanchis J, Sanchis F, Gil-Suay V. Pleurodesis in malignant pleural effusions: a randomized study of tetracycline versus bleomycin. Eur Respir J 1997; 10: 2380-2383. (PMID: 9387969) [Crossref]
19. Windsor PG, Como JA, Windsor KS. Sclerotherapy for malignant pleural effusions: alternatives to tetracycline. South Med J 1994; 87: 709-714. (PMID: 7517579) [Crossref]
20. Varshney S, Goddord J. The optimal timing of drains removal following mastectomy and axillary clearance. Eur J Surg Oncol 2004; 29: 46. [Crossref]
21. Gupta R, Patel K, Royle GT. A comparison of 5-day and 8-day drainage following mastectomy and axillary clearance. Eur J Surg Oncol 2002; 28: 15-18. (PMID: 11237488) [Crossref]

**Original Article**

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# High-Grade Ductal Carcinoma *In Situ* of the Breast With Regressive Changes: Radiological and Clinicopathological Findings

Merve Gursoy[1], Aysenur Oktay[2], Ozge Aslan[2], Osman Zekioglu[3]

[1]Izmir Katip Celebi University Faculty of Medicine, Department of Radiology, Izmir, Turkey
[2]Ege University Faculty of Medicine, Department of Radiology, Izmir, Turkey
[3]Ege University Faculty of Medicine, Department of Pathology, Izmir, Turkey

**ABSTRACT**

**Objective:** Tumour regression is defined as continuity of changes leading to the elimination of a neoplastic population and is reflected as periductal fibrosis and intraductal tumour attenuation. The aim of this study was to describe the radiological and clinicopathological characteristics of high-grade breast ductal carcinoma *in situ* (DCIS) with regressive changes (RC).

**Materials and Methods:** Thirty-two cases of high-grade DCIS with RC on biopsy specimens followed by excision were included. The mammographic, ultrasonographic (US), and magnetic resonance imaging (MRI) findings of cases were retrospectively reviewed according to the breast imaging reporting and data system (BI-RADS) lexicon. Clinical and histopathological findings [comedonecrosis, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status and Ki-67 proliferation index] were recorded. The rate of upgrade to invasive cancer after surgical excision and lymph node involvement were evaluated.

**Results:** The most common mammographic finding was microcalcifications alone (68.8%). The most frequently seen findings on US were microcalcifications only (21.9%), followed by microcalcifications and hypoechoic area (18.7%). On MRI, most lesions presented as clumped non-mass enhancement with segmental distribution. ER/PR negativity (53.1%, 65.6%), HER2 positivity (56.3%) and high Ki-67 (62.5%), which are known to be associated with more aggressive behavior, were found to be proportionally higher. The rate of upgrade to invasive cancer was 21.8%.

**Conclusion:** DCIS with RC lesions present most often as microcalcifications alone on both mammography and US. MRI features are not distinguishable from those of other DCIS lesions. DCIS with RC lesions show biomarker status reflecting more aggressive behavior and high upgrade rate to invasive cancer.

**Keywords:** Ductal carcinoma *in situ*, regressive changes, mammography, ultrasound, breast magnetic resonance imaging

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**Key Points**

- Ductal carcinoma *in situ* (DCIS) with regressive changes (RC) lesions present most often as microcalcifications alone on mammography and ultrasonographic.
- Magnetic resonance imaging features are not distinguishable from those of other DCIS lesions.
- DCIS with RC lesions show biomarker status reflecting more aggressive behavior and high upgrade rate to invasive cancer.

## Introduction

Ductal carcinoma *in situ* (DCIS) of the breast, is intraductal proliferation of malignant epithelial cells which do not pass through the basal membrane (1). DCIS of the breast is a heterogenous lesion group with a broad spectrum of biological behaviour. Compared to low-grade DCIS, high-grade DCIS has more risk of progression to invasive cancer in follow-up resection specimens, axillary lymph node involvement, and recurrence (2-4). Differences between lesions, and the effects of these differences on prognosis are not limited by tumour grade alone. Stromal changes are another of these, which have been defined as regressive changes (RC) and the effect of which on prognosis has been shown in very few publications (5, 6). Tumour regression is defined as continuity of changes leading to the elimination of a neoplastic population. RC has been defined not only in breast cancer but also for several malignancies, such as malignant melanoma, prostate cancer, and cervix cancer. Although not fully understood, regression is believed to represent the host immune system response working to eliminate the neoplastic population (7).

**Corresponding Author:**
**Merve Gursoy; gursoymerve@yahoo.com**

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RC in DCIS of the breast was first described by Muir and Aitkenhead (8) in 1934 and was defined as collagen tissue layers surrounding neoplastic epithelium, interpreted as a part of the scarring/healing process. These changes described in the first studies were thought to be a protective barrier preventing spread of the tumour. However, more aggressive behaviour of cases of DCIS of the breast with RC was shown in later studies (more frequent axillary lymph node involvement and relationship with invasive cancer) causing this to be accepted, not as a protective mechanism, but as a harmful mechanism (5, 6).

An examination of the relevant literature showed that extremely few studies have been conducted related to high-grade DCIS of the breast with RC, and published studies are in the pathology literature (5, 6, 8). Although there are many studies that have examined the imaging findings of breast DCIS, very few studies could be found that have evaluated the imaging findings of a subgroup showing RC. Therefore, the aim of this study was to describe the radiological, including mammography, ultrasonography (US) and magnetic resonance imaging (MRI) and clinicopathological characteristics of high-grade breast DCIS with RC.

## Materials and Methods

This retrospective study was approved by the Institutional Review Board of Ege University (21-5.1T/62). As the study was retrospective, informed consent by patients and providers was not required.

### Patients

Patients were identified from those who underwent US-guided core biopsy or stereotactic-guided vacuum-assisted core biopsy because of any lesion seen in the breast in examination in the Radiology Department of our hospital between 2016 and 2021, and received a histopathological diagnosis of high-grade DCIS with RC [with or without microinvasion (invasive focus of ≤1 mm)]. Patients were excluded from the study if they had no radiological images before biopsy, if they had a history of breast cancer surgery, or if invasive cancer was diagnosed on biopsy. A total of 32 patients who met the criteria were included in the study. Patient age and gender were recorded in each case.

### Radiological Analysis

The findings of all the imaging modalities (mammography, US, MRI) obtained before the biopsy were determined. Evaluation of the findings was made in accordance with the Breast Imaging Reporting and Data System (BI-RADS) version 5.

Mammography in two standard positions (craniocaudal and mediolateral-oblique) was performed using a Selenia Dimensions device (Hologic, Bedford, MA, USA). The mammographic parenchymal pattern was recorded according to the BI-RADS mammographic lexicon. The presence of microcalcification, if any, morphology (amorphous, coarse heterogeneous, fine pleomorphic, fine linear or fine-linear branching) and distribution (diffuse, regional, grouped, linear or segmental) were determined on mammography. Microcalcifications were evaluated according to the presence or absence of accompanying mass, architectural distortion or asymmetry.

US evaluations were performed with a 7-12 MHz linear probe [Siemens Acuson S 2000 (Helx, Evolution), Siemens Medical Solutions Inc, USA]. All of the US records and images which were archived were retrospectively reevaluated. The radiologist was aware of the patients' mammographic results before the sonographic examinations. The sonographic findings were classified as negative in patients who had no findings on US. When microcalcifications were present, the sonographic findings were classified as microcalcifications only, microcalcifications and mass, microcalcifications and architectural distortion, microcalcifications and ductal changes, and microcalcifications and a hypoechoic area. A hypoechoic area was defined as a focal heterogeneity that was different from the surrounding parenchyma or the same area in the ipsilateral breast. Ductal changes were defined as an abnormal caliber, branching of ducts or intraductal echoes. Findings of patients without microcalcification (mass only or architectural distortion only) were also noted.

MRI scans were obtained on a 1.5-Tesla MRI unit (Magnetom Amira, Siemens) or 3-Tesla MRI unit (Magnetom Verio, Siemens) using a dedicated breast coil with the patient in a prone position. Images were acquired in the axial plane with the following sequences: axial, T2-weighted, fat-suppressed, fast spin-echo imaging; pre- and post-contrast, axial, T1-weighted three-dimensional fast spoiled gradient echo sequence. Gadolinium- diethylenetriamine pent acetic acid (Magnevist; Schering, Berlin, Germany) was administered with an intravenous bolus injection at 0.1 mmol/kg. Imaging was performed before the intravenous contrast agent bolus injection and five times after this injection for a period of six minutes. Subtractions of the dynamic contrast enhanced series were obtained by subtracting pre-contrast from post-contrast sequences. Maximum intensity projections were also performed. According to the Fifth edition of the MRI BI-RADS descriptors, the morphology of the lesion was described as mass, non-mass enhancement (NME) and focus. The distribution (focal, linear, segmental, regional, multiple and diffuse) and internal enhancement patterns (homogeneous, heterogeneous, clumped and clustered ring) of NME lesions and the shape (round, oval and irregular), margin (circumscribed and not-circumscribed) and internal enhancement characteristics (homogeneous, heterogeneous, rim enhancement and dark internal septations) of mass lesions were determined.

All mammograms, ultrasonograms, and MRIs were retrospectively reviewed in consensus by one radiologist with 30 years of experience and by one radiologist with seven years of experience in breast imaging.

### Clinicopathological Analysis

Clinical features (asymptomatic, palpable mass or nipple discharge) obtained from the referring clinician's records were recorded in each case. The presence or absence of comedonecrosis and expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 proliferation index were recorded. Positive expression for ER/PR status was defined as nuclear staining in 1% or more of tumour cells. Positive immunohistochemistry staining (3+) or HER2 gene amplification by fluorescence *in situ* hybridisation was judged to be HER2 positive. Ki-67 proliferation index was categorised as high if 20% of tumour cells showed staining. Reports from follow-up surgical resections (lumpectomy or mastectomy) after a biopsy diagnosis of high-grade DCIS with RC were reviewed, and the final diagnosis, including the presence or absence of invasive carcinoma and axillary lymph node involvement (if sampled) was noted.

### Statistical Analysis

Data analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) software, version 22.0. Data distributions were evaluated with the Shapiro-Wilk test for normality. All variables without normal

distribution were reported as median and ranges. Normally distributed variables were reported in means and standard deviation.

## Results

### Radiological Findings of High-Grade DCIS with RC

All patients were female, and the mean age was 55 years (SD, ±13.03; range, 32–78 years) at the time of diagnosis. All patients underwent preoperative mammography. The parenchymal patterns of the breasts were almost entirely fatty in 1 (3.2%) patient, scattered fibroglandular densities in 13 (40.6%) patients, heterogeneously dense in 16 (50%) patients, and extremely dense in 2 (6.2%) patients.

Microcalcifications (30/32, 93.7%) were the most common findings of high-grade DCIS with RC on mammography. Two patients (2/32, 6.3%) presented with other findings; one patient with mass only, and one patient with architectural distortion only. Of the 30 patients with microcalcifcation detected on mammography, 22 (22/32, 68.8%) had microcalcifications only (Figure 1), 6 (6/32, 18.8%) patients had focal asymmetry and microcalcifications (Figures 2, 3), 1 (1/32, 3.1%) patient had a mass and microcalcifications and 1 (1/32, 3.1%) patient had architecural distortion and microcalcifications. The microcalcifications seen in high-grade DCIS with RC were most often of fine pleomorphic morphology with segmental distribution (Table 1, Figure 4).

US was performed in all patients. In 8 of 32 patients (25%), the US examination was negative with no finding observed (Figure 1). The most frequently seen findings were microcalcifications only (7/32, 21.9%) (Figure 5) followed by microcalcifications and hypoechoic area (6/32, 18.7%) (Figure 6). In 5 (5/32, 15.6%) patients, there was a mass and accompanying microcalcifications on US (Figure 2). There was architectural distortion and microcalcifications in 2 patients (2/32, 6.2%) and ductal changes and microcalcifications in 2 (2/32, 6.2%) patients (Figure 4). In the two patients without microcalcifications on mammography, 1 (1/32, 3.1%) was determined with mass only, and 1 (1/32, 3.1%) with architectural distortion only on US (Table 2).

Sixteen of the 32 patients with high grade DCIS with RC underwent breast MRI. The findings of the 16 patients on MRI were a mass in only one patient (1/16, 6.2%) and NME in 15 patients (15/16, 93.8%). One patient with breast mass had irregular shape, irregular margin and heterogeneous internal enhancement characteristics. Most patients had a NME with segmental distribution and clumped internal enhancement characteristics (Figure 4). The MRI characteristics of the patients are shown in detail in Table 3.

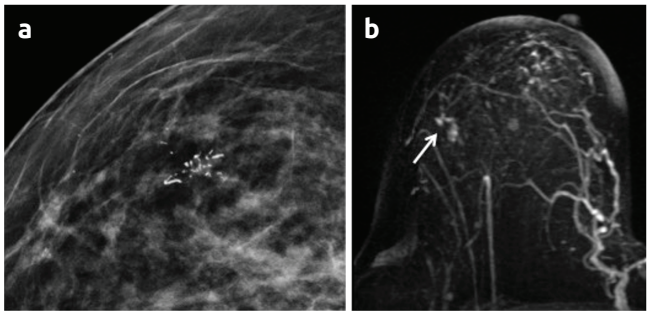


**Figure 1.** A 69-year-old asymptomatic female patient who presented with microcalcifications detected on screening mammography. a. Mammography image shows pleomorphic grouped microcalcifications. There was no finding on US. b. Axial post-contrast maximal intensity projection MR image shows focal clumped NME (arrow). High grade DCIS with RC was diagnosed using stereotactic-guided vacuum-assisted core biopsy. Both the estrogen and progesterone receptors were negative, HER2 was positive, and the Ki-67 index was more than 20%

*US: ultrasonography; MR: magnetic resonance; NME: non-mass enhancement; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2*

### Clinicopathological Characteristics of High-Grade DCIS with RC

Twenty (20/32, 62.5%) patients were asymptomatic and the lesion was detected on screening mammography, while the remaining 12 (12/32, 37.5%) had symptoms. Of the 12 patients with symptomatic high-grade DCIS with RC lesions, 9 (9/32, 28.1%) had a palpable mass, 1 (1/32, 3.1%) had both a palpable mass and nipple discharge; and 2 (6.3%) had nipple discharge (Table 4).

Histopathological diagnosis was obtained using US-guided core biopsy

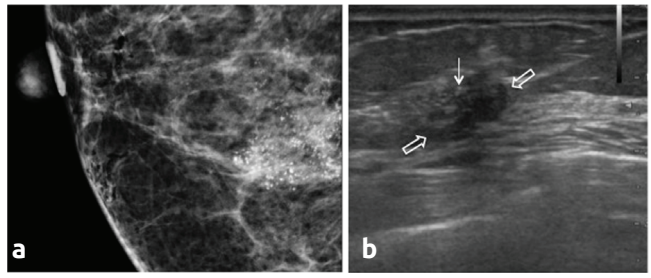


**Figure 2.** A 45-year-old female patient who presented with a palpable mass. a. Mammography image shows coarse heterogeneous calcifications with segmental distribution and focal asymmetry. b. US image shows irregular, hypoechoic mass with indistinct margins (open arrows). Note the internal bright echoes (arrow) within the mass correspond to microcalcifications on mammography. High grade DCIS with RC was diagnosed using US-guided core biopsy. The lesion was upgraded to invasive ductal carcinoma on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative, and the Ki-67 index was less than 20%

*US: ultrasonography; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2*

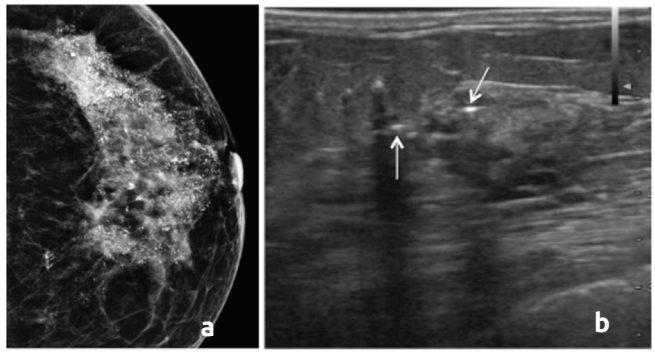


**Figure 3.** A 55-year-old female patient who presented with a palpable mass. a. Mammography image shows coarse heterogeneous calcifications with diffuse distribution and asymmetry. b. US image shows hypoechoic areas with microcalcifications (arrows). High grade DCIS with RC and with microinvasion was diagnosed using US-guided core biopsy. The lesion was upgraded to invasive ductal carcinoma on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative, and the Ki-67 index was more than 20%

*US: ultrasonography; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2*

in 24 of 32 patients and using stereotactic-guided vacuum-assisted core biopsy in 8 patients (Figure 7). Comedonecrosis was present in 21 (65.6%) and absent in 11 (34.4%) lesions. ER status was positive in 15 (46.9%) and negative in 17 (53.1%) patients. PR status was positive in 11 (34.4%) and negative in 21 (65.6%) patients. HER2 status was positive in 18 (56.3%) and negative in 14 (43.7%) patients. Ki-67 proliferation index was high (≥20) in 20 (62.5%) and low (<20) in 12 (37.5%) patients.

All patients underwent lumpectomy (n=17) or mastectomy (n=15). The non-palpable lesions were preoperatively localized by mammographically or sonographically guided needle-wire localization technique. When the final histopathology results were reviewed, invasive ductal carcinoma was diagnosed on follow-up surgical resection (lumpectomy or mastectomy) in 7 (7/32, 21.8%) patients. The median size of invasive carcinomas was 4 mm (range, 2-24 mm). Of the seven invasive carcinomas in the cohort, one was T2 and the others were T1 tumors. The median size of DCIS was 20 mm (range, 7–100 mm) in the excision specimens. In addition, microinvasion was detected in the final histopathology in 7 (7/32, 21.8%) patients, although it was not observed on core biopsy. Sentinel lymph node mapping was performed in 22 patients. Axillary lymph node involvement was identified in one (1/32, 3.1%) patient. Clinicopathological characteristics of high-grade DCIS with RC are summarised in Table 4.

## Discussion and Conclusion

The incidence of DCIS has increased in parallel with the more widespread implementation of breast cancer screening programs, and now constitutes approximately 20–30% of all breast cancers (9, 10). This increases the importance of knowing the imaging findings of DCIS on all modalities. Many studies have described the radiological findings of low- and high-grade DCIS lesions and the correlation of these findings with the clinicopathological and biologic features of the tumor (11, 12). However, information about DCIS of the breast with RC is mainly limited to the histopathological features of the tumour and the biological behaviour spectrum, and the radiological findings have not been well defined. Therefore, the aim of the current study was to describe the radiological findings of high-grade DCIS with RC, and the results showed that the most common presentation on mammography was in the form of a microcalcification associated lesion (93.8%). In a study by Mun et al. (13), DCIS seen with mammographic calcifications were shown to have more aggressive behavior. In addition, most high-grade DCIS lesions include comedonecrosis and this is a necrotic remnant generally produced by a high-grade tumour undergoing calcification. It has been reported that in low-grade DCIS not including comedonecrosis there is a lower probability of showing microcalcification on mammography and the probability of showing as normal or with non-calcified abnormalities is high (14). The extremely high rate (93.8%) of microcalcifications in the current study can be attributed to all the lesions being high-grade and the majority (65.6%) including comedonecrosis. The most common form of presentation of the calcified lesions in this study was as microcalcifications alone, seen in 68.8% of the patients. As there are few studies in the literature

Table 1. Mammographic characteristics of high-grade DCIS with RC

| Findings (n = 32) | n (%) |
|---|---|
| **Lesion type** | |
| • Microcalcifications only | 22 (68.8%) |
| Microcalcifications with | |
| - mass | 1 (3.1%) |
| - architectural distortion | 1 (3.1%) |
| - focal asymmetry | 6 (18.8%) |
| • Mass only | 1 (3.1%) |
| • Architectural distortion only | 1 (3.1%) |
| **Morphology (for microcalcifications)** | |
| • Amorphous | 2 (6.7%) |
| • Coarse heterogeneous | 6 (20%) |
| • Fine pleomorphic | 18 (60%) |
| • Fine linear or fine-linear branching | 4 (13.3%) |
| **Distribution (for microcalcifications)** | |
| • Segmental | 9 (30%) |
| • Linear | 5 (16.7%) |
| • Grouped | 8 (26.7%) |
| • Regional | 7 (23.3%) |
| • Diffuse | 1 (3.3%) |

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients

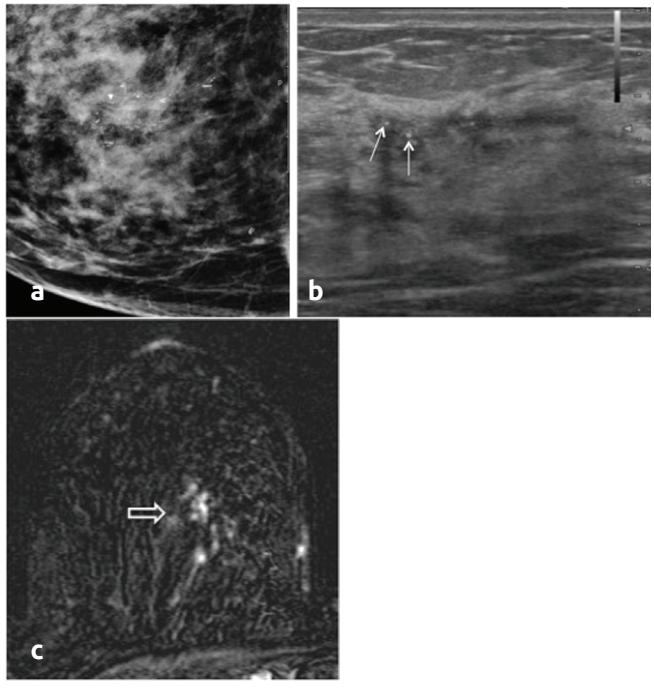


**Figure 4.** A 48-year-old asymptomatic female patient who presented with microcalcifications detected on screening mammography. a. Mammography image shows pleomorphic microcalcifications with segmental distribution. b. US shows microcalcifications (arrows) within irregularly dilated ducts, which appear as bright intraductal echoes. c. Axial post-contrast subtraction MR image shows clumped NME with segmental distribution (open arrow). High grade DCIS with RC was diagnosed using US-guided core biopsy. Microinvasion was detected on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative and the Ki-67 index was more than 20%

*US: ultrasonography; MR: magnetic resonance; NME: non-mass enhancement; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2*

examining the imaging findings of DCIS with RC, the results of the present study could only be compared with previous studies of the radiological findings of DCIS cases, which did not examine whether or not they showed RC. Similar to the current study, Scoggins et al. (11) reported that the most frequently seen finding of DCIS lesions on mammography was microcalcifications alone, which was present in 69% of the patients. When the morphology and distribution of the calcifications was examined, the most common were seen to be fine pleomorphic in appearance with diffuse distribution (11). In the current study, the microcalcifcations were similar in morphology, but segmental distribution was more usually seen.

Of all the DCIS with RC cases in the current study, 25% could only be seen on mammography and were occult on US. In the study by Scoggins et al. (11), 48% of the DCIS lesions could not be determined on US and could only be determined on mammography. It has been shown in several studies that approximately 50% of DCIS lesions can be seen on US (15, 16). It has also been reported that there is a higher probability of visualising microcalcifications associated with isolated microcalfications within normal breast tissue has been thought to be more difficult on US (19). This view was supported by the fact that there was no threshold finding such as mass or asymmetry on the mammography of all the patients with negative US in the current study.

The most common US finding of US-visible high-grade DCIS with RC lesions in this study was microcalcifications only, followed by microcalcifications and hypoechoic area. In this study, hypoechoic area was defined as a focal heterogeneity that was different from the surrounding parenchyma. As this term is not found in the BI-RADS sonographic lexicon, several studies have used terms such as non-mass lesion or abnormal-appearing mixed echogenicity, corresponding to non-mass enhancement on MRI (11, 20). When all DCIS lesions are evaluated without grade differentiation, several studies have shown the most common US finding to be mass (21, 22). The US images of high-grade and low-grade DCIS lesions show differences. Cha et al. (20) reported that microcalcification and non-mass lesions on

Table 2. Sonographic characteristics of high-grade DCIS with RC

| Findings (n = 32) | n (%) |
|---|---|
| Negative | 8 (25%) |
| Microcalcifications only | 7 (21.9%) |
| Mass | |
| • Microcalcifications and mass | 5 (15.6%) |
| • Mass only | 1 (3.1%) |
| Architectural distortion | |
| • Microcalcifications and architectural distortion | 2 (6.2%) |
| • Architectural distortion only | 1 (3.1%) |
| Microcalcifications and ductal changes | 2 (6.2%) |
| Microcalcifications and hypoechoic area | 6 (18.7%) |

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients

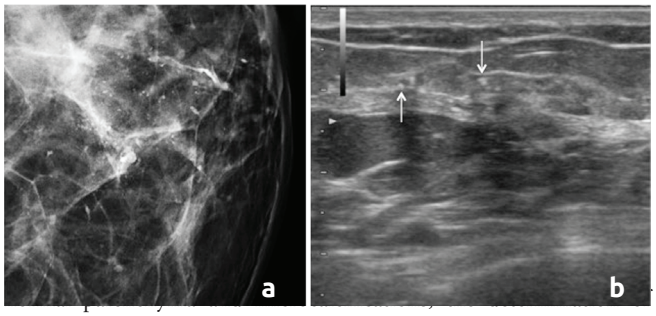


**Figure 5.** A 46-year-old female patient who presented with bloody nipple discharge. a. Mammography image shows pleomorphic microcalcifications with regional distribution. b. US image shows microcalcifications (arrows) embedded within normal breast tissue (microcalcifications only on US). High grade DCIS with RC was diagnosed using US-guided core biopsy. The estrogen receptor was positive, progesterone receptor was negative, HER2 was positive, and the Ki-67 index was less than 20%

*US: ultrasonography; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2*

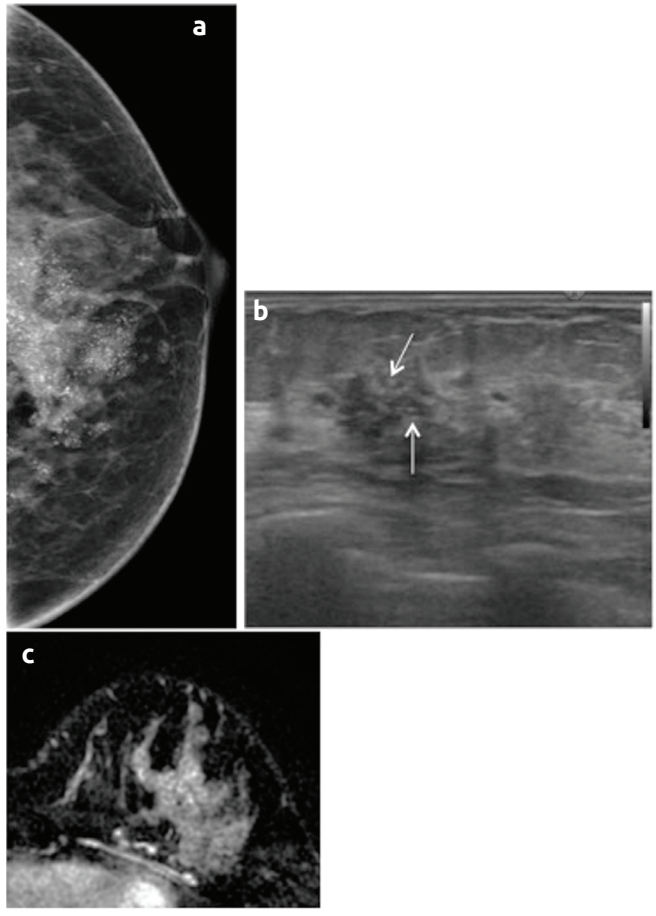


**Figure 6.** A 45-year-old female patient who presented with a palpable mass. a, Mammography image shows coarse heterogeneous calcifications with regional distribution and asymmetry. b, US image shows hypoechoic areas with microcalcifications (arrows). c, Axial post-contrast subtraction MR image shows NME with heterogeneous internal enhancement in regional distribution. High grade DCIS with RC was diagnosed using US-guided core biopsy. Microinvasion was detected on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative, and the Ki-67 index was more than 20%

*US: ultrasonography; MR: magnetic resonance; NME: non-mass enhancement; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2*

US were seen more often in high-grade DCIS lesions. Non-calcified abnormalities, such as mass, asymmetry, and architectural distortion, are seen more often in non-high-grade DCIS lesions (17). The US findings of the DCIS lesions with RC in the current study showed similar characteristics to those of high-grade DCIS lesions.

It has been reported that DCIS most commonly manifests as NME (60–81%), and less frequently as a mass (14–41%) or as a focus (1–12%) on MRI (23-25). Only one case in the current study presented in the form of mass and NME presentation was more common than in literature (93.8%). Clumped, followed by a heterogeneous internal enhancement patterns and segmental or linear distribution are hallmarks of NME DCIS on MRIs (26). Similar to the literature, the most common MRI appearance of DCIS with RC in the current study was NME with segmental distribution and clumped internal enhancement characteristics. DCIS with RC did not have a distinct enough appearance to allow it to be differentiated from other DCIS lesions solely on the basis of MRI findings.

Chivukula et al. (5), in their study on high-grade DCIS lesions, showed that RC is a biological change that can lead to invasive cancer with the loss of myoepithelial cells. In the same study, the rate of upgrade to invasive cancer following surgical excision was 20% in the high-grade DCIS with RC group, which was significantly higher than that of the group without RC (4%). In the current study, the rate of upgrade to invasive cancer was similar at 21.8% (7/32) in the final pathology. Furthermore, although microinvasion was not observed in the core biopsy of seven patients in the current study, it was identified as a result of surgical excision. In a study by Zhang et al. (27), DCIS lesions with and without microinvasion were compared, and larger tumour size, high grade, comedo-type, negative PR/ER, high Ki-67 and more axillary lymph node metastasis were present in the microinvasion group. Therefore, if the patients shown to have microinvasion in the final pathology when not observed in core biopsy, were evaluated as upgrade lesions, the upgrade rate in the current study increased to 43.6%. In addition, the rates of axillary lymph node metastasis were determined to be similar in the current study and the study by Chivukula et al. (5) (3.1% and 2.8%, respectively).

When the imaging studies were examined of the seven patients determined with invasive cancer in the current study, in one case presentation was in the form of mass only on mammography, and in four cases there was focal asymmetry accompanying microcalcifications. In other words, of the seven patients with invasive cancer in surgical resection, there were findings other than microcalcification in five (71.4%). Presentation was in the form of microcalcifications alone in two patients. When all the patients included in the study were taken into consideration, of the 10 patients with findings other than microcalcifications only on mammography (microcalcifications with mass, architectural distortion or asymmetry, mass only and architectural distortion only), invasive cancer was identified in follow-up surgical resection in five. The invasive component of the tumour, if present, in DCIS cases cannot usually be found in the microcalcification region, as the invasive component usually presents as mammographic density (mass, architectural distortion or asymmetry) (28). In the current study, 50% of all patients with findings other than microcalcifications on mammography were found to have invasive

Table 3. MRI characteristics of high-grade DCIS with RC

| Findings (n = 16) | n (%) |
|---|---|
| Mass | 1 (6.2%) |
| NME | 15 (93.8%) |
| **Distribution (for NME lesions)** | |
| • Focal | 1 (6.7%) |
| • Linear | 3 (20%) |
| • Segmental | 8 (53.3%) |
| • Regional | 2 (13.3%) |
| • Diffuse | 1 (6.7%) |
| **Internal enhancement patterns (for NME lesions)** | |
| • Heterogeneous | 4 (26.7%) |
| • Clumped | 11 (73.3%) |

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients; NME: non-mass enhancement; MRI: magnetic resonance imaging

Table 4. Clinicopathological characteristics of high-grade DCIS with RC

| Findings (n = 32) | n (%) |
|---|---|
| **Clinical presentation** | |
| • Asymptomatic | 20 (62.5%) |
| • Palpable mass | 9 (28.1%) |
| • Nipple discharge | 2 (6.3%) |
| • Palpable mass+ nipple discharge | 1 (3.1%) |
| **Comedonecrosis** | |
| • Present | 21 (65.6%) |
| • Absent | 11 (34.4%) |
| **ER status** | |
| • Positive | 15 (46.9%) |
| • Negative | 17 (53.1%) |
| **PR status** | |
| • Positive | 11 (34.4%) |
| • Negative | 21 (65.6%) |
| **HER2 status** | |
| • Positive | 18 (56.3%) |
| • Negative | 14 (43.7%) |
| **Ki-67 proliferation index** | |
| • ≥20 | 20 (62.5%) |
| • <20 | 12 (37.5%) |
| **Upgrade to invasive carcinoma** | |
| • Yes | 7 (21.9%) |
| • No | 25 (78.1%) |
| **Axillary node status** | |
| • Positive | 1 (3.1%) |
| • Negative | 21 (65.6%) |
| • Unknown | 10 (31.3%) |

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2

cancer in surgical resection, or 71.4% of patients with invasive cancer in the final pathology had density other than microcalcifications on mammography that confirms that this assumption is also valid for high-grade DCIS with RC. Therefore, in core biopsy, the histopathological diagnosis can be made on the sampled tissue only and this may not represent all the pathological findings of that case.

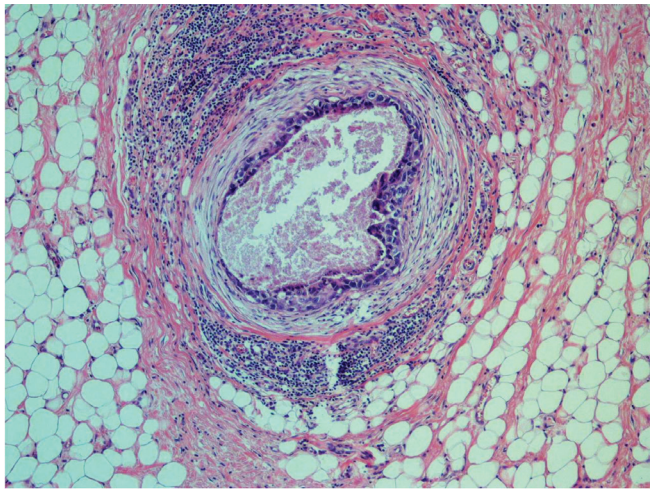

**Figure 7.** High grade DCIS with RC. Central necrosis and periductal massive fibrosis with lymphocytic infiltration (H&E X 10)

*DCIS: ductal carcinoma in situ; RC: regressive changes*

In a study by Wasserman and Parra-Herran (6), in which grading was applied according to the severity of RC, it was reported that more advanced RC was more frequent in ER and PR negative tumours. In the same study, despite a tendency to more advanced RC in HER2 positive tumours, the difference was not statistically significant. There is not published study examining the relationship between RC and Ki-67 proliferation index in this type of breast cancer. RCs were not pathologically graded in the current study but in the high-grade DCIS with RC cases included in the study, there were proportionally higher rates of negative ER (53.1%), negative PR (65.6%), positive HER2 (56.3%), and/or high Ki-67 proliferation index (62.5%), which represented more aggressive tumour behaviour. In some studies in the literature, RC are termed neoductgenesis, which is synonymous. Tabar et al. (29) described that neoductgenesis was a typical feature of some high-grade DCIS and was regularly associated with signs of altered epithelial-stromal interaction, like periductal lymphocytic infiltration and remodelling of the specialized periductal stroma. Similar to our study, they also found that neoductgenesis according to their definition correlated with more aggressive tumour biology (30). Wasserman et al suggested that this relationship was due to intrinsic immunogenic characteristics of hormone-negative *in situ* neoplasms and that the immune response leading to RC targetted one or more lineage-specific markers (6). Compared to low or intermediate-grade DCIS, the probability of high-grade DCIS lesions being ER/PR-negative and HER2 positive has been reported to be higher (31). However, whether there is any difference or not between high-grade DCIS with and without RC in respect of biomarkers has not been researched. Therefore, there is a clear need for comparative studies of large series to be conducted.

This study has some limitations. First, it was retrospective in design, so all patients had mammography and US but not all patients underwent breast MRI. Second, the study lacked a control group of patients who were diagnosed with high-grade DCIS without RC. The comparison of the radiological findings of DCIS with and without RC and the correlations of these with histopathological findings would contribute to a clearer determination of lesion character. A further limitation was that the Pathology Department of our hospital has only routinely reported RC seen in DCIS cases in the histopathology reports in the last four years. Therefore, only cases of breast DCIS with RC in the last four years could be included in the study so the sample size was relatively small. However, the study can be considered of value as there are very few studies in the literature that have focused on the radiological findings of DCIS with RC. Nevertheless, there is a need for further studies with larger series on this subject.

In conclusion, to the best of our knowledge, this is one of the few studies to have analyzed the imaging findings of high-grade DCIS with RC and adds to the clinicopathological findings reported by Chivukula et al. (5) and Wasserman and Parra-Herran (6). The results of this study demonstrated that high-grade DCIS with RC presented most often in the form of microcalcifications alone with fine pleomorphic morphology and segmental distribution on mammography. On US, 75% of the lesions could be visualised and the most common appearance was again of microcalcifications alone, followed by microcalcifications and hypoechoic area. On MRI, the most common appearance of DCIS with RC was NME with segmental distribution and clumped internal enhancement characteristics, which is typical for all DCIS lesions. ER/PR negativity, HER2 positivity and high Ki-67, which are known to be associated with more aggressive tumour behavior, were found to be proportionally higher in this study. In addition, upgrade to invasive cancer was made after surgical resection in approximately one in five cases of high-grade DCIS with RC. Knowing the radiological findings of DCIS with RC lesions, which have been shown in a few studies to be associated with more aggressive tumour behavior, will help in the implementation of patient management and treatment planning more safely.

**Ethics Committee Approval:** This retrospective study was approved by the Institutional Review Board of Ege University (IRB number 21-5.1T/62).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: A.O., O.A., O.Z.; Concept: M.G., A.O.; Design: M.G., A.O.; Data Collection or Processing: M.G., O.A., O.Z.; Analysis or Interpretation: M.G., A.O., O.A., O.Z.; Literature Search: M.G.; Writing: M.G.

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## References

1. Ozzello L. Ultrastructure of intra-epithelial carcinomas of the breast. Cancer 1971; 28: 1508-1515. (PMID: 4108411) [Crossref]
2. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991; 19: 403-410. (PMID: 1757079) [Crossref]
3. Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, et al. Surgical excision without radiation for ductal carcinoma in situ of the

breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol 2015; 33: 3938-3944. (PMID: 26371148) [Crossref]

4. Sagara Y, Mallory MA, Wong S, Aydogan F, DeSantis S, Barry WT, et al. Survival benefit of breast surgery for low-grade ductal carcinoma in situ: a population-based cohort study. JAMA Surg 2015; 150: 739-745. (PMID: 26039049) [Crossref]
5. Chivukula M, Domfeh A, Carter G, Tseng G, Dabbs DJ. Characterization of high-grade ductal carcinoma in situ with and without regressive changes: diagnostic and biologic implications. Appl Immunohistochem Mol Morphol 2009; 17: 495-499. (PMID: 19407654) [Crossref]
6. Wasserman JK, Parra-Herran C. Regressive change in high-grade ductal carcinoma in situ of the breast: histopathologic spectrum and biologic importance. Am J Clin Pathol 2015; 144: 503-510. (PMID: 26276781) [Crossref]
7. Horimoto Y, Hayashi T, Arakawa A. Pathology of healing: what else might we look at? Cancer Med 2016; 5: 3586-3587. (PMID: 27781408) [Crossref]
8. Muir R, Aitkenhead AC. The healing of intra-duct carcinoma of mamma. J Pathol 1934; 18: 115-127. [Crossref]
9. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 2010; 102: 170-178. (PMID: 20071685) [Crossref]
10. Ozanne EM, Shieh Y, Barnes J, Bouzan C, Hwang ES, Esserman LJ. Characterizing the impact of 25 years of DCIS treatment. Breast Cancer Res Treat 2011; 129: 165-173. (PMID: 21390494) [Crossref]
11. Scoggins ME, Fox PS, Kuerer HM, Rauch GM, Benveniste AP, Park YM, et al. Correlation between sonographic findings and clinicopathologic and biologic features of pure ductal carcinoma in situ in 691 patients. AJR Am J Roentgenol 2015; 204: 878-888. (PMID: 25794082) [Crossref]
12. Barreau B, de Mascarel I, Feuga C, MacGrogan G, Dilhuydy MH, Picot V, et al. Mammography of ductal carcinoma in situ of the breast: review of 909 cases with radiographic-pathologic correlations. Eur J Radiol 2005; 54: 55-61. (PMID: 15797293) [Crossref]
13. Mun HS, Shin HJ, Kim HH, Cha JH, Kim H. Screening-detected calcified and noncalcified ductal carcinoma in situ: differences in the imaging and histopathological features. Clin Radiol 2013; 68: e27-e35. (PMID: 23177096) [Crossref]
14. Wright B, Shumak R. Part II: medical imaging of ductal carcinoma in situ. Curr Probl Cancer 2000; 24: 112-124. (PMID: 10919314) [Crossref]
15. Moon WK, Myung JS, Lee YJ, Park IA, Noh DY, Im JG. US of ductal carcinoma in situ. RadioGraphics 2002; 22: 269-280; discussion,280-281. (PMID: 11896217) [Crossref]
16. Gwak YJ, Kim HJ, Kwak JY, Lee SK, Shin KM, Lee HJ, et al. Ultrasonographic detection and characterization of asymptomatic ductal carcinoma in situ with histopathologic correlation. Acta Radiol 2011; 52: 364-371. (PMID: 21498298) [Crossref]
17. Park JS, Park YM, Kim EK, Kim SJ, Han SS, Lee SJ, et al. Sonographic findings of high-grade and non-high-grade ductal carcinoma in situ of the breast. J Ultrasound Med 2010; 29: 1687-1697. (PMID: 21098839) [Crossref]
18. Yang WT, Tse GM. Sonographic, mammographic, and histopathologic correlation of symptomatic ductal carcinoma in situ. AJR Am J Roentgenol 2004; 182: 101-110. (PMID: 14684521) [Crossref]
19. Gufler H, Buitrago-Téllez CH, Madjar H, Allmann KH, Uhl M, Rohr-Reyes A. Ultrasound demonstration of mammographically detected microcalcifications. Acta Radiol 2000; 41: 217-221. (PMID: 10866074) [Crossref]
20. Cha H, Chang YW, Lee EJ, Hwang JY, Kim HJ, Lee EH, et al. Ultrasonographic features of pure ductal carcinoma in situ of the breast: correlations with pathologic features and biological markers. Ultrasonography 2018; 37: 307-314. (PMID: 29169230) [Crossref]
21. Izumori A, Takebe K, Sato A. Ultrasound findings and histological features of ductal carcinoma in situ detected by ultrasound examination alone. Breast Cancer 2010; 17: 136-141. (PMID: 19575283) [Crossref]
22. Wang LC, Sullivan M, Du H, Feldman MI, Mendelson EB. US appearance of ductal carcinoma in situ. RadioGraphics 2013; 33: 213-228. (PMID: 23322838) [Crossref]
23. Jansen SA, Newstead GM, Abe H, Shimauchi A, Schmidt RA, Karczmar GS. Pure ductal carcinoma in situ: kinetic and morphologic MR characteristics compared with mammographic appearance and nuclear grade. Radiology 2007; 245: 684-691. (PMID: 18024450) [Crossref]
24. Rosen EL, Smith-Foley SA, DeMartini WB, Eby PR, Peacock S, Lehman CD. BI-RADS MRI enhancement characteristics of ductal carcinoma in situ. Breast J 2007; 13: 545-550. (PMID: 17983393) [Crossref]
25. Chan S, Chen JH, Agrawal G, Lin M, Mehta RS, Carpenter PM, et al. Characterization of pure ductal carcinoma in situ on dynamic contrast-enhanced MR imaging: do non high grade and high grade show different imaging features? J Oncol 2010; 2010: 431341. (PMID: 20885929) [Crossref]
26. Greenwood HI, Heller SL, Kim S, Sigmund EE, Shaylor SD, Moy L. Ductal carcinoma in situ of the breasts: review of MR imaging features. Radiographics 2013; 33: 1569-1588. (PMID: 24108552) [Crossref]
27. Zhang M, Lin Q, Su XH, Cui CX, Bian TT, Wang CQ, et al. Breast ductal carcinoma in situ with micro-invasion versus ductal carcinoma in situ: a comparative analysis of clinicopathological and mammographic findings. Clin Radiol 2021; 76: 787.e1-787.e7. (PMID: 34052010) [Crossref]
28. Hoorntje LE, Schipper ME, Peeters PH, Bellot F, Storm RK, Borel Rinkes IH. The finding of invasive cancer after a preoperative diagnosis of ductal carcinoma-in-situ: causes of ductal carcinoma-in-situ underestimates with stereotactic 14-gauge needle biopsy. Ann Surg Oncol 2003; 10: 748-753. (PMID: 12900365) [Crossref]
29. Tabar L, Tony Chen HH, Amy Yen MF, Tot T, Tung TH, Chen LS, et al. Mammographic tumor features can predict long-term outcomes reliably in women with 1-14-mm invasive breast carcinoma. Cancer 2004; 15: 101: 1745-1759. (PMID: 15386334) [Crossref]
30. Tabar L, Tot T, Dean P. Breast Cancer: Early Detection with Mammography: Crushed Stone-Like Calcifications: The Most Frequent Malignant Type, Thieme Medical Publishers, 2007. [Crossref]
31. Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, et al. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. Breast Cancer Res 2008; 10: R67. (PMID: 18681955) [Crossref]

**Original Article**

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# Altered Expression of CYSLTR1 is Associated With Adverse Clinical Outcome in Triple Negative Breast Tumors: An *In Silico* Approach

Andrés Galindo Céspedes[1], Mércia Patrícia Ferreira Conceição[2], Daniel Rodrigues de Bastos[2], Gabriela Ávila de Grazia[2], Jean Michel Rocha Sampaio Leite[3], Renan Gomes do Nascimento[4], Matthew Thomas Ferreira[2], Rossana Mendoza Lopez[2]

[1]Clinical Pathology Service, Almanzor Aguinaga Asenjo National Hospital, Chiclayo, Peru
[2]Instituto do Cancer do Estado de Sao Paulo ICESP, Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo FMUSP HC, São Paulo, Brazil
[3]Department of Nutrition, School of Public Health, University of São Paulo, São Paulo, Brazil
[4]Department of Clinical Oncology Pharmacy, São Camilo Hospital, São Paulo, Brazil

**ABSTRACT**

**Objective:** Triple negative breast cancer (TNBC) has high relapse rates due to dysregulated inflammatory signaling pathways and significant changes in the tumor microenvironment, probably influencing the failure of several therapies. The Cysteinyl Leukotriene Receptor 1 (CYSLTR1), a leukotriene modulator of inflammation, has been shown to play an important role in cancer pathogenesis and survival but few studies have been reported on its role in breast cancer.

**Materials and Methods:** The present work was conducted using publicly available platforms that have omics data to assess the clinical potential of CYSLTR1 expression and its prognostic validation in large cohorts of samples from breast cancer patients. Web platforms containing clinical information, RNA-seq and protein data were selected to perform *in silico* analyses of the potential marker CYLSTR1. Added together, the platforms included modules for correlation, expression, prognosis, drug interactions, and construction of gene networks.

**Results:** Kaplan–Meier curves revealed that reduced levels of CYSLTR1 corresponded to an unfavorable outcome for overall survival ($p$<0.005) as well as relapse-free survival ($p$<0.001) in the basal subtype. Additionally, CYSLTR1 was downregulated in breast tumor samples compared to adjacent healthy tissue ($p$<0.01) and the basal subtype exhibited the lowest expression of CYSLTR1 relative to the other subtypes ($p$<0.0001). Furthermore, gene networking analysis showed strong associations of CYSLTR1 with two protein-coding genes (*P2RY10* and *XCR1*) when tested on a TNBC dataset.

**Conclusion:** Our data highlighted the relevance of CYSLTR1 since it may play an important role in TNBC therapy. However, further *in vitro* and *in vivo* studies should be directed towards validating our findings in an effort to improve our understanding of TNBC pathology.

**Keywords:** CYSLTR1, leukotriene, mediators of inflammation, triple-negative breast cancer

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**Key Points**

- CYSLTR1 is downregulated in breast tumors.
- TNBC exhibited less CYSLTR1 than Luminals and HER2 subtypes.
- Low CYSLTR1 expression was associated with worse survival in breast cancer patients.
- Low CYSLTR1 expression was associated with worse survival in TNBC.

## Introduction

It is widely known that the severity of breast cancer (BCa) results from a multitude of extrinsic and intrinsic factors, including tumor heterogeneity, which has been identified as the most relevant cause of poor outcome in patients with different subtypes of BCa (1). BCa can be stratified in hormone-dependent tumors, with receptor of human epidermal growth factor 2 (HER2) overexpression or triple negative (TNBC) according to immunohistochemical (IHC) staining for estrogen receptor (ER), progesterone receptor (PR), HER2, and the cell proliferation marker Ki-67. Another form of classification widely used in clinical practice is based on the transcriptomic profiles in Luminal A, Luminal B, HER2+, basal-like, normal-like, and claudin-low (2-4). This molecular classification has been confirmed by several research groups in different populations of patients with BCa (5-7). Patients with TNBC do not benefit from hormone therapy or targeted

**Corresponding Author:**
**Rossana Mendoza Lopez; rossana.veronica@hc.fm.usp.br**

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therapies commonly used in luminal and HER2+ cases. This lack of therapeutic options increases the chances of tumor recurrence, leading to a high mortality rate (8, 9).

On the other hand, BCa is strongly associated with inflammation and the release of signaling molecules derived from arachidonic acid, such as leukotrienes, as well as G protein-coupled receptors in the tumor microenvironment (TMev), which results in mediation of allergic, infectious, and inflammatory reactions through a phosphatidylinositol-calcium second messenger cascade (10-12). Among these messengers, Cysteinyl Leukotriene Receptor 1 (CYSLTR1) is implicated in mediating bronchoconstriction and asthma, and its dysregulation may be of concern in inflammation-related neoplasms (13). For example, in colorectal tumor cells, overexpression of CYSLTR1 is associated with proliferation, survival, and migration, as well as a poor prognosis in patients with colorectal adenocarcinoma (14). Furthermore, in patients with breast tumors, high expression levels of CYSLTR1 and low levels of CYSLTR2 were correlated with high mortality rates in univariate analyses for 144 patients (15). Another study suggests that CYSLTR1 is positively correlated with clinical features, such as tumor size, histologic type, lymph node metastasis, and TNM staging in a BCa population of 90 subjects (16).

Data mining represents a useful aproach to strengthen the knowledge and status of malignant neoplasms. With the era of omics, there is an increasing amount of genomic, transcriptomic, proteomic, and epigenetic data generated by high performance technologies available in public databases. Many of the studies deposited on these platforms have helped to characterize intrinsic cancer subtypes, predict survival, and therapeutic responses, generating a large amount of molecular biomarkers for BCa. There are only a few studies, with limited samples, that have explored the role of CYSLTR1 in women diagnosed with BCa. Therefore, the central objective of this study was to explore the status of CYSLTR1 according to expression levels and its potential prognostic value in BCa using datasets deposited in public repositories.

## Materials and Methods

### UALCAN and GENT2

UALCAN is a user-friendly online platform that provides easy access to OMICS cancer data. Thus, it allows for easy expression profiling of possible biomarkers, in associations with survival and gene regulation data, rendering a robust profile analysis (17). With this tool, we identified the difference between the CYSLTR1 expression levels of normal and breast tumor tissues. Moreover, in order to confirm our results, we accessed GENT2, a new tool focused on the expression analysis of normal and tumor tissue samples (18).

### cBioPortal

The TCGA database (Firehose Legacy) was accessed through the cBioPortal platform to select mRNA expression Z-scores related to 1.108 samples (log RNA Seq V2 RSEM) with a ±2 threshold (19, 20). Clinical pathological data were obtained and cross-linked with CYSLTR1 expression data. Male cases (n = 16) and those who had no information of CYSLTR1 levels (n = 4) were excluded, resulting in 1.088 patients to be assessed.

### bc-GenExMiner

The bc-GenExMiner v.5 is a microarray and RNA-seq data-mining tool containing data of BCa patients only. Three analysis modules were explored: Correlation, expression, and prognosis (21, 22). For this study, we considered only RNA-seq data, excluding samples from TCGA.

### Kaplan–Meier Plotter

Kaplan–Meier (KM) Plotter is a publicly available platform that hosts data of 21 different types of cancer and contains Affymetrix gene signatures (probes of 20.129 genes) of 3.421 patients (23). For this study, we selected the best probe option corresponding to the *CYSLTR1* gene: 230866_at; *P2RY10* gene: 236280_at; and *XCR1* gene: 221468_at. The overall survival (OS) and relapse-free survival (RFS), adjusted for 120 months' total follow-up time, were available for all of them. The patients were also stratified by high and low expression of the target gene as the best cut-off between the lower and upper quartile was selected. Analyses were performed according to all deposited cases and only with the basal-like subtype, considering the prognostic value and its impact on poor clinical outcome.

### Metascape

Metascape is a user-friendly tool for omics data analysis (24). Here, we accessed CYSLTR1 co-expressed genes previously obtained on bc-GenExMiner for interaction analysis. The protein network data was downloaded and analyzed on Cytoscape v.8.0 (25).

### Geo Database

The Geo Database is a microarray and RNA-seq data deposit platform. In order to analyze the expression profile of *CYSLTR1* in different subtypes of breast tumors, we accessed the GSE76275 and GSE96058 files (26).

### Gene Co-expression Network

The co-expression analysis was conducted using RNA-seq data of TNBC from the bc-GenExMiner v.5 database. A correlation value >0.7 was used as a cut-off, then the data was accessed using the String platform to generate CYSLTR1 co-expressed genes network data and to export it to Cytoscape v8.0 software to select the genes with close interactions with CYLSTR1. In addition, the co-expressed gene list was also accessed using the Metascape software in order to conduct enrichment analyses.

### Comparative Toxicogenomics Database

The Comparative Toxicogenomics Database (CTD) is a publicly available tool for manually curated information about chemical interactions with genes, proteins, and chemical relationships with diseases (27). The CTD was accessed to obtain potential drugs capable of interacting positively or negatively with CYSLTR1.

### mirTarBase Repository

By using the mirTarBase database we accessed the prediction of experimentally validated miRNAs targeting CYSTLR1 and significant co-expressed genes (28). In addition, we carried out survival analyses of both genes and best-predicted miRNAs in TNBC population.

### Statistical Analysis

For platforms with integrated statistical capabilities, the analyzes were performed as described in the topics above. For additional data, analyses were conducted with the Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Inc., Armonk, NY USA) or GraphPad v.7 (California, USA). The chi-square or Fisher's exact test was applied to compare categorical variables. For univariate and multivariate analysis, the Cox regression method was used. All groups were tested for

Gaussian distribution. The Mann–Whitney or t test was used to assess the difference between two groups, and ANOVA (analysis of variance) or Kruskal–Wallis for more than two groups. For survival analysis, survival curves were performed by KM method and compared using log-rank test; additionally, Cox regression univariate and multivariate were performed calculating hazard ratio (HR) with 95% confident interval. A significance level of 5% was adopted.

## Results

### CYSLTR1 is Downregulated in Breast Tumors and Correlated with Clinical Pathological Parameters

Our study evaluated data from different platforms (Firehose Legacy, cBioPortal and TCGA) which together represented a massive cohort of 1.097 tumor and 114 non-tumor breast samples. Our findings showed that samples from patients with breast tumors had low levels of CYSLTR1 mRNA compared to adjacent healthy tissues ($p$<0.01) (Figure 1A) and, in a larger cohort, we observed the same profile ($p$ = 0.01) (Supplementary Figure 1A). In addition, significant associations were observed between differential expression of CYSLTR1 with patient age ($p$ = 0.01), histological subtype ($p$<0.0001), *TP53* mutational status ($p$<0.0001), ER status ($p$<0.0001), PR status ($p$<0.0001), and molecular subtype ($p$<0.0001) (Table 1).

Using the TCGA dataset, we performed analyses to identify the expression profile of CYSLTR1 according to clinicopathological parameters. Initially, we observed significant differences between the histological subtypes, where in invasive ductal carcinoma tumors showed low expression of CYSLTR1 when compared to invasive lobular carcinoma ($p$<0.0001) (Figure 1B). We also describe expression patterns in accordance with the PAM50 subtype classification, where the basal-like type exhibited a decreased transcriptional distribution of CYSLTR1 compared to the other subtypes (Basal-like *vs* HER2, $p$<0.0001; Basal-like vs Luminal A, $p$<0.0001; Basal-like *vs* Luminal B, $p$<0.0001; Basal-like vs Normal-like, $p$<0.0001) (Figure 1C). In addition, patients whose tumors were negative for hormone receptors (ER and PR) and HER2 had lower levels of CYSLTR1 compared to those with positive expression for these receptors (ER+ vs ER-, $p$<0.0001; PR+ vs PR-, $p$<0.0001; HER2- vs HER2+, $p$ = 0.02) (Figures 1D-F).

In order to confirm our findings in a larger cohort, we performed an analysis on bc-GenExMiner database. Consequently, a similar profile was observed in terms of expression levels according to the PAM50 classification ($p$<0.0001) (Supplementary Figure 1B), as well as estrogen ($p$<0.0001) (Supplementary Figure 2A), progesterone ($p$<0.0001) (Supplementary Figure 2B), and HER2+ receptors ($p$<0.0001) (Supplementary Figure 2C). Moreover, within the TCGA cohort, we assessed the possible differences between Basal-like and non-Basal-like ($p$<0.0001) (Supplementary Figure 2D), TNBC and non-TNBC ($p$<0.0001) (Supplementary Figure 2E), Basal-like and TNBC *vs* non- Basal-like and non-TNBC ($p$<0.0001) (Supplementary Figure 2F); thus, we confirmed that CYSLTR1 transcription levels were downregulated in samples with negative expression for hormone receptors.

Interestingly, the Basal-like immune-suppressed (BLIS) samples showed lower CYSLTR1 expression compared to Basal-like immune-activated samples ($p$ = 0.004) (Figure 2B), while luminal androgen receptor (LAR) ($p$ = 0.001) (Figure 2B) and mesenchymal (MES) samples ($p$<0.0001) (Figure 2B) exhibited higher levels when compared to BLIS. Similarly, Basal-like 1 and Basal-like 2 triple-negative tumors levels were lower in the cohort from TCGA/UALCAN ($p$<0.01 and $p$<0.001, respectively) (Supplementary Figure 3).

### Low CYSLTR1 Expression was Associated with Worse Prognosis

Reduced CYSLTR1 mRNA expression levels were significantly correlated with unfavorable prognosis for both OS (Figure 3A; Supplementary Figure 4A-C) and RFS (Figures 3C; Supplementary Figure 4D-F) for all intrinsic BCa subtypes, but especially in basal subtype (Figure 3B, D).

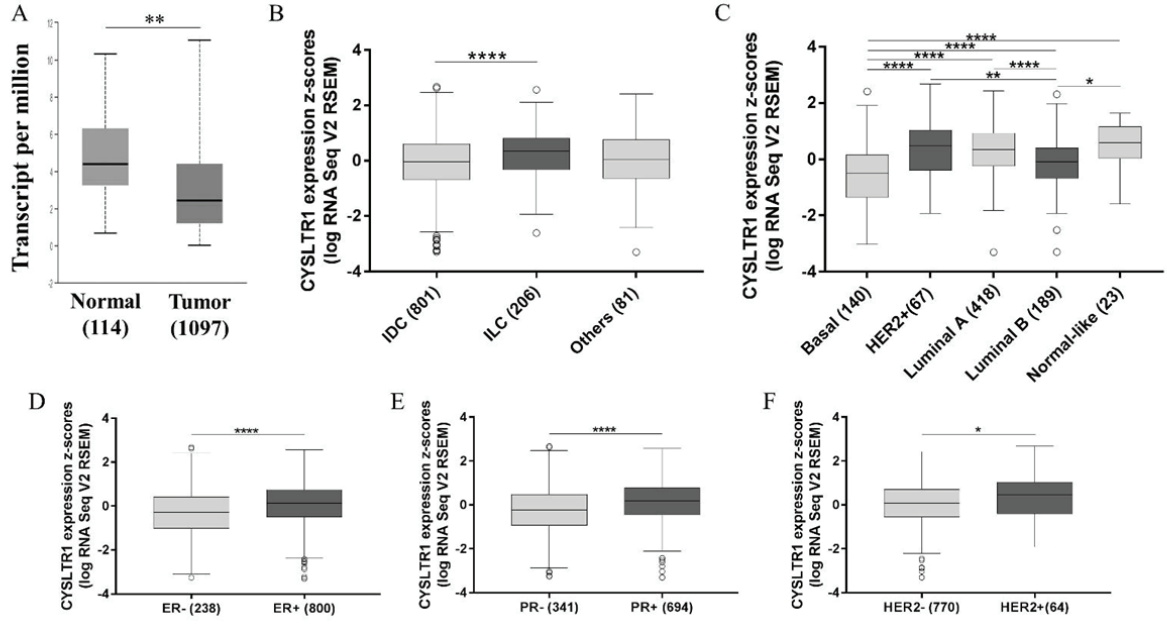


**Figure 1.** Expression of *CYSLTR1*. Expression of *CYSLTR1* in **A.** Normal and tumor breast tissue; **B.** According to histological subtype; **C.** PAM50 classification; **D.** Estrogen receptor; **E.** Progesterone receptor and **F.** HER2. Data obtained from the Firehose Legacy, cBioPortal, TCGA. *P* values indicate significance according to Wilcoxon or ANOVA tests: *$p$<0.05, **$p$<0.01, ***$p$<0.001 and ****$p$<0.0001

Table 1. Associations between clinic-pathological parameters and *CYSLTR1* expression

| Parameters | High | | Low | | *p*-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Age | | | | | |
| ≤50 | 147 | 27.0 | 186 | 34.2 | 0.010* |
| >50 | 397 | 73.0 | 358 | 65.8 | |
| Menopause status | | | | | |
| Peri | 17 | 3.1 | 23 | 4.2 | |
| Post | 366 | 67.3 | 339 | 62.3 | 0.325 |
| Pre | 110 | 20.2 | 120 | 22.1 | |
| NA | 51 | 9.4 | 62 | 11.4 | |
| Cancer type | | | | | |
| IDC | 372 | 68.4 | 429 | 78.9 | |
| ILC | 131 | 24.1 | 75 | 13.8 | <0.0001* |
| Other | 41 | 7.5 | 40 | 7.4 | |
| TP53 | | | | | |
| Mutated | 125 | 23.0 | 175 | 32.2 | |
| Wild type | 373 | 68.6 | 297 | 54.6 | <0.0001* |
| Not profiled | 46 | 8.5 | 72 | 13.2 | |
| TNM | | | | | |
| Stage I/II | 403 | 74.1 | 390 | 71.7 | |
| Stage III/IV | 130 | 23.9 | 141 | 25.9 | 0.692 |
| Stage X | 6 | 1.1 | 7 | 1.3 | |
| NA | 5 | 0.9 | 6 | 1.1 | |
| ER Status By IHC | | | | | |
| Negative | 89 | 16.4 | 149 | 27.4 | |
| Positive | 437 | 80.3 | 363 | 66.7 | <0.0001* |
| NA | 18 | 3.3 | 32 | 5.9 | |
| PR status by IHC | | | | | |
| Negative | 134 | 24.6 | 207 | 38.1 | |
| Positive | 391 | 71.9 | 303 | 55.7 | <0.0001* |
| NA | 19 | 3.5 | 34 | 6.3 | |
| HER2 status by IHC | | | | | |
| Negative | 287 | 52.8 | 271 | 49.8 | |
| Positive | 84 | 15.4 | 77 | 14.2 | 0.868 |
| NA | 173 | 31.8 | 196 | 36.0 | |
| TN/nTN | | | | | |
| nTN | 490 | 90.1 | 434 | 79.8 | |
| TN | 37 | 6.8 | 79 | 14.5 | <0.0001* |
| NA | 17 | 3.1 | 31 | 5.7 | |
| PAM50Call_RNAseq | | | | | |
| Basal | 39 | 7.2 | 101 | 18.6 | |
| Her2 | 44 | 8.1 | 23 | 4.2 | |
| Luminal A | 264 | 48.5 | 154 | 28.3 | <0.0001* |
| Luminal B | 79 | 14.5 | 110 | 20.2 | |
| Normal-like | 17 | 3.1 | 6 | 1.1 | |
| NA | 101 | 18.6 | 150 | 27.6 | |

NA: not available; ER: estrogen receptor; PR: progesterone receptor; TN: triple-negative; nTN: non-triple negative. Data obtained from TCGA – Firehose Legacy, cBioPortal database (*p<0.05)

We employed the GSE96058 dataset to execute univariate and multivariate regression analyses. The low expression of CYSLTR1 was an independent factor associated with lower OS in women with Bca (HR = 1.40, $p$ = 0.002) (Table 2). Tumor size, lymph node status, and age were also related to high risk of the disease.

### Gene-interaction and Enrichment Analyses

A list of correlated genes (cut-off ≤ or ≥0.7) within the basal subtype is available in Supplementary Table 1. Among the CYLSTR1 co-expressed genes, it was mainly observed that *P2RY10* and *XCR1* proteins interact directly with CYSLTR1 (Figure 4A-B). The Gene Ontology enrichment analyses demonstrated that several genes co-expressed with CYLSTR1 are involved in the immune system response and immune cell processing and activation (Figure 4C).

### Identification and Prognostic Value of Predicted Genes and MicroRNAs

According to KM plotter repository, *P2RY10* and *XCR1* were assessed for RFS and OS of transcripts. *P2RY10* demonstrated a lower but significant expression associated to poor outcome in all subtypes, as well as in the basal subtype [Supplementary Figure 5A-B (RFS) and 5C-D (OS), respectively]. Moreover, by using the mirTarBase repository, three microRNAs: has-miR-335-5p, has-miR-3130-3p, and has-miR-3607-3p were identified as potential regulatory elements of *CYSLTR1*, *P2RY10* and *XCR1*, respectively. However, OS in the same TNBC patients according to miRNAs (Figure 5) and transcript expression levels (Supplementary Figure 6) were not significantly associated.

### Modulation of CYSLTR1 Expression

Through the CTD, we obtained a list of six drugs capable of interacting with CYSLTR1. Leukotrienes C4, D4, and E4 can bind to CYSLTR1 and increase its activity (Figure 6). Other effects might occur depending on the drug in use; for example, the administration of leukotrienes C4 and E4 results in an abundance of calcium, while D4 increases the expression of widely studied proteins such as interleukin (IL)-6, tumor necrosis factor (TNF), and CXCL8. However, Montelukast, Pobilukast, and Zafirlukast (composts of leukotrienes receptors antagonist, LTRAs) induced a reduction in CYSLTR1 protein activity.

## Discussion and Conclusion

CYSLTR1 belongs to the cysteinyl leukotriene synthesis pathway and codes for a transmembrane protein receptor that when coupling with many ligands, triggers inflammation-related signaling which leads to a determined phenotype or disease state (15, 29, 30). Yet, there is no consistent evidence to link CYSLTR1 with underlying Bca pathogenesis or even with prognostic values in individuals with aggressive breast tumors.

According to our findings, breast tumor tissue samples showed reduced levels of CYSLTR1 compared to healthy tissue samples. To date, little is known about the profile of CYSLTR1 transcripts in BCa. A study performed by Wang et al. (16) using the RT-qPCR technique, showed that CYSLTR1 was significantly upregulated in tumor samples (n = 90) vs. paraneoplastic breast tissues (n = 30) (16). However, we have to be careful when comparing our findings to this data due to the sample type and size, and approach utilized. Additionally, we observed that a decrease in CYSLTR1 transcripts leads to an unfavorable survival outcome in patients with TNBC tumors, being the first study that evaluated two different datasets and with a relevant sample size.

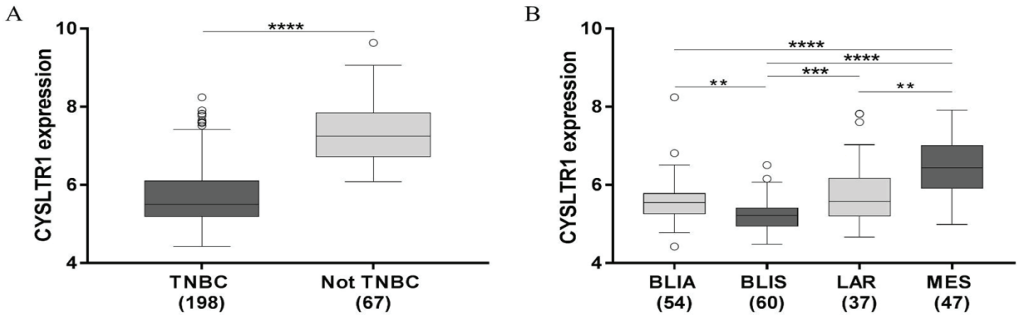


**Figure 2.** Expression of *CYSLTR1* in TNBC. **A.** *CYSLTR1* expression profile in TNBC in a population from GSE76275 and in **B.** TNBC subtypes. BLIA: basal-like immune-activated; BLIS: basal-like immune-suppressed; LAR: luminal androgen receptor; MES: mesenchymal. *P* values indicate significance according to Wilcoxon or ANOVA tests: ***p*<0.01, ****p*<0.001 and *****p*<0.0001

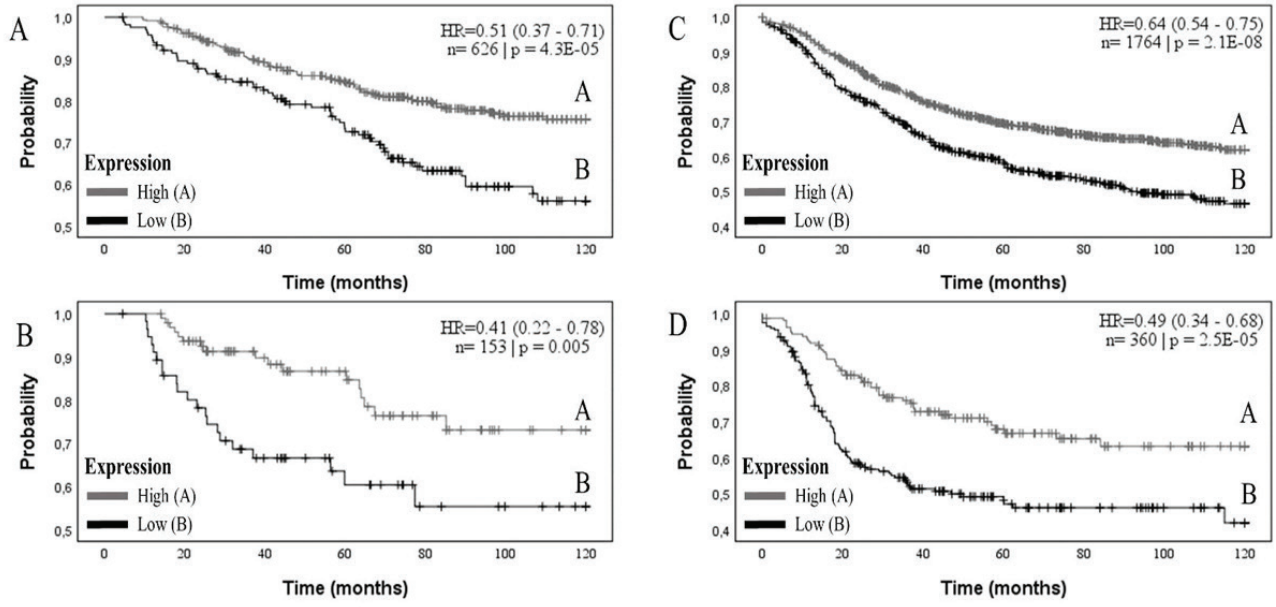


**Figure 3.** Survival probability of BCa patients stratified by *CYSLTR1* relative expression. Overall survival of **A.** all subtypes and **B.** Basal. Relapse-free survival of **C.** all subtypes and **D.** Basal. Data obtained from the KM Plotter online platform using the 230866_at probe

Table 2. Univariate and multivariate regression analysis of BCa patients for overall survival

| Variables* | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Ki67 (Ki67+ vs Ki67-) | 1.89 (1.24–2.88) | 0.003 | | |
| Basal status (Basal vs nBasal) | 2.37 (1.83–3.07) | <0.0001 | | |
| TN status (TN vs nTN) | 2.52 (1.72–3.70) | <0.0001 | | |
| Age (>50 vs ≤50 vs) | 3.88 (2.54–5.93) | <0.0001 | 4.05 (2.60–6.30) | <0.0001 |
| Tumor size (>20 mm vs ≤20 mm) | 2.74 (2.22–3.39) | <0.0001 | 2.58 (2.06–3.23) | <0.0001 |
| Lymph status (N+ vs N-) | 1.54 (1.24–1.91) | <0.0001 | 1.25 (1.00–1.56) | 0.047 |
| CYSLTR1 (High vs Low) | 1.40 (1.13–1.73) | 0.002 | 1.46 (1.17–1.82) | 0.001 |

*In all analyzed categories, the reference extract is the second group into the parenthesis. nBasal: non-basal; TN: triple-negative; nTN: non-triple negative; N+: positive lymph-node status; N-: negative lymph-node status; CI: confidence interval; HR: hazard ratio

However, it is necessary to reinforce the idea of working with different tumor stages and treatment cohorts to better understand this possible relationship of CYSLTR1 as a potential biomarker in cancer.

Our univariate prognostic analysis according to the Cox proportional hazards regression model confirmed the results observed in the Kaplan–Meier curves as a function of the differential expression of CYSLTR1. Furthermore, the high CYSLTR1 expression group

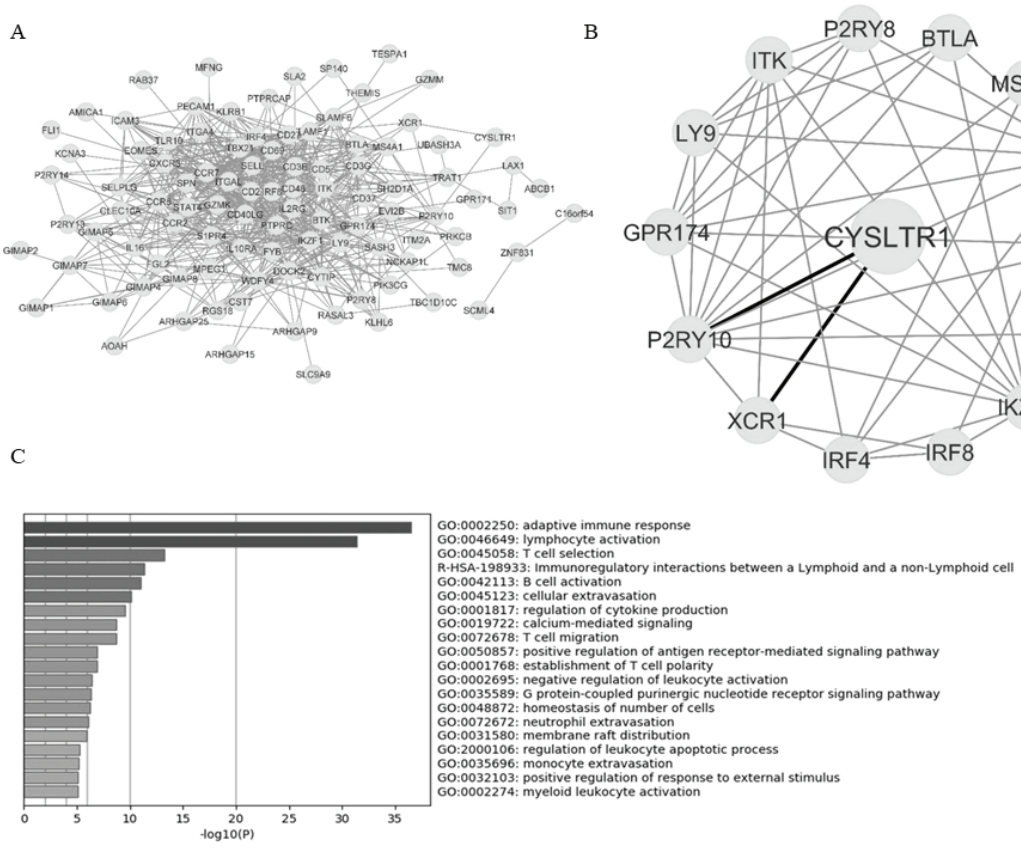


**Figure 4.** Network and Gene Ontology enrichment of main co-expressed proteins with CYLSTR1 in TNBC subtype. **A.** Representative network of CYSLTR1 co-expressed proteins and **B.** representative of protein with the closest interactions with CYLSTR1; **C.** Bar charts represent enriched pathways categories in which *CYLSTR1* co-expressed genes participates

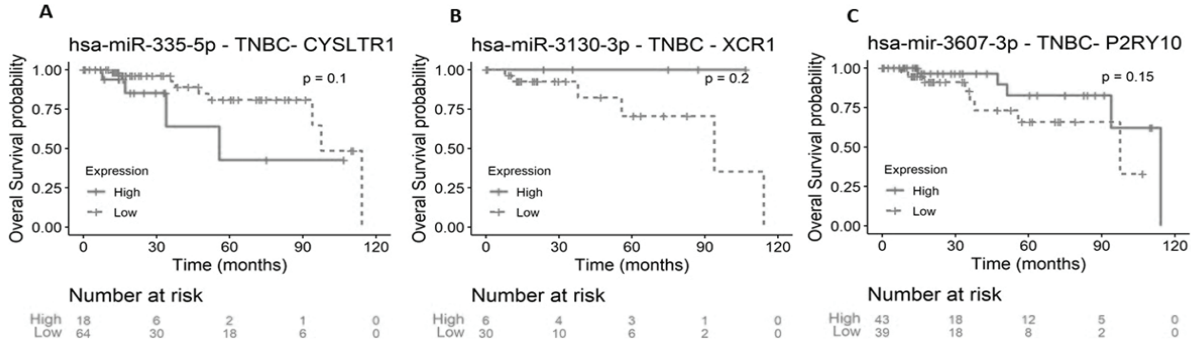


**Figure 5.** Overall survival in TNBC. Patients stratified by predicted miRNAs expression targeting **A.** *CYSLTR1*, **B.** *XCR1*, and **C.** *P2RY10* genes. Data obtained from the Firehose Legacy, cBioPortal, TCGA

remained an independent prognostic factor in relation to the risk of cancer-specific death, when adjusted for age, tumor size, and lymph node involvement. Our results differ from the study by Magnusson et al. (15) who did not observe a statistical association between the differential expression of CYSLTR1 and the prognosis of patients with BCa. We have to emphasize that the study evaluated the immunoreactivity of the CYSLTR1 protein and had a small set of samples (n = 139).

Considering that *CYLSTR1* gene expression in the basal subtype was significantly decreased when compared to the other subtypes, we were led to carry out an in-depth investigation into this clinically more aggressive molecular subtype of BCa. Therefore, we evaluated the expression patterns of CYSLTR1 in the four stable TNBC subtypes, characterized by the expression of distinct molecular profiles that present different prognoses, proposed through studies by the Burstein and Lehman groups (26, 31). Our results showed that CYSLTR1 is consistently expressed in the MES subgroup. Here, we hypothesize that it is possible that CYSLTR1 is more actively involved in epithelial mesenchymal transition and angiogenesis, than in the processes of tumor differentiation and immune activity. This may be supported by the role of cysteinyl leukotrienes (cys-LTs) since they are pro-inflammatory mediators that modulate vascular leakage, permeability and microvasculature response via other leukotriene molecules (32-34). Furthermore, CYSLTR1 transcripts were also expressed to a greater extent in tumors of the LAR subgroup, which is highly expressed on

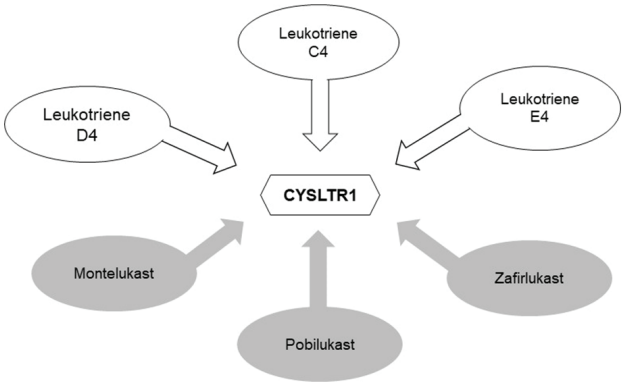


**Figure 6.** Drug interactions with *CYSLTR1* obtained from the Comparative Toxicogenomic Database. The image shows six drugs capable of modulating the expression of *CYSLTR1* positively or negatively. For example, leukotriene C4 binds to *CYSLTR1* and increases its activity (white). On the other hand, Montelukast binds to *CYSLTR1* inhibiting its activity (gray). White: increases CYLSTR1 activity; Gray: decreases CYLSTR1 activity

the nuclear androgen receptor receptor. Consequently, as CYSLTR1 is linked to kinase activity (35, 36), this could lead us to hypothesize that CYSLTR1 could participate in blocking androgen-dependent signaling and PIK3. To date, no work has focused on studying its possible role in tumorigenesis in TNBC cases. Thus, our work brings unprecedented data about this aggressive type of BCa.

Our analyses of signaling and enrichment pathways for CYSLTR1 have indicated some immunological mechanisms related to inflammation in which toll-like family genes and cytokines may participate. It is noteworthy that two protein-coding genes: *P2RY10* and *XCR1* exhibited a positive correlation with CYSLTR1 in a TNBC dataset. Eosinophils can be found in the TMev, as they secrete different types of leukotrienes as part of the induction of inflammatory processes (10). Furthermore, they also generate significant amounts of platelet activating factor and promote the production of characteristic cytokines such as TNFα and IL-5 (37, 38). *P2RY10* is a G-couple protein receptor that participates in the inflammatory response, stimulated by many molecules such as chemokines, lysophospholipids and prostanoids. Its biological role has not been fully elucidated, but it may participate in eosinophil maturation and eosinophilopoiesis *in vitro* (38). On the other hand, Yang et al. (39) suggest that XCR1 may act as a progression factor in ER-responsive Bca cell lines through the MAPK/ERK and PI3K/AKT/mTOR pathways that promote migration and invasion by significantly decreasing the protein level of β-catenin (40). Regarding the possible prognostic role, patients with TNBC cases who had high gene expression of *XCR1* and *P2RY10* exhibited a trend towards greater survival, further confirmed by an independent dataset.

As for epigenetic mechanisms of gene regulation, has-miR-355-5p showed a certain tendency to downregulate CYSLTR1 expression in a TNBC setting. To date, there is no evidence that describes consistent associations between these genes and their Bca-targeted miRNAs. Therefore, we suggest IHC studies to unravel mechanisms underlying survival and immunological processes in TNBC.

Regarding possible drug interactions, we observed that Montelukast, Zafirlukast and Pobilucast played a role in reducing CYSLTR1 expression levels in our *in silico* experiments. Based on the above, Suknuntha et al.'s (30) group observed that MDA-MB-231 BCa cells, when treated with Montelukast and Zafirlukast molecules, can inhibit cell proliferation and apoptosis, but only Zafirlukast can induce cell cycle arrest. On the other hand, leukotrienes appear as possible positive modulators of CYSLTR1 expression. Both strategies are promising and need to be carefully investigated.

### Study Limitations

Some limitations of the analysis performed here must be acknowledged. First, we employed different expression analysis methods compared to other studies examining CYSLTR1 in Bca. Second, as seen in *in silico* analyses, RNA-seq based expression data were not complemented with protein data to corroborate our findings. Third, many studies available in public databases were deficient in clinicopathological information, and the most important, TNBC studies only accounted for up to 15% of the Bca population, so it is difficult to reach significant conclusions. Nonetheless, based on our findings, we can provide insights into the possible role of CYSLTR1 in BCa disease survival, particularly in TNBC cases.

Our study showed that CYSLTR1 is transcriptionally less expressed in breast tumors compared to adjacent tissue. Additionally, among the tumor subtypes, TNBC had lower levels of CYSLTR1. Low CYSLTR1 expression was associated with worse survival in BCa patients and especially in TNBC. CYSLTR1 is co-expressed with genes that participate in the adaptive immune response and lymphocyte activation. Finally, we suggest that CYSLTR1 may not be working alone, but with linked proteins and miRNAs that could serve as new possible targets for other therapies in Bca, especially in TNBC subtypes.

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**Ethics Committee Approval:** Not necessary.

**Informed Consent:** Not necessary.

**Peer-review:** Externall and internally peer-reviewed.

### Authorship Contributions

Concept: M.P.F.C., D.R.d.B.; Design: M.P.F.C., D.R.d.B.; Data Collection or Processing: A.G.C., M.P.F.C., D.R.d.B.; Analysis or Interpretation: A.G.C., M.P.F.C., D.R.d.B.; Literature Search: A.G.C., M.P.F.C., D.R.d.B.; Writing: A.G.C., M.P.F.C., D.R.d.B., G.Á.d.G., J.M.R.S.L., R.G.d.N., M.T.F., R.M.L.

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

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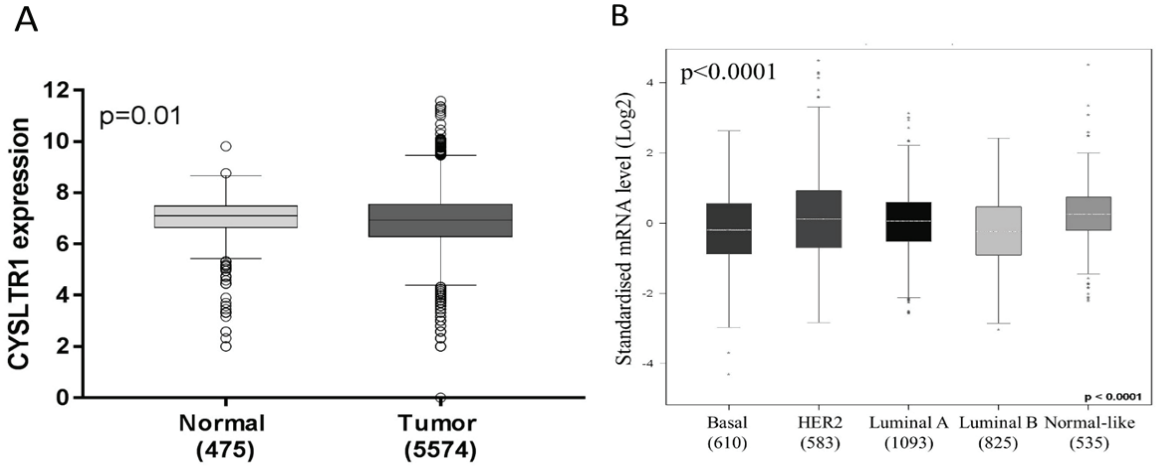
## References

1. Turashvili G, Brogi E. Tumor heterogeneity in breast cancer. Front Med (Lausanne) 2017; 4: 227. (PMID: 29276709) [Crossref]
2. Hu Z, Fan C, Oh DS, Marron JS, He X, Qaqish BF, et al. The molecular portraits of breast tumors are conserved across microarray platforms. BMC Genomics 2006; 7: 96. (PMID: 16643655) [Crossref]
3. Sorlie T et al, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001; 98: 10869-10874. (PMID: 11553815) [Crossref]
4. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000; 406: 747-752. (PMID: 10963602) [Crossref]

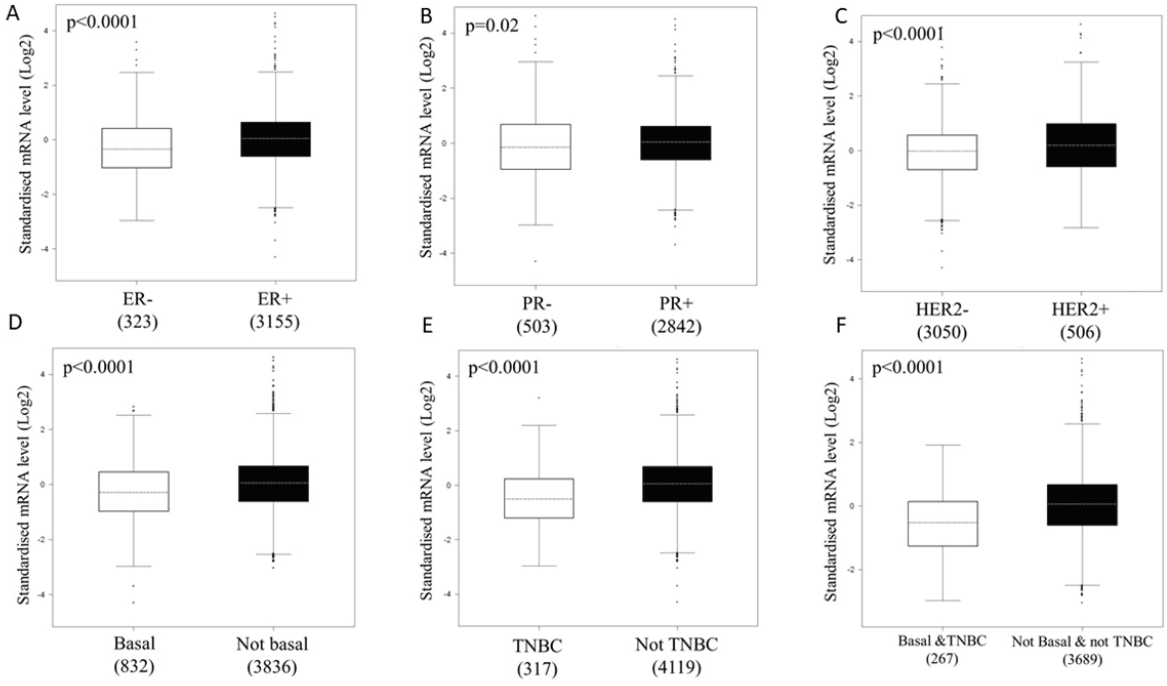
5. Bertucci F, Finetti P, Rougemont J, Charafe-Jauffret E, Cervera N, Tarpin C, et al. Gene expression profiling identifies molecular subtypes of inflammatory breast cancer. Cancer Res 2005; 65: 2170-2178. (PMID: 15781628) [Crossref]
6. Di Cosimo S, Baselga J. Management of breast cancer with targeted agents: importance of heterogeneity. [corrected]. Nat Rev Clin Oncol 2010; 7: 139-147. Epub 2010 Feb 2. Erratum in: Nat Rev Clin Oncol 2010; 7: 184. (PMID: 20125090) [Crossref]
7. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003; 100: 8418-8423. (PMID: 12829800) [Crossref]
8. Ellsworth RE, Blackburn HL, Shriver CD, Soon-Shiong P, Ellsworth DL. Molecular heterogeneity in breast cancer: State of the science and implications for patient care. Semin Cell Dev Biol 2017; 64: 65-72. (PMID: 27569190) [Crossref]
9. Lehmann BD, Jovanović B, Chen X, Estrada MV, Johnson KN, Shyr Y, et al. Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection. PLoS One 2016; 11: e0157368. (PMID: 27310713) [Crossref]
10. Savari S, Vinnakota K, Zhang Y, Sjölander A. Cysteinyl leukotrienes and their receptors: bridging inflammation and colorectal cancer. World J Gastroenterol 2014; 20: 968-977. (PMID: 24574769) [Crossref]
11. Lukic A, Wahlund CJE, Gómez C, Brodin D, Samuelsson B, Wheelock CE, et al. Exosomes and cells from lung cancer pleural exudates transform LTC4 to LTD4, promoting cell migration and survival via CysLT1. Cancer Lett 2019; 444: 1-8. (PMID: 30508568) [Crossref]
12. Cheng Y, Pereira M, Raukar N, Reagan J, Quesenberry M, Goldberg L, et al. Inflammation-related gene expression profiles of salivary extracellular vesicles in patients with head trauma. Neural Regen Res 2020; 15: 676-681. (PMID: 31638091) [Crossref]
13. Massoumi R, Sjölander A. The role of leukotriene receptor signaling in inflammation and cancer. ScientificWorldJournal 2007; 7: 1413-1421. (PMID: 17767358) [Crossref]
14. Ohd JF, Nielsen CK, Campbell J, Landberg G, Löfberg H, Sjölander A. Expression of the leukotriene D4 receptor CysLT1, COX-2, and other cell survival factors in colorectal adenocarcinomas. Gastroenterology 2003; 124: 57-70. (PMID: 12512030) [Crossref]
15. Magnusson C, Liu J, Ehrnström R, Manjer J, Jirström K, Andersson T, et al. Cysteinyl leukotriene receptor expression pattern affects migration of breast cancer cells and survival of breast cancer patients. Int J Cancer 2011; 129: 9-22. (PMID: 20824807) [Crossref]
16. Wang X, Liu W, Han Y, Feng Y, Li D. Significance of cysteinyl leukotriene receptor in breast cancer. Chinese Journal of Clinical Oncology 2012; 39: 1522-1526. [Crossref]
17. Chandrashekar DS, Bashel B, Balasubramanya SAH, Creighton CJ, Ponce-Rodriguez I, Chakravarthi BVSK, et al. UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. Neoplasia 2017; 19: 649-658. (PMID: 28732212) [Crossref]
18. Park S-J, Yoon B-H, Kim S-K, Kim S-Y. GENT2: an updated gene expression database for normal and tumor tissues. BMC Medical Genomics 2019; 12(Suppl 5): 101. (PMID: 31296229) [Crossref]
19. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio Cancer Genomics Portal: An open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012; 2: 401-404. (PMID: 22588877) [Crossref]
20. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013; 6: pl1. (PMID: 23550210) [Crossref]
21. Jézéquel P, Campone M, Gouraud W, Guérin-Charbonnel C, Leux C, Ricolleau G, et al. Bc-GenExMiner: An easy-to-use online platform for gene prognostic analyses in breast cancer. Breast Cancer Res Treat 2012; 131: 765-775. (PMID: 21452023) [Crossref]
22. Jézéquel P, Frénel JS, Campion L, Guérin-Charbonnel C, Gouraud W, Ricolleau G, et al. bc-GenExMiner 3.0: New mining module computes breast cancer gene expression correlation analyses. Database (Oxford) 2013; 2013. (PMID: 23325629) [Crossref]
23. Győrffy B, Lanczky A, Eklund AC, Denkert C, Budczies J, Li Q, et al. An online survival analysis tool to rapidly assess the effect of 22,277 genes on breast cancer prognosis using microarray data of 1,809 patients. Breast Cancer Res and Treat 2010; 123: 725-731. (PMID: 20020197) [Crossref]
24. Zhou Y, Zhou B, Pache L, Chang M, Khodabakhshi AH, Tanaseichuk O, et al. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. Nat Commun 2019; 10: 1523. (PMID: 30944313) [Crossref]
25. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks. Genome Res 2003; 13: 2498-2504. (PMID: 14597658) [Crossref]
26. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SAW, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res 2015; 21: 1688-1698. (PMID: 25208879) [Crossref]
27. Mattingly CJ, Rosenstein MC, Colby GT, Forrest JN, Boyer JL. The Comparative Toxicogenomics Database (CTD): a resource for comparative toxicological studies. J Exp Zool A Comp Exp Biol 2006; 305: 689-692. (PMID: 16902965) [Crossref]
28. Chou CH, Chang NW, Shrestha S, Hsu S Da, Lin YL, Lee WH, et al. miRTarBase 2016: Updates to the experimentally validated miRNA-target interactions database. Nucleic Acids Res 2016; 44: D239-247. (PMID: 26590260) [Crossref]
29. Trinh HKT, Lee SH, Cao TBT, Park HS. Asthma pharmacotherapy: an update on leukotriene treatments. Expert Rev Respir Med 2019; 13: 1169-1178. (PMID: 31544544) [Crossref]
30. Suknuntha K, Yubolphan R, Krueaprasertkul K, Srihirun S, Sibmooh N, Vivithanaporn P. Leukotriene receptor antagonists inhibit mitogenic activity in triple negative breast cancer cells. Asian Pac J Cancer Prev 2018; 19: 833-837. (PMID: 29582642) [Crossref]
31. Lehmann BD, Bauer JA, Schafer JM, Pendleton CS, Tang L, Johnson KC, et al. PIK3CA mutations in androgen receptor-positive triple negative breast cancer confer sensitivity to the combination of PI3K and androgen receptor inhibitors. Breast Cancer Res 2014; 16: 406. (PMID: 25103565) [Crossref]
32. Colazzo F, Gelosa P, Tremoli E, Sironi L, Castiglioni L. Role of the Cysteinyl Leukotrienes in the Pathogenesis and Progression of Cardiovascular Diseases. Mediators Inflamm 2017; 2017: 2432958. (PMID: 28932020) [Crossref]
33. Maekawa A, Frank Austen K, Kanaoka Y. Targeted gene disruption reveals the role of cysteinyl leukotriene 1 receptor in the enhanced vascular permeability of mice undergoing acute inflammatory responses. J Biol Chem 2002; 277: 20820-20824. (PMID: 11932261) [Crossref]
34. Duah E, Adapala RK, Al-Azzam N, Kondeti V, Gombedza F, Thodeti CK, et al. Cysteinyl leukotrienes regulate endothelial cell inflammatory and proliferative signals through CysLT 2 and CysLT 1 receptors. Sci Rep 2013; 3: 1-6. (PMID: 24253666) [Crossref]
35. Omarini C, Guaitoli G, Pipitone S, Moscetti L, Cortesi L, Cascinu S, et al. Neoadjuvant treatments in triple-negative breast cancer patients: Where we are now and where we are going. Cancer Manag Res 2018; 10: 91-103. (PMID: 29391830) [Crossref]
36. Kondeti V, Duah E, Al-Azzam N, Thodeti CK, Boyce JA, Paruchuri S. Differential Regulation of Cysteinyl Leukotriene Receptor Signaling by

Protein Kinase C in Human Mast Cells. PloS One 2013; 8: e71536. (PMID: 23977066) [Crossref]

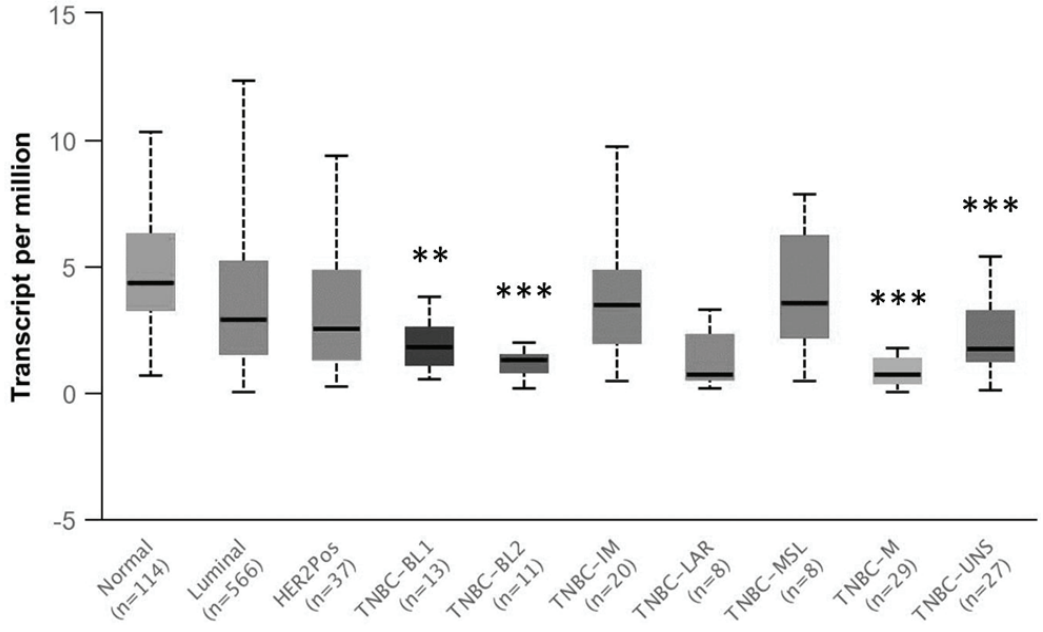
37. Gurusamy M, Tischner D, Shao J, Klatt S, Zukunft S, Bonnavion R, et al. G-protein-coupled receptor P2Y10 facilitates chemokine-induced CD4 T cell migration through autocrine/paracrine mediators. Nat Commun 2021; 12: 6798. (PMID: 34815397) [Crossref]
38. Hwang SM, Kim HJ, Kim SM, Jung Y, Park SW, Chung IY. Lysophosphatidylserine receptor P2Y10: A G protein-coupled receptor that mediates eosinophil degranulation. Clin Exp Allergy 2018; 48: 990-999. (PMID: 29700886) [Crossref]
39. Yang XL, Qi LG, Lin FJ, Ou ZL. The role of the chemokine receptor XCR1 in breast cancer cells. Breast Cancer (Dove Med Press) 2017; 9: 227-236. (PMID: 28408852) [Crossref]
40. Gantsev SK, Umezawa K, Islamgulov DV, Khusnutdinova EK, Ishmuratova RS, Frolova VY, et al. The role of inflammatory chemokines in lymphoid neoorganogenesis in breast cancer. Biomed Pharmacother 2013; 67: 363-366. (PMID: 23602049) [Crossref]



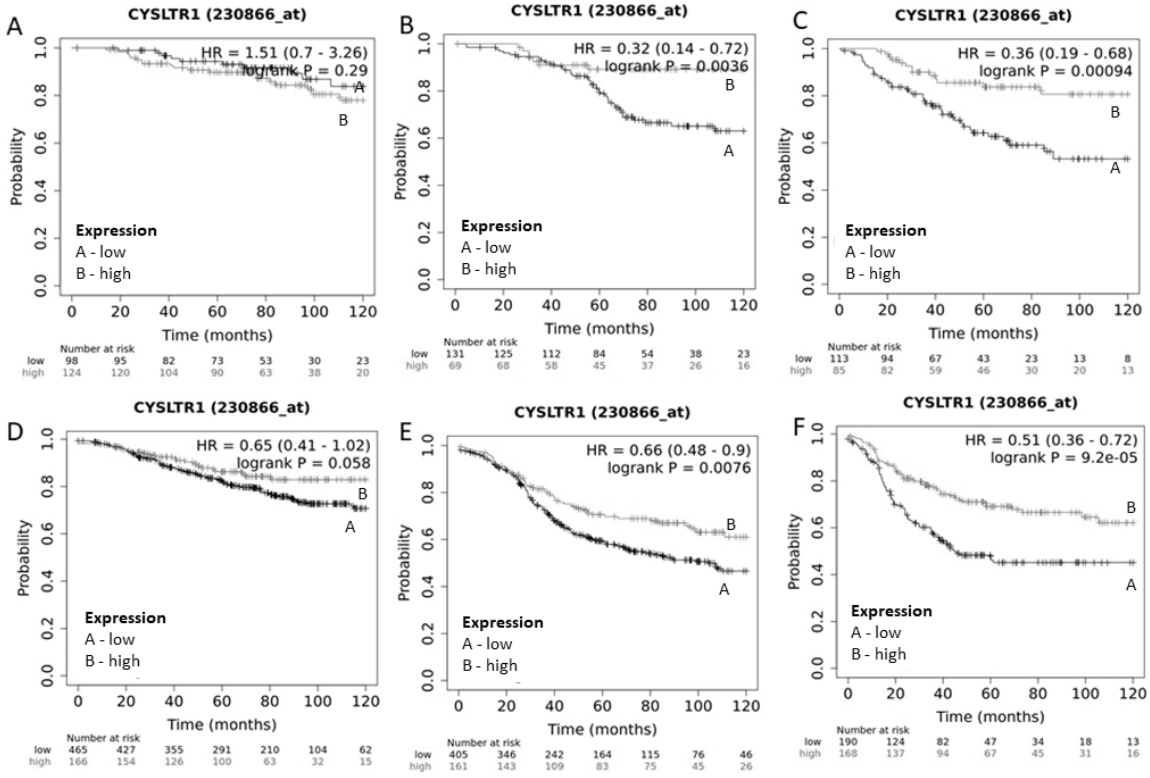

**Supplementary Figure 1.** CYSLTR1 transcript expression levels in breast cancer patients. According to: A. Sample type and B.- PAM50 classification. Data obtained from bcGenExMiner database. *P* values indicate significance according to Wilcoxon or ANOVA tests: **p*<0.05, ***p*<0.01, ****p*<0.001 and *****p*<0.0001



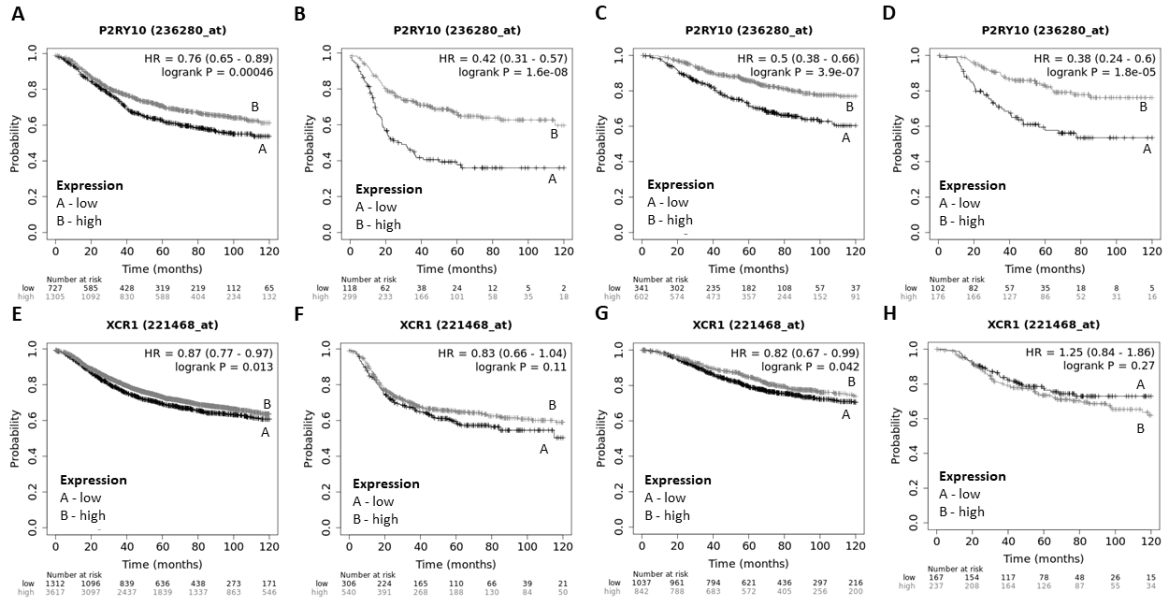

**Supplementary Figure 2.** *CYSLTR1* mRNA levels. According to: **A.** ER receptor, **B.** PR receptor, **C.** HER2 Status, data obtained from bcGenExMiner platform. Basal and Not Basal subtype, **E.** TNBC and Not TNBC subtype, **F.** Basal/TNBC and Not Basal/Not TNBC subtype, Data obtained from BRCA-TCGA dataset. *P* values indicate significance according to Wilcoxon or ANOVA tests: **p*<0.05, ***p*<0.01, ****p*<0.001 and *****p*<0.0001



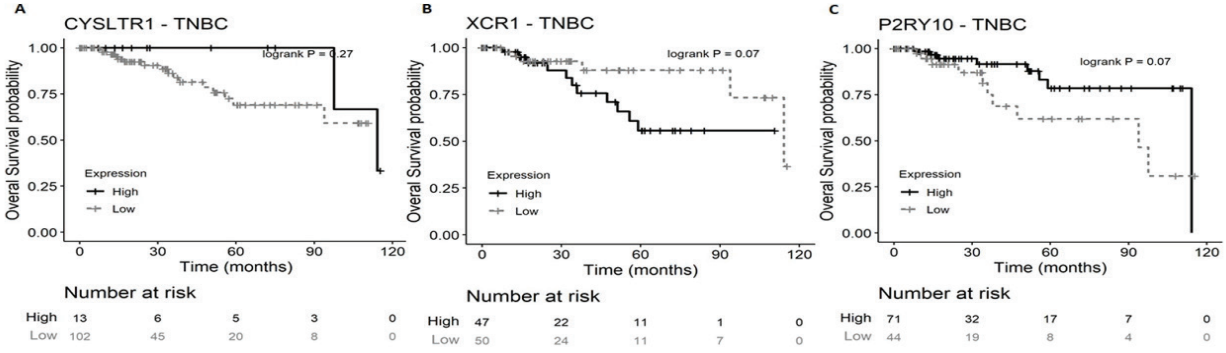

**Supplementary Figure 3.** Correlation of *CYSLTRL1* expression according to Lehmann et al. TNBC subtypes. *P* values indicate significance according to Wilcoxon or ANOVA tests: **p*<0.05, ***p*<0.01, ****p*<0.001 and *****p*<0.0001




**Supplementary Figure 4.** Survival probability of BCa patients stratified by the relative expression of *CYSLTR1*. OS in accord with **A.** Luminal **A, B.** Luminal **B, C.** HER2 subtypes. RFS according to **D.** Luminal **A, E.** Luminal B, and **C.** HER2 subtypes. Data obtained from KM Plotter platform with follow up threshold adjusted for 120 months




**Supplementary Figure 5.** Survival probability of patients stratified by the relative expression of *P2RY10* and *XCR1*. RFS considering all BCa subtypes **(A, E);** basal subtype **(B, F).** OS according to all BCa subtypes **(C, G);** basal subtype **(D, H).** Data obtained from KM Plotter platform with follow up threshold adjusted for 120 months




**Supplementary Figure 6.** Overall survival of TNBC patients. Stratified by the relative expression of **A.** *CYSLTR1*; **B.** *XCR1*; and **C.** *P2RY10*. Data obtained from TCGA repository with follow up threshold adjusted for 120 months

**Original Article**

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# Role of F-18 FDG PET/CT in Predicting Response to Neoadjuvant Chemotherapy in Invasive Ductal Breast Cancer

Tarik Sengoz[1], Yeliz Arman Karakaya[2], Aziz Gültekin[1], Sevda Yilmaz[3], Ergun Erdem[3], Burcu Yapar Taskoylu[4], Zehra Kesen[5], Olga Yaylali[1], Dogangun Yuksel[1]

[1]Department of Nuclear Medicine, Pamukkale University Faculty of Medicine, Denizli, Turkey
[2]Department of Pathology, Pamukkale University Faculty of Medicine, Denizli, Turkey
[3]Department of General Surgery, Pamukkale University Faculty of Medicine, Denizli, Turkey
[4]Department of Medical Oncology, Pamukkale University Faculty of Medicine, Denizli, Turkey
[5]Kesen Pathology Laboratory, Denizli, Turkey

**ABSTRACT**

**Objective:** The role of baseline and post-treatment standardized uptake value ($SUV_{max}$) values in predicting pathological response in patients with breast cancer after neoadjuvant chemotherapy (NAC).

**Materials and Methods:** Thirty patients with invasive ductal breast cancer were included in this retrospective study. F-18 fluorodeoxyglucose (FDG) positron emission tomography/computerized tomography (PET/CT) examinations were performed before and after NAC. Pretreatment $SUV_{max}$ ($SUV_{max}$ I), post-treatment $SUV_{max}$ ($SUV_{max}$ II) and $\Delta SUV_{max}$ values of primary breast cancer were obtained. Breast tumor pathology preparations were examined for the evaluation of tumor response according to the Miller and Payne classification. Patients were grouped as responding to treatment (pCR) and unresponsive to treatment (nonpCR). In all analyses, $p<0.05$ was considered statistically significant.

**Results:** The mean age of the 30 patients included in the study was 51.2±11.98 years. In the study-defined grouping, 13 patients (43.3%) were nonresponders and 17 patients (56.7%) were responders. $\Delta SUV_{max}$ was significantly greater in the responders group compared to the nonresponders group, while $SUV_{max}$ II was lower ($p = 0.001$ and $p = 0.004$, respectively). There was no significant difference between the responders and nonresponders in terms of age, tumor diameter, and $SUV_{max}$ I values. Multivariate logistic regression analysis showed $\Delta SUV_{max}$ to be the only independent predictive factor for pCR.

**Conclusion:** F-18 FDG PET/CT was an effective method in evaluating the treatment response after NAC in breast cancer, and $\Delta SUV_{max}$ and post-treatment $SUV_{max}$ can be used to predict the response of the primary tumor to treatment.

**Keywords:** Breast cancer, F-18 FDG, $SUV_{max}$, neoadjuvant chemotherapy

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**Key Points**

- F-18 FDG PET/CT is an effective method in evaluating the treatment response after NAC in breast cancer.
- $\Delta SUV_{max}$ and post-treatment $SUV_{max}$ values correlate with pathological evaluation in predicting pCR.
- Multivariate logistic regression analysis showed $\Delta SUV_{max}$ to be the only independent predictive factor for pCR.

## Introduction

Breast cancer is the most common type of cancer among women and its incidence has been increasing over the years (1). In the treatment of breast cancer, neoadjuvant chemotherapy (NAC) has recently become more frequently used. NAC is preferred, especially in locally advanced breast cancer, to reduce tumor volume and to allow breast-conserving surgery (2). In addition, it is stated that NAC has advantages, such as early detection of possible resistance to chemotherapy and predicting prognosis (3). Patients with pathological complete response (pCR) after NAC had better disease-free survival and overall survival rates than patients without a complete response (4). Although anatomical imaging methods are primarily used in the evaluation of response after NAC, there are some limitations. Conventional methods may not be able to clearly distinguish between viable tumor tissue and fibrotic scar tissue in patients with residual tissue after treatment.

**Corresponding Author:**
**Tarik Sengoz; tsengoz@pau.edu.tr**

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2-deoxy-2-[18F]-fluoro-D-glucose positron emission tomography/computed tomography (F-18 FDG PET/CT) is a molecular imaging method frequently used in oncology practice to evaluate response to treatment. Glucose metabolism is increased in cancer tissue and this a decrease in the metabolic activity of the residual tumor tissue after NAC is indicative of the response to treatment. In the literature, there are several studies investigating the accuracy of F-18 FDG PET/CT in evaluating response to treatment after NAC, with the pathological response criteria as reference (5-9). Due to the cytotoxic effect of chemotherapy, a decrease in cellular glycolysis is observed before tumor shrinkage. Therefore, standardized uptake value ($SUV_{max}$), which is a semi-quantitative parameter, is used to show the metabolic activity change more accurately.

In this study, the role of baseline and post-treatment $SUV_{max}$ values and $SUV_{max}$ change in predicting pathological response in patients with breast cancer after NAC was investigated.

## Materials and Methods

### Patients

Thirty patients with newly diagnosed, non-inflammatory, non-metastatic, invasive breast cancer were included in this retrospective study. In all patients, the diagnosis of invasive breast cancer was made with tru-cut biopsy and NAC treatment was given. F-18 FDG PET/CT examinations were performed on the patients before and after NAC. F-18 FDG PET/CT examination after NAC was performed at least 15 days after the end of the treatment. All patients underwent mastectomy/breast-conserving surgery 4-6 weeks after post-treatment F-18 FDG PET/CT. Exclusion criteria of the patients in the study were: patients who were diagnosed with inflammatory breast cancer; whose F-18 FDG PET/CT examination was contraindicated (for example with pregnancy or high blood sugar); who had a chronic disease; and who had previously received surgery or radiotherapy as treatment were excluded from the study.

Different NAC regimens were administered to the patients as follows: Six patients received cyclophosphamide and doxorubicin; 17 patients received cyclophosphamide and adriamycin; three patients received cyclophosphamide, doxorubicin and docetaxel; one patient received pertuzumab, herceptin and docetaxel; one patient received herceptin, paclitaxel and carboplatin; and two patients received herceptin and paclitaxel. The patients were administered 4-6 cycles of NAC.

This study was approved by the Faculty Ethics Committee of Pamukkale University (60116787-020/71416).

### F-18 FDG PET/CT Imaging

After fasting and resting for six hours, the patients received 259–407 MBq (7–11 mCi) of F-18 FDG intravenously when their fasting bloodglucose level was <200 mg/dL. The patients were examined using a dedicated PET/CT scanner (Gemini TF TOF PET-CT; Philips, Cleveland, OH, USA). Emission scans were acquired from the calvaria base to the middle of the thigh for 1.5 minutes per position without intravenous contrast medium injection. Transmission images were obtained by low-dose CT (50–120 mA s, 90–140 kVp, 16 sections of 5 mm thickness).

Attenuation correction was performed for PET images using CT findings and the ordered subsets-expectation maximization (OSEM) algorithm (33 subsets, 3 iterations). PET images were reconstructed by the iterative method. Transverse, sagittal and coronal sections (5 mm thickness) were created from PET/CT fusion images and evaluated using Philips Fusion Viewer software (ver.2.1; Philips Healthcare, Best, The Netherlands).

In this study, patients underwent two F-18 FDG PET/CT scans; basal scan for staging before NAC and post-treatment scan for response to treatment after NAC. Both examinations were performed on the patients under the same conditions and the same acquisition parameters.

### Image Analysis

F-18 FDG PET/CT images were evaluated by two nuclear medicine physicians and consensus was reached in all patients. The isocontour method was used to create volume of interest (VOI) around the tumor. A 40% $SUV_{max}$ threshold was used for the isocontour. $SUV_{max}$ was defined as the maximum SUV from a single voxel anywhere within the VOI. Tumor size was obtained by carefully measuring the longest diameter of the tumor from PET/CT images.

Metabolic response assessment with F-18 FDG PET/CT was performed by looking at the relative change in tumoral F-18 FDG uptake before and after treatment, and the following formula was used:

$\Delta SUV_{max}$=100 x (post-treatment $SUV_{max}$ – baseline $SUV_{max}$)/baseline $SUV_{max}$

### Pathological Evaluation

Pathological responses of primary tumors were evaluated by the pathologist according to the Miller and Payne grading system (10). Breast tumor pathology preparations were re-evaluated for the evaluation of tumor response according to Miller and Payne classification. This was divided into five grades based on the comparison of tumor cellularity between the pre-neoadjuvant core biopsy and the post-surgical sample. The Miller and Payne grading system rates the postoperative curative effect from levels 1 to 5 according to the reduction in tumor cells.

The grades were determined as follows:

Grade 1 (G1): No or some change in individual malignant cells, but no reduction in overall cellularity;

Grade 2 (G2): Minimal tumor cell loss (up to 30% loss), but overall cellularity still high;

Grade 3 (G3): 30% to 90% reduction in tumor cells;

Grade 4 (G4): Marked disappearance of tumor cells, leaving only small clumps or widely scattered individual cells; more than 90% loss of tumor cells;

Grade 5 (G5): No identifiable malignant cells in sections from tumor site, only vascular fibroelastotic stroma remaining, usually containing macrophages. Ductal carcinoma *in situ* (DCIS) may be present (11).

G1, G2 and G3 were included in the nonresponder group (nonpCR), and G4 and G5 were included in the responder group (pCR).

### Statistical Analysis

Data were analyzed with SPSS, version 25.0 (IBM Inc., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, median (minimum-maximum values), and categorical variables as number and percentage. The compatibility of the data

with the normal distribution was examined by the Kolmogorov-Smirnov test, and the homogeneity was examined by the Levene's test. Student's t-test was used to compare independent group differences with normal distribution. The Mann-Whitney U test was used to compare the independent group differences that did not fit the normal distribution. A logistic regression model was created using $\Delta SUV_{max}$ and $SUV_{max}$ II parameters, which were found to be independent statistically significant, to predict response to treatment.

A receiver-operating characteristics (ROC) analysis was performed, and cut-off values of the quantitative parameters of F-18 FDG PET/CT were obtained to evaluate the response to treatment. Sensitivity and specificity were calculated at 95% CI to measure the validity. In all analyses, $p<0.05$ was considered statistically significant.

## Results

The mean age of the 30 patients included in the study was 51.2±11.98 (28–75) years. According to their pathological response scores, the patients were distributed as follows: One patient (3.3%) was G1, four patients (13.3%) G2, 8 patients (26.7%) G3, nine patients (30%) G4, and eight patients (26.7%) G5. Thus, for study purposes, 13 patients (43.3%) were nonresponders and 17 patients (56.7%) were responders. Ten (33.3%) of the patients were premenopausal and 20 (66.7%) were postmenopausal. Patient characteristics are listed in Table 1.

$\Delta SUV_{max}$ was statistically significantly higher in the responders group compared to the nonresponders group, while $SUV_{max}$ II was lower ($p$ = 0.001 and $p$ = 0.004, respectively). There was no statistically significant difference between the responders and nonresponders groups in terms of age, tumor diameter, and $SUV_{max}$ I values (Table 2).

With multivariate logistic regression analysis, $\Delta SUV_{max}$ was found to be the only independent predictive factor for pCR (Table 3).

In the ROC curve analysis performed to determine the cut-off values of PET/CT parameters in the differentiation of pCR and non-pCR after neoadjuvant chemotherapy, the cut-off value for $\Delta SUV_{max}$ was found to be -59.69%, and the sensitivity and specificity values for this value were 82% and 85%, respectively [area under the ROC curve (AUC): 0.878, $p$ = 0.001, 95% confidence interval (CI) (0.74–1); see Figure 1], while the cut-off value for $SUV_{max}$ II was found to be 2.14, and the sensitivity and specificity values for this value were 70% and 85%, respectively [AUC: 0.810, $p$ = 0.004, 95% CI (0.62-0.99); see Figure 2].

## Discussion and Conclusion

While NAC allows breast-conserving surgery by reducing tumor size in breast cancer, it also makes a significant contribution to survival. It has been reported that patients with pCR after NAC had better disease-free survival and overall survival rates than patients whose response was evaluated by other methods (4). For this reason, in the present study, pCR was chosen as the reference standard for evaluating tumor response after NAC. In the present study, patients in the G4 and G5 groups were included in the pCR group according to the Miller and Payne classification system. In the literature, no difference was found in terms of prognosis between minimal residual disease and complete response (12), and in previous studies, pCR (G4, G5) and non-pCR (G1, G2, G3) groups were formed in this way (13, 14). In the present study, the pCR rate was 56.7%. In different studies, response rates after NAC have been reported to vary between 16.3%

Table 1. Patient and tumor characteristics

| Characteristics | n | % |
|---|---|---|
| **Histological grade** | | |
| 1 | 7 | 23.4 |
| 2 | 13 | 43.3 |
| 3 | 10 | 33.3 |
| **Nuclear grade** | | |
| 1 | 3 | 10.0 |
| 2 | 16 | 53.3 |
| 3 | 11 | 36.7 |
| **Mitosis rate** | | |
| 1 | 9 | 30.0 |
| 2 | 16 | 53.3 |
| 3 | 5 | 16.7 |
| **ER status** | | |
| Positive | 24 | 80.0 |
| Negative | 6 | 20.0 |
| **PR status** | | |
| Positive | 26 | 86.7 |
| Negative | 4 | 13.3 |
| HER2 status | | |
| 0/+ | 21 | 70.0 |
| ++/+++ | 9 | 30.0 |
| **Subtype** | | |
| Luminal A | 6 | 20.0 |
| Luminal B-HER2 negative | 12 | 40.0 |
| Luminal B-HER2 positive | 6 | 20.0 |
| HER2+ | 5 | 16.7 |
| Basal | 1 | 3.3 |
| **P53 status** | | |
| Positive | 19 | 63.3 |
| Negative | 5 | 16.7 |
| Unknown | 6 | 20.0 |
| **Ki-67 index** | | |
| <%20 | 9 | 30.0 |
| >%20 | 21 | 70.0 |
| **Axillary lymph node** | | |
| Negative | 6 | 20.0 |
| Positive | 24 | 80.0 |
| | **Mean ± SD** | **Median (min-max)** |
| Age | 51.2±11.98 | 51 (28–75) |
| $\Delta SUV_{max}$ | -57.06%±18.73% | -63.65% (-21.5–83.4) |
| $SUV_{max}$ I | 6.25±2.33 | 6.48 (2.43–11.23) |
| $SUV_{max}$ II | 2.51±1.31 | 2.17 (1.12–6.20) |
| Tumor size (mm) | 29.42±15.17 | 27.30 (10.5–82.3) |

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; $SUV_{max}$ I: pretreatment $SUV_{max}$; $SUV_{max}$ II: posttreatment $SUV_{max}$; $\Delta SUV_{max}$=100 x (post-treatment $SUV_{max}$ – basaline $SUV_{max}$)/basaline $SUV_{max}$

Table 2. Relationship between primary tumor characteristics and response to treatment

| | Mean ± SD | Median (min-max) | *p*-value |
|---|---|---|---|
| **Age** | | | |
| Responders (17) | 47.58±9.77 | 48 (28–59) | 0.058 |
| Nonresponders (13) | 55.92±13.31 | 59 (32–75) | |
| Tumor size (mm) | | | |
| Responders (17) | 25.34±8.39 | 27 (10.50–41.40) | 0.135 |
| Nonresponders (13) | 34.76±20.20 | 29 (12.30–82.30) | |
| $SUV_{max}$ I | | | |
| Responders (17) | 6.31±1.45 | 6.56 (3.38–8.27) | 0.88 |
| Nonresponders (13) | 6.17±3.21 | 5.89 (2.42–11.23) | |
| $\Delta SUV_{max}$ | | | |
| Responders (17) | -68.07%±11.16% | -69.66% (-41.70–83.04) | **0.001** |
| Nonresponders (13) | -42.66%±16.91% | -40.52% (-21.05–74.66) | |
| $SUV_{max}$ II | | | |
| Responders (17) | 1.89±0.46 | 1.87 (1.12–2.84) | **0.004** |
| Nonresponders (13) | 3.22±1.63 | 2.87 (1.17–6.20) | |

$SUV_{max}$ I, pretreatment $SUV_{max}$; $SUV_{max}$ II, posttreatment $SUV_{max}$;
$\Delta SUV_{max}$=100 x (post-treatment $SUV_{max}$ – basaline $SUV_{max}$)/basaline $SUV_{max}$

Table 3. Logistic regression

| | B | S.E. | *p*-value | 95% CI |
|---|---|---|---|---|
| $\Delta SUV_{max}$ | 0.108 | 0.044 | 0.015 | 1.021–1.216 |
| $SUV_{max}$ II | -1.57 | 0.897 | 0.079 | 0.360–1.199 |

$SUV_{max}$ II, posttreatment $SUV_{max}$;
$\Delta SUV_{max}$=100 x (post-treatment $SUV_{max}$ – basaline $SUV_{max}$)/basaline $SUV_{max}$

and 55.6% (15-17). This variation was thought to be due to the use of different pathological assessment and scoring methods.

In the present study, $\Delta SUV_{max}$ was found to be a highly effective parameter for predicting pCR after NAC in breast cancer patients. The cut-off value for $\Delta SUV_{max}$ was found to be -59.69%, and the sensitivity and specificity values for this value were 82% and 85%, respectively (Figures 3 and 4). In a meta-analysis evaluating 19 studies, to predict histopathological response in primary breast lesions by PET, the pooled sensitivity and specificity were 84% (95% CI, 78–88%) and 66% (95% CI, 62–70%), respectively (18). Our specificity value was found to be higher than the specificity value determined in the meta-analysis. Studies in the meta-analysis used very different NAC regimens, and the timing of the F-18 FDG PET/CT scan was different from each other. In our study, PET/CT examination times were the same, and the same device and the same examination protocol were used. In the 43-patient study of García-Esquinas et al. (9), the sensitivity and specificity were found to be 90.9% and 90.6% when the $\Delta SUV_{max}$ cut-off was taken at -90.4%. In that study, the same NAC regimen was used in each patient, unlike ours, and the high $\Delta SUV_{max}$ cut-off value may have increased the sensitivity and specificity. This may explain the higher sensitivity and specificity than we found. The values obtained for $\Delta SUV_{max}$ in several studies in the literature

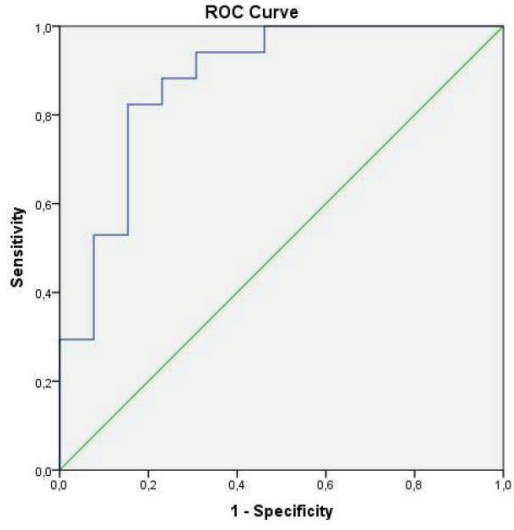


**Figure 1.** Receiver operating characteristic (ROC) curve for the prediction of pathological complete response (pCR) using $\Delta SUV_{max}$ in F-18 FDG PET/CT [Area under ROC curve (AUC)=0.878]

*FDG: fluorodeoxyglucose; PET: positron emission tomography; CT: computerized tomography*

were similar to or lower than our results (5, 8, 19-21). In the study of Berrido-Rieninger et al. (20), specificity was found to be 86% when $\Delta SUV_{max}$ was -60% (20). This finding is consistent with our result. In the 50-patient study of Park et al. (22), the sensitivity was 100% while the specificity was 62%. About half of the primary tumors in this study were <1 cm. In our study, the primary tumor size was greater than 1 cm in all patients. The low specificity can be attributed to the small tumor size. In another study, sensitivity was 82.3% and specificity 82.4% when $\Delta SUV_{max}$ was -87.9% (5). Although the $\Delta SUV_{max}$ cut-off value of this study was higher than ours, we obtained similar sensitivity and specificity values.

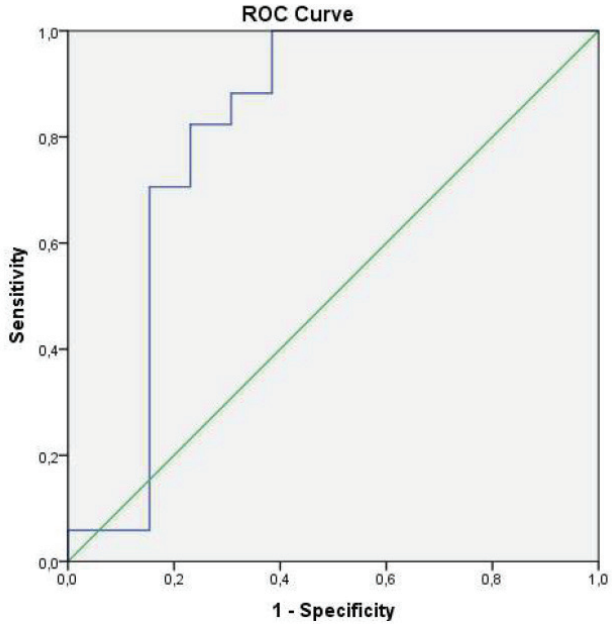


**Figure 2.** Receiver operating characteristic (ROC) curve for the prediction of pathological complete response (pCR) using posttreatment $SUV_{max}$ ($SUV_{max}$ II) in F-18 FDG PET/CT [Area under ROC curve (AUC)=0.810]

*FDG: fluorodeoxyglucose; PET: positron emission tomography; CT: computerized tomography*

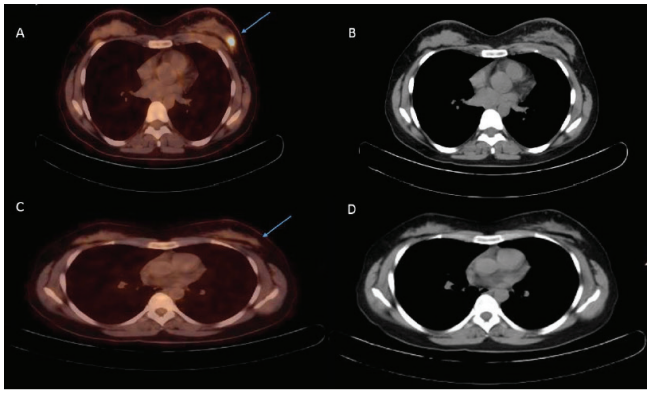


**Figure 3.** Forty-six years old woman. Left breast localized invasive ductal carcinoma (primary tumor axial diameter 14.6 mm, primary tumor $SUV_{max}$: 8.02) is seen in pretreatment CT and fusion PET/CT transaxial images (blue arrow) **(A, B).** There is a significant decrease in F-18 FDG uptake ($SUV_{max}$:1.36; $\Delta SUV_{max}$:-83.04%) in post-treatment CT and fusion PET/CT transaxial images (blue arrow) after four cycles of cyclophosphamide/adriamycin chemotherapy **(C, D).** Histopathological features of the primary tumor: histological grade 3, nuclear grade 3, mitosis rate 2, ER and PR negative, HER2 +3 positive, K-67 40%, p53 positive, and subtype HER2 positive. Miller and Payne grading system pathological score 4

*FDG: fluorodeoxyglucose; PET: positron emission tomography; CT: computerized tomography; SUV: standardized uptake value; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor*

$SUV_{max}$ was used as a semi-quantitative parameter in most of the studies on the value of F-18 FDG PET/CT in response assessment after NAC. In the study of Berriolo-Riedinger et al. (20), except $SUV_{max}$, SUV parameters corrected for total body weight, body surface area and blood glucose were used (8). However, no significant difference was found between SUV parameters in estimating pCR. Therefore, in our

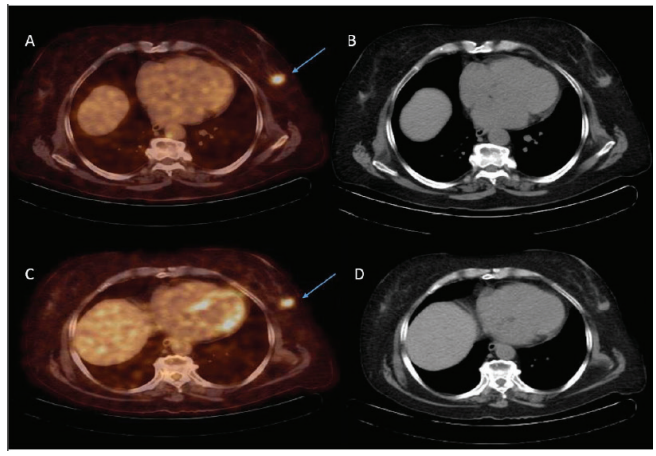


**Figure 4.** Seventy-eight years old woman. Left breast localized invasive ductal carcinoma (primary tumor axial diameter 18.7 mm, primary tumor $SUV_{max}$:6.55) is seen in pretreatment CT and fusion PET/CT transaxial images (blue arrow) **(A, B).** There is a slight decrease in F-18 FDG uptake ($SUV_{max}$:4.51; $\Delta SUV_{max}$:-44.25%) in post-treatment CT and fusion PET/CT transaxial images (blue arrow) after four cycles of cyclophosphamide/adriamycin chemotherapy **(C, D).** Histopathological features of the primary tumor: histological grade 2, nuclear grade 2, mitosis rate 2, ER 90% positive, PR 90% positive, HER2 negative, Ki-67 30%, p53 positive, and subtype luminal B/HER2 negative. Miller and Payne grading system pathological score 3

*FDG: fluorodeoxyglucose; PET: positron emission tomography; CT: computerized tomography; SUV: standardized uptake value; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor*

study, we used $SUV_{max}$ parameters ($SUV_{max}$ I, $SUV_{max}$ II and $\Delta SUV_{max}$) in accordance with the literature.

In the present study, we evaluated the potential of pretreatment $SUV_{max}$ ($SUV_{max}$ I) and post-treatment $SUV_{max}$ ($SUV_{max}$ II) to predict pCR, as well as $\Delta SUV_{max}$. The cut-off value for $SUV_{max}$ II was found to be 2.14, and the sensitivity and specificity values for this value were 70% and 85%, respectively. In the literature, there are few studies evaluating the efficacy of post-treatment $SUV_{max}$ in predicting the response to treatment after NAC in breast cancer. In the study of Yıldırım et al. (21), consisting of 51 patients, no significant difference was observed between pCR and nonpCR in terms of pretreatment $SUV_{max}$, but a significant difference was found between post-treatment $SUV_{max}$ values. Our findings are consistent with this study. In the present study, it was revealed that, like $\Delta SUV_{max}$, the value of post-treatment $SUV_{max}$ was an effective parameter in predicting the response to treatment after NAC in breast cancer. However, this finding needs to be supported by new studies. There are different results in the literature regarding the value of pretreatment $SUV_{max}$ in predicting the response to treatment after NAC in breast cancer. In some studies, basal $SUV_{max}$ was found to be higher in the pCR group (23-25), while in some studies, higher SUVmax values were found in unresponsive patients (26, 27). In addition, and in contrast to these studies, there are also publications that argue that there is no difference in basal $SUV_{max}$ between pCR and nonpCR (15, 20, 28). Therefore, the findings in the literature suggest that there is no consensus regarding the value of pretreatment $SUV_{max}$ in predicting the response to treatment after NAC.

The present study has some limitations. It was designed retrospectively and the number of patients was low. Due to the low number of patients, subgroup-related to prognostic factors (receptor status, grade, subtype, Ki-67 ratio, etc.) of breast cancer could not be formed and their

relationship with PET parameters could not be evaluated. Different NAC regimens were administered to the patients and the relationship between the different NAC regimens could not be evaluated due to the small number of patients.

F-18 FDG PET/CT was an effective method in predicting the response to treatment after NAC in breast cancer. $\Delta SUV_{max}$ and post-treatment $SUV_{max}$ values correlate with pathological evaluation in predicting pCR. We did not find that pretreatment $SUV_{max}$ was effective in predicting response to treatment.

**Ethics Committee Approval:** This study was approved by the Faculty Ethics Committee of our institution (60116787-020/71416) (Pamukkale University Non-Invasive Clinical Research Ethics Committee).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Y.A.K., A.G., S.Y., E.E., B.Y.T.; Concept: T.S.; Design: T.S., B.Y.T.; Data Collection or Processing: Y.A.K., A.G., B.Y.T., O.Y.; Analysis or Interpretation: T.S., A.G., D.Y.; Literature Search: T.S., S.Y., E.E., D.Y.; Writing: T.S.

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## References

1. Taghipour M, Wray R, Sheikhbahaei S, Wright JL, Subramaniam RM. FDG avidity and tumor burden: survival outcomes for patients with recurrent breast cancer. AJR Am J Roentgenol 2016; 4: 846-855. (PMID: 27003053) [Crossref]
2. Honkoop AH, van Diest PJ, de Jong JS, Linn SC, Giaccone G, Hoekman K, et al. Prognostic role of clinical, pathological and biological characteristics in patients with locally advanced breast cancer. Br J Cancer 1998; 77: 621-626. (PMID: 9484820) [Crossref]
3. Esserman LJ, Berry DA, DeMichele A, Carey L, Davis SE, Buxton M, et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL–CALGB 150007/150012, ACRIN 6657. J Clin Oncol 2012; 30: 3242-3249. (PMID: 22649152) [Crossref]
4. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164-172. (PMID: 24529560) [Crossref]
5. Akdeniz N, Kömek H, Küçüköner M, Kaplan MA, Urakçı Z, Oruç Z, et al. The role of basal 18F-FDG PET/CT maximum standard uptake value and maximum standard uptake change in predicting pathological response in breast cancer patients receiving neoadjuvant chemotherapy. Nucl Med Commun 2021; 42: 315-324. (PMID: 33315727) [Crossref]
6. Vicente AMG, Mora MAC, Martín AAL, Sánchez MMM, Calatayud FR, López OVG, et al. Glycolytic activity with 18F-FDG PET/CT predicts final neoadjuvant chemotherapy response in breast cancer. Tumor Biol 2014; 35: 11613-11620. (PMID: 25139100) [Crossref]
7. Sarhan EAS, El Gohary MI, El Moneim LA, Ali SA. Role of 18 fluorine-fluorodeoxyglucose positron emission tomography/computed tomography in assessment of neoadjuvant chemotherapy response in breast cancer patients. Egypt J Radiol Nucl Med 2020; 51: 116. [Crossref]
8. Erdi YE, Macapinlac H, Rosenzweig KE, Humm JL, Larson SM, Erdi AK, et al. Use of PET to monitor the response of lung cancer to radiation treatment. Eur J Nucl Med 2000; 27: 861-866. (PMID: 10952499) [Crossref]
9. García-Esquinas MAG, García JA, García-Sáenz JA, Furió-Bacete V, Ferrer MEF, Candil AO, et al. Predictive value of PET-CT for pathological response in stages II and III breast cancer patients following neoadjuvant chemotherapy with docetaxel. Rev Esp Med Nucl Imagen Mol 2014; 33: 14-21. (PMID: 23809513) [Crossref]
10. Song D, Man X, Jin M, Li Q, Wang H, Du Y. A Decision-Making Supporting Prediction Method for Breast Cancer Neoadjuvant Chemotherapy. Front Oncol 2021; 10: 592556. (PMID: 33469514) [Crossref]
11. Ying M, He Y, Qi M, Dong B, Lu A, Li J, et al. Value of pre-treatment biomarkers in prediction of response to neoadjuvant endocrine therapy for hormone receptor-positive postmenopausal breast cancer. Chin J Cancer Res 2013; 25: 397-404. (PMID: 23997526) [Crossref]
12. Ueda S, Tsuda H, Asakawa H, Shigekawa T, Fukatsu K, Kondo N, et al. Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in primary breast cancer. Jpn J Clin Oncol 2008; 38: 250-258. (PMID: 18407934) [Crossref]
13. Duch J, Fuster D, Muñoz M, Fernández PL, Paredes P, Fontanillas M, et al. 18F-FDG PET/CT for early prediction of response to neoadjuvant chemotherapy in breast cancer. Eur J Nucl Med Mol Imaging 2009; 36: 1551-1557. (PMID: 19326117) [Crossref]
14. Kiyoto S, Sugawara Y, Hosokawa K, Nishimura R, Yamashita N, Ohsumi S, et al. Predictive ability of 18F-fluorodeoxyglucose positron emission tomography/computed tomography for pathological complete response and prognosis after neoadjuvant chemotherapy in triple-negative breast cancer patients. Asia Ocean J Nucl Med Biol 2016; 4: 3-11. (PMID: 27904868) [Crossref]
15. Koolen BB, Pengel KE, Wesseling J, Vogel WV, Peeters MJV, Vincent AD, et al. FDG PET/CT during neoadjuvant chemotherapy may predict response in ER-positive/HER2-negative and triple negative, but not in HER2-positive breast cancer. Breast 2013; 22: 691-697. (PMID:23414930) [Crossref]
16. Zucchini G, Quercia S, Zamagni C, Santini D, Taffurelli M, Fanti S, et al. Potential utility of early metabolic response by 18F-2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in a selected group of breast cancer patients receiving preoperative chemotherapy. Eur J Cancer 2013; 49: 1539-1545. (PMID: 23369464) [Crossref]
17. Rousseau C, Devillers A, Sagan C, Ferrer L, Bridji B, Campion L, et al. Monitoring of early response to neoadjuvant chemotherapy in stage II and III breast cancer by [18F]fluorodeoxyglucose positron emission tomography. J Clin Oncol 2006; 24: 5366-5372. (PMID:17088570) [Crossref]
18. Wang Y, Zhang C, Liu J, Huang G. Is 18F-FDG PET accurate to predict neoadjuvant therapy response in breast cancer? A meta-analysis. Breast Cancer Res Treat 2012; 131: 357-369. [PMID: 21960111) [Crossref]
19. Jung S-Y, Kim S-K, Nam B-H, Min SY, Lee SJ, Park C, et al. Prognostic impact of [18F] FDG-PET in operable breast cancer treated with neoadjuvant chemotherapy. Ann Surg Oncol 2009; 17: 247-253. (PMID: 19777177) [Crossref]
20. Berriolo-Riedinger A, Touzery C, Riedinger J-M, Toubeau M, Coudert B, Arnould L, et al. [18F]FDG-PET predicts complete pathological response of breast cancer to neoadjuvant chemotherapy. Eur J Nucl Med Mol Imaging 2007; 34: 1915-1924. (PMID: 17579854) [Crossref]
21. Yildirim N, Simsek M, Aldemin MN, Bilici M, Tekin SB. The relationship between 18-FDG-PET/CT and clinicopathologic features, pathologic

response in patients with locally advanced breast cancer. Eurasian J Med 2019; 51: 154-159. (PMID: 31258356) [Crossref]

22. Park JS, Moon WK, Lyou CY, Cho N, Kang KW, Chung J-K. The assessment of breast cancer response to neoadjuvant chemotherapy: comparison of magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography. Acta Radiol 2011; 52: 21-28. (PMID: 21498321) [Crossref]
23. Schwarz-Dose J, Untch M, Tiling R, Sassen S, Mahner S, Kahlert S, et al. Monitoring primary systemic therapy of large and locally advanced breast cancer by using sequential positron emission tomography imaging with [18F]fluorodeoxyglucose. J Clin Oncol 2009; 27: 535-541. (PMID: 19075273) [Crossref]
24. Buchbender C, Kuemmel S, Hoffmann O, Stahl AR, Kimming R, Otterbach F, et al. FDG-PET/CT for the early prediction of histopathological complete response to neoadjuvant chemotherapy in breast cancer patients: initial results. Acta Radiol 2012; 53: 628-636. (PMID: 22761341) [Crossref]
25. Ueda S, Saeki T, Shigekawa T, Omata J, Moriya T, Yamamoto J, et al. 18F-Fluorodeoxyglucose positron emission tomography optimizes neoadjuvant chemotherapy for primary breast cancer to achieve pathological complete response. Int J Clin Oncol 2012; 17: 276-282. (PMID: 21830087) [Crossref]
26. Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Charlop A, Lawton TJ, et al. Blood flow and metabolism in locally advanced breast cancer: relationship to response to therapy. J Nucl Med 2002; 43: 500-509. (PMID: 11937594) [Crossref]
27. Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Schubert EK, Tseng J, et al. Changes in blood flow and metabolism in locally advanced breast cancer treated with neoadjuvant chemotherapy. J Nucl Med 2003; 44: 1806-1814. (PMID: 14602864) [Crossref]
28. Kolesnikov-Gauthier H, Vanlemmens L, Baranzelli M-C, Vennin P, Servent V, Fournier C, et al. Predictive value of neoadjuvant chemotherapy failure in breast cancer using FDG-PET after the first course. Breast Cancer Res Treat 2012; 131: 517-525. (PMID: 22037787) [Crossref]

**Original Article**

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# Evaluation of Benign Breast Diseases With or Without Atypical Epithelial Hyperplasia Accompanying Radial Scars

Zeliha Turkyilmaz[1], Elif Sarisik[2], Enver Ozkurt[3], Mustafa Tukenmez[3], Selman Emiroglu[3], Baris Emiroglu[3], Semen Onder[4], Ravza Yilmaz[5], Mahmut Muslumanoglu[3], Abdullah Igci[3], Vahit Ozmen[3], Neslihan Cabioglu[3]

[1]Department of General Surgery, Trakya University Faculty of Medicine, Edirne, Turkey
[2]Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[3]Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[4]Department of Pathology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[5]Department of Radiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

**ABSTRACT**

**Objective:** A radial scar (RS) is a benign breast lesion (BBL) that has an obscure etiology. RS is easily confused with breast carcinoma and therefore correct identification radiologically and pathologically is important. The aim of this study was to determine the incidence of atypical lesions by evaluating RS detected with BBL and to investigate whether atypia and RS are related to their characteristics.

**Materials and Methods:** A total of 1.370 patients with a diagnosis of BBL postoperatively in a single department were analyzed retrospectively. Forty-six confirmed RS/complex sclerosing lesion (CSL) cases were selected. The demographic and clinical characteristics of the patients and the relationship between RS and other BBL were evaluated. In addition, the relationship between RS/CSL and the presence of atypia was interpreted.

**Results:** The mean age was 45.17±8.72 years. Spiculated lesion (34.8%) on mammography and microcalcification (37%) on histopathological examination were the most common features. The most common BBL accompanying RS/CSL was adenosis. Atypical epithelial hyperplasia (AEH) was presented in 15 (32.6%) of those diagnosed with RS. Although all patients were benign, the frequency of AEH accompanying RS was found to be significantly higher. The mean size of RS was 10.8±8.4 mm (2-30 mm). The size of RS/CSL was not significantly associated with atypia.

**Conclusion:** RS/CSLs usually present as suspicious lesions that must be distinguished radiologically from malignancy. However RS, which can be present with malign breast lesions, can be also seen with all BBL. Therefore, core biopsy and/or excisional biopsy continue to be important for definitive histopathological diagnosis.

**Keywords:** Radial scar; complex sclerosing lesion; benign breast lesions; spiculated lesion

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**Key Points**

- Radial scar (RS) often has a spicule appearance mimicking breast carcinoma on mammography, so the definitive diagnosis of the lesion with mammography is difficult.
- The high incidence of atypical epithelial hyperplasia accompanying RS in the study suggests that RS is strongly associated with atypia.
- The follow up of RS without atypia requires a multidisciplinary approach.

## Introduction

Radial scar (RS) and complex sclerosing lesion (CSL) may be confusing, benign breast lesions (BBL). RS is a proliferative BBL that includes central sclerosis. Distortion and pseudo-infiltrative appearance have been confused with carcinoma (1). When the size is smaller than 1 cm, the lesion is termed RS, whereas, if it is bigger than 1 cm, it is designated a CSL (1, 2). Small lesions usually present as incidental microscopic findings but the mammographic findings of large lesions are typical (2, 3). The incidence of RS and CSL is reported to be 0.03–0.09% in all core needle biopsies (CNB) (4, 5). RS pathogenesis is not exactly clear. Inflammatory process, chronic ischemia, previous trauma and surgical operations may all play a role in the pathogenesis of RS

**Corresponding Author:**
**Zeliha Turkyilmaz; turkyilmazz@yahoo.com**

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(6). RS is characterized by a central area of fibroelastosis with radiating ducts and lobules. These ducts and lobules have the appearance of spicules on mammography, which often mimics breast carcinoma (1, 7). Therefore, it is difficult for a definitive mammographic diagnosis of this lesion (6, 7). The results of studies examining the relationship between breast cancer and RS are controversial. Currently, it is unclear whether RS/CSL only act as an independent risk factor in increasing breast cancer or are in themselves premalignant (6, 8). Although RS/CSL is mostly associated with malignancy by clinicans, it can frequently be seen with various BBLs. Proliferative BBLs, with or without atypia, may accompany RS (5, 6, 8).

The aim of this study was to determine the benefits of imaging modalities and core needle biopsy and to investigate the frequency of benign lesions in the breast associated with RS. Furthermore, the association of RS with or without atypical BBL was assessed.

## Materials and Methods

Between 1995-2015, 1.370 operated cases were diagnosed with BBL and retrospectively analyzed at Istanbul University, Faculty of Medicine Surgery, Department C Clinical Services. Forty-nine cases with histopathology confirming cases of RS or CSL were selected.

As the aim was to consider etiologically non-traumatic and idiopathic RS in patients without history of breast operation, 3 of 49 (6.1%) cases that had excisional biopsies performed on the same breast previously were excluded. Demographic and clinical characteristics of the remaining 46 patients including age, menopausal status, age at menarche, lactation period, number of births, family history of cancer, oral contraceptive use, hormonal therapy, complaint, palpability of lesions, and side of lesions were evaluated.

Ultrasonography, mammography, and magnetic resonance imaging (MRI) results were also evaluated by size and Breast Imaging Reporting and Data System (BI-RADS) score. If the lesion was 1.0 cm or less, the lesion was designated RS and if greater than 1.0 cm it was defined as CSL.

We gathered and reviewed follow-up reports in order to examine the risk of developing carcinoma or other lesions. Lesions accompanying RS were further investigated to assess the relationship between RS and other benign lesions

### Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. While evaluating the study data, chi-square tests (Pearson chi-square, Yates chi-square, Fisher's Exact test) were used for qualitative comparisons between groups and to produce descriptive statistics. The results were evaluated within the 95% confidence interval and significance was assummed when $p<0.05$.

## Results

The mean ± standard deviation (range) age of the patients was 45.17±8.72 (22–61) years. Seven patients (15.2%) had a family history of breast cancer. Fourteen (30.4%) patients had palpable mass at presentation. The lesion was in the right breast in 47.8% and in the left breast in 52.2%. Demographic and clinical characteristics of the patients are given in Table 1. Twenty-five cases (54.3%) cases were identified by the mammography screening program (MSP).

Table 1. Demographic and clinical characteristics of patients

| | n | % |
|---|---|---|
| **Age** | 45.17±8.72 (22–61) | |
| **Age groups** | | |
| 20-30 | 3 | 6.5 |
| 31-40 | 8 | 17.4 |
| 41-50 | 21 | 45.7 |
| 50+ | 14 | 30.4 |
| Premenopausal | 31 | 67.4 |
| Postmenopausal | 15 | 32.6 |
| Used oral contraceptives | 10 | 21.7 |
| Family history of breast cancer | 7 | 15.2 |
| Age at menarche (year) | 13.5±1.4 | |
| Lactation period (month) | 22.72±19.31 | |
| | **n** | **%** |
| **Presenting symptoms** | | |
| Screening | 25 | 54.3 |
| Mass | 13 | 28.3 |
| Pain | 5 | 10.9 |
| Mass+pain | 3 | 6.5 |
| **Imaging techniques** | | |
| Ultrasound | 46 | 100 |
| Mammogram | 37 | 80.4 |
| Magnetic Resonance Imaging | 16 | 34.7 |
| **MMG findings (total 37 patients)** | | |
| Microcalcifications | 19 | 51.3 |
| Spiculated lesion | 16 | 43.2 |
| Opacity | 11 | 29.7 |
| Asymmetric density | 3 | 8.1 |
| Distortion | 2 | 5.4 |
| **CNB findings (total 24 patients)** | | |
| Pure RS/CSL | 8 | 33.3 |
| Intraductal papilloma | 3 | 12.5 |
| Stromal fibrosis | 3 | 12.5 |
| Fibroadenoma | 2 | 8.8 |
| ADH | 2 | 8.8 |
| Adenosis | 1 | 4.1 |
| Phyllodes tumour | 1 | 4.1 |
| RS&Adenozis&DCIS | 1 | 4.1 |
| RS&Intraductal papilloma | 1 | 4.1 |
| Fibroadenolipoma | 1 | 4.1 |
| Sclerosing adenosis | 1 | 4.1 |
| **Surgery techniques** | | |
| Wire localization biopsy | 31 | 67.4 |
| Excisional biopsy | 14 | 30.4 |
| Radioguided occult lesion localization & surgical biopsy | 1 | 2.2 |

RS: radial scar; CSL: complex sclerozing lesion; ADH: Atypical ductal hyperplasia; DCIS: ductal carcinoma *in situ*; RS: radial scar

Microcalcification was detected in 19/37 (51.3%) of the mammograms, and spiculated lesion was observed in 16/37 (43.2%). Distributions of mammography findings appear in Table 1. Six patients (23.1%) were designated as BIRADS III, 14 as BIRADS IV (53.8%) and six as BIRADS V (23.1%). Mammographic appearance is shown in Figure 1. RS/CSL was detected in only 10 (41.7%) of 24 CNB performed. In the other 14 CNB results, the presence of RS was not identified but other benign lesions were detected. Histopathological results of 24 core biopsy specimens are shown in Table 1.

Radiologically suspicious lesions were excised without CNB in 22 patients. Of the 22 patients, 16 who had not undergone CNB, were excised with wire-guidance. The lesions were excised due to a spicule contour mass in 8 (50%) patients, microcalcifications in 5 (31.25%), lobulated contour in 2 (12.5%), and suspicious contrast enhancement in MRI in 1 (6.25%) case. When pathology results of 5 patients who underwent biopsy due to microcalcification were evaluated, the mean RS dimension was 3.8±2.5 mm. The most common surgical method was wire localization excision with a frequency of 67.4%.

RS was detected in 34 cases (73.9%) while CSL was found in 11 cases (23.9%). Only 1 (2.2%) had both RS and CSL. RS/CSL were multiple in 8 cases (17.4%) whereas 38 lesions (82.6%) were single. Five (10.9%) cases had pure RS/CSL. The most common RS/CSL accompanying lesion was adenosis (39.1%) (Figure 2 shows CSL, sclerosing, papilloma and adenosis). Microcalcification was identified in 17 of 46 (36.9%) cases by histopathological examination. The distribution of BBL accompanying RS is shown in Table 2.

The mean size of RS/CSL was 10.8±8.4 mm 2–30 mm). RS size was less than 5 mm in 22 (47.83%) patients and greater than 5 mm in 24 (52.17%) patients. RS/CSL size was less than 1 cm in 31 (67.4%) patients and greater than 1 cm in 15 (32.6%) patients. Atypical epithelial hyperplasia (AEH) was seen with a frequency of 32.6% (15/46). Twelve patients had atypical ductal hyperplasia (ADH), two patient had atypical lobular hyperplasia (ALH), and one patient had both ADH and ALH. The incidence of atypia in patients with RS according to age is given in Table 3. There was no statistical relationship between the age of patients and the presence of AEH.

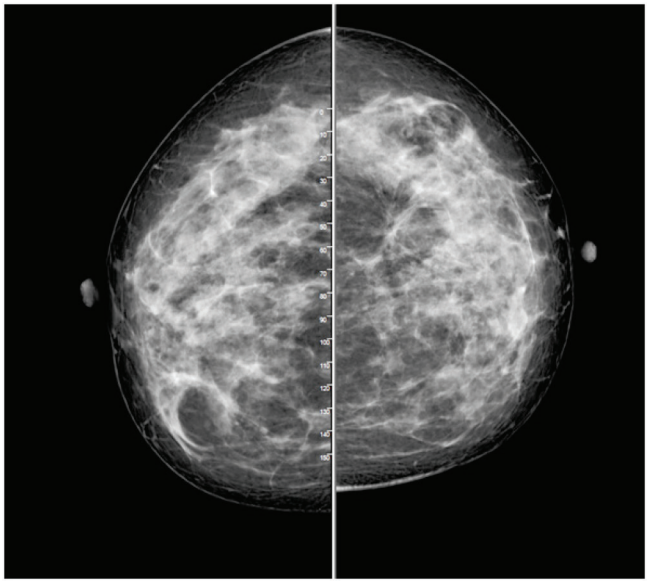

**Figure 1.** RS mammographic appearance

*RS: radial scar*

While 33.3% percent of 24 cases (with RS dimension 0.5 cm or larger) had AEH, 66.7% percent didn't have AEH. In contrast, in 22 cases with RS smaller than 0.5 cm, 32.8% percent had AEH and 68.2% didn't have AEH. Taking a cut-off at 1 cm, while 26.7% percent of 15 cases (with CSL 1 cm and larger) had AEH, 73.3% didn't have AEH. Whereas 35.5% percent of 31 cases with RS smaller than 1 cm had AEH, 64.5% didn't have AEH. No statistically significant correlation was found between RS/CSL size and atypia (Table 4). Among 15 RS with AEH, three cases were multiple, while 12 cases were solitary. AEH was present in 3 of 8 (37.5%) multiple lesions, and it was found in 12 of 38 solitary lesions (31.6%). The number of lesions did not reveal any statistically significant relation with atypia.

Benign phyllodes tumor, hamartoma, and lobular carcinoma in situ (LCIS) was an accompanying lesion in three different patients. In a 35-year-old patient diagnosed with hamartoma, a rare breast tumor, RS was detected in this hamartoma. In the wire localization biopsy of a 53-year-old postmenopausal patient, RS was accompanied by LCIS. The mean follow-up period of the patients was 48 months, and RS recurrence and malignancy did not develop in any of the patients during the follow-up period.

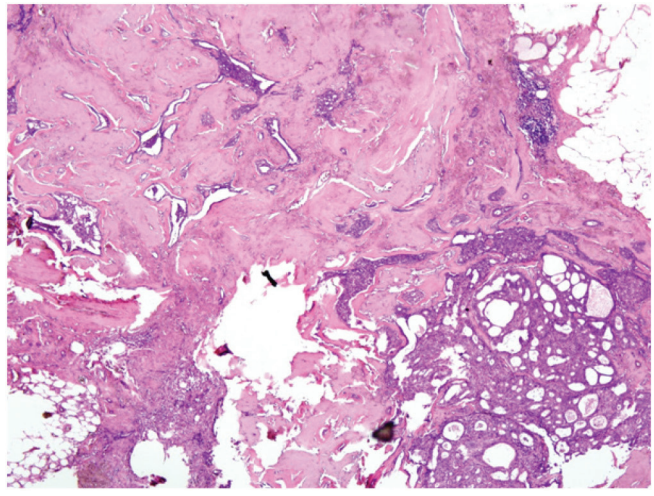

**Figure 2.** CSL with sclerosan papilloma, adenosis and radial scar (H&E, x100)

Table 2. Associated benign breast lesions with radial scar

| Concominant benign breast lesions | n | % |
|---|---|---|
| Adenosis | 18 | 39.1 |
| Intraductal papilloma | 16 | 34.8 |
| Ductal ectasia | 16 | 34.8 |
| Apocrine metaplasia | 15 | 32.6 |
| Fibroadenoma | 12 | 26.1 |
| Sclerosing adenosis | 12 | 26.1 |
| ADH | 12 | 26.1 |
| Florid ductal hyperplasia | 10 | 21.7 |
| Ductal hyperplasia | 2 | 4.4 |
| ALH | 2 | 4.4 |
| ADH &ALH | 1 | 2.2 |

ADH: atypical ductal hyperplasia; ALH: atypical lobular hyperplasia

Table 3. Relationship between age and atypia in patients with RS

| | AEH | | | |
|---|---|---|---|---|
| Age | Absent n (%) | Present n (%) | Total n (%) | p |
| 20-30 | 2 (6.5) | 1 (6.7) | 3 (6.5) | 0.593 |
| 31-40 | 4 (12.9) | 4 (26.7) | 8 (17.4) | |
| 41-50 | 16 (51.6) | 5 (33.3) | 21 (45.7) | |
| 50+ | 9 (29.0) | 5 (33.3) | 14 (30.4) | |
| Total n (%) | 31 (100.0) | 15 (100.0) | 46 (100.0) | |

AEH: atypical epithelial hyperplasia; RS: radial scar

Table 4. Size of RS/CSL-AEH relations

| Size (cm) | AEH | | |
|---|---|---|---|
| | Absent n (%) | Present n (%) | Total n (%) |
| **Cut off 0.5 cm** | | | |
| <0.5 | 15 (48.4) | 7 (46.7) | 22 (47.8) |
| >0.5 | 16 (51.6) | 8 (53.3) | 24 (52.2) |
| Total, n (%) | 31 (100.0) | 15 (100.0) | 46 (100.0) |
| **Cut off 1 cm** | | | |
| <1 | 20 (64.5) | 11 (73.3) | 31 (67.4) |
| 1 + | 11 (35.5) | 4 (26.7) | 15 (32.6) |
| Total, n (%) | 31 (100.0) | 15 (100.0) | 46 (100.0) |

AEH: atypical epithelial hyperplasia; RS: radial scar

## Discussion and Conclusion

Fenoglio and Lattes first described RS as "sclerosing papillary proliferation". In 1975 Hamperl et al. named it "Strahlige Narbenquot", translated as "radial scar" (9, 10). RS are usually incidental microscopic findings in excised breast tissue (11). In the present study, RS was not detected in 14 (58%) of 24 patients who underwent CNB, and these were found as incidental RS accompanying other BBL as a result of histopathological examination of excisional biopsies. Mammography was performed in 37 patients. RS was suspected on mammography images in only seven (18.9%) of these. King et al. (6) reported that only 19 of 45 cases were diagnosed by mammography, which is similar to our results.

RS is generally encountered in premenopausal women. This lesion is uncommon before 40 years old and after 60 years old (6, 12). The mean age in our series was 45.17±8.72 and around two thirds of the patients were premenopausal. Patients with RS routinely have non-palpable lesion. Egyed et al. (13) determined the rate of palpable RS lesions as 6.5%. Our cases were selected from excisional biopsy, which results in pure RS or accompanying BBL with RS. Our high rates of palpable lesions can be explained by the presence of other BBL such as fibroadenomas and papillomas with RS. The RS's precise incidence is unknown, but with the increasing use of MSP, RS is seen more often (2, 14).

In the present study, 54.3% of the patients were detected as a result of biopsies performed from suspicious lesions on mammography screening. In mammography, RS is defined as a central radiolucency, presence of multiple long and thin spicules, varying appearance in different projections, and radiolucent linear structures parallel to the spicules (15). The central areas contain fat and this fat appears as a "black star". A '"black star" aspect is typical of RS but it is not specific to RS (16). The varying appearances seen in different projections in mammography can be attributed to small invasive carcinoma seen simultaneously. This appears to be one reason for the confusion between small-sized breast carcinoma and RS (17). In a study, 52.8% of RS was presented as architectural distortion where 27.8% has spiculated opacity. In the same study, the frequency of microcalcification was reported as 19.4% (11). In another study 50% was detected as an architectural distortion, where calcifications were 29%, and masses made up 21% (3). The most common mammography finding we detected was microcalcifications in 51.3%. In 43.2% of our cases, spiculated lesions were detected, while opacity was the other common finding (29.7%). Opric et al. (12) reported that RS was seen more frequently in the glandular breast rather than lipomatous breast tissue. On histopathological examination, RS is morphologically similar to breast carcinoma, especially because of the creamy-yellow elastotic center which is common for both and fibroelastotic area with entrapped ducts. The ducts consist of dual epithelial and myoepithelial rows (12). This feature is one of the most significant similarities between RS and tubular carcinoma, which may often cause confusion during diagnosis (18). Cawson et al. (17) showed that the sensitivity rate of stereotactic biopsy was 85% while the sensitivity rate of ultrasound-guided core needle biopsy was 63% in a definitive diagnosis of RS/CSL (19).

RS/CSL can be single, multiple, or appear in clusters (5). In one study, a single lesion was detected with a frequency of 87%, while it was reported that 13.0% had two or more lesions (8). In our study, RS was solitary in 38 cases (82.6 %), while in eight cases (17.4%) there were multiple lesions. Five (10.8%) cases had pure RS/CSL. The average size as of RS has been reported as 1.01 cm and 1.42 cm (13, 20). In the present study, the average size of RS/CSL was 1.08 cm (0.2–3). Previous studies have suggested that malignancy occurs more frequently in larger and multiple RS (19, 20). Bacci et al. (1) reported that upgrade malignancy lesions were notably larger in size than non-upgraded lesions, but they could not define a statistically significant threshold. However, other studies have reported no relation between the size of the lesion and the risk of developing breast cancer (14). In the present study, there was no significant association between RS number and atypia. While AEH was seen in 37.5% of cases with multiple lesions, it was detected in 31.6% of cases with solitary lesions. We did not find a significant relationship between RS number and atypia. Also, there was no relation between RS size and atypia. When the cut-off value was taken as 1 cm for RS size, no statistically significant difference was found in terms of AEH detection rates. Similarly, when the RS dimension was evaluated as values below and above 5 mm, we did not find a statistically significant difference between the RS dimension and AEH. When age groups and presence of AEH were evaluated, although there were fewer cases with atypia in the 20–30 year-old age range, there was no statistically significant relationship between age groups and the presence of AEH. Similarly, in a study, when BBL cases with RS and high-risk lesions with RS were compared, the mean age was reported as 49 and 50 years, respectively (7).

RS/CSL may be found concurrently with a range of proliferative epithelial lesions, such as sclerosing adenosis and papillomas. Besides,

it may be associated with non-proliferative benign lesions, like simple cysts and fibroadenomas (21). In the present study, adenosis was the most common lesion accompanying RS/CSL (39.1%) while Opric et al. (12) found 23.1% adenosis in their study.

Jacobs et al. (19) suggested that RS was an independent risk factor for breast cancer. In contrast, Berg et al. (8) reported that RS was not an independent risk factor for cancer but that RS was associated with concomitant atypical hyperplasia. It is claimed that RS represents a natural pattern of carcinogenesis that starts from a proliferative lesion and then progresses to an atypical and then carcinomatous lesion (20). ADH is considered a marker for ductal carcinoma *in situ*, and invasive ductal carcinoma. In recent years, they have been found to be molecularly similar to each other. In studies, ADH is detected in 5–20% of all breast biopsies (22). Berg et al. (8) encountered atypia in proliferative lesions with RS more than proliferative lesions without RS. In one study, ADH or LCIS was observed in 15 of 164 patients with RS (14). Osborn et al. (23) reported that 18% of RSs were accompanied by atypia. In the present study, AEH was present in 15 cases (32.6%), while 12 patients had ADH, two had ALH, and one patient had both ADH and ALH. Although all our patients had benign lesions, the frequency of ADH accompanying RS was found to be significantly higher (32.6%). Recent studies have shown low upgrade to malignancy in RS without atypia. Therefore, it has recently been highlighted that radiological follow-up after CNB may be preferred to an excision in RS without atypia and malignancy (24-26). Some investigators have reported that excised RS/CSL was associated with atypical hyperplasia, *in situ* and invasive carcinoma on follow-up (14). Five of 149 patients who were followed for 68 months developed cancer according to the study of Bunting et al. (14). In comparison, in the pressent study, the mean of follow-up was 48 months, and none of the patients developed breast cancer by last follow-up.

In conclusion, 32.6% of the patients with RS had AEH. No correlation was found between the presence of atypia and RS size, number of RS, and patient age. Although all our patients had benign lesions, the incidence of AEH accompanying RS was higher than generally reported in the literature. This suggests that RS has a strong relationship with atypia. There is a consensus that surgical excision is required in the presence of atypia accompanying RS in CNB. However, cases without atypia are still clinically challenging. We believe that if RS patients without atypia are to followed up, it would be safer to follow up with core-needle biopsy, especially in specialized breast centers and with an emphasis on radiology-pathology cooperation.

**Ethics Committee Approval:** This study approved by the Institutional Review Board (IRB) of Istanbul University (approval date/number: 04.11.2022/1359568).

**Informed Consent:** Informed consent was obtained.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:**

Surgical and Medical Practices: M.M., M.T., A.I., V.O., N.C.; Concept: N.C., Z.T., M.M. A.I; Design: N.C., V.O., Z.T., S.E.; Data Collection and/or Processing: Z.T., E.S., E.O., B.E., Analysis and/or Interpretation: S.O., M.T., R.Y. E.O.; Literature Searc: E.S., Z.T., S.E., S.O.; Writing: Z.T., E.S., N.C., B.E., S.E.

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## References

1. Bacci J, MacGrogan G, Alran L, Labrot-Hurtevent G. Management of radial scars/complex sclerosing lesions of the breast diagnosed on vacuum-assisted large-core biopsy: is surgery always necessary? Histopathology 2019; 75: 900-915. (PMID: 31286532) [Crossref]
2. Trombadori CML, D'Angelo A, Ferrara F, Santoro A, Belli P, Manfredi R. Radial Scar: a management dilemma. Radiol Med 2021; 126: 774-775. (PMID: 33743143) [Crossref]
3. Linda A, Zuiani C, Furlan A, Londero V, Girometti R, Machin P, et al. Radial Scars Without Atypia Diagnosed at Imaging-Guided Needle Biopsy: How Often Is Associated Malignancy Found at Subsequent Surgical Excision, and Do Mammography and Sonography Predict Which Lesions Are Malignant? AJR Am J Roentgenol 2010; 194: 1146-1151. (PMID: 20308524) [Crossref]
4. Fasih T, Jain M, Shrimankar J, Staunton M, Hubbard J, Griffith CDM. All radial scars/complex sclerosing lesions seen on breast screening mammograms should be excised. Eur J Surg Oncol 2005; 31: 1125-1128. (PMID: 16024215) [Crossref]
5. Nassar A, Conners AL, Çelik B, Jenkins SM, Smith CY, Hieken TJ. Radial scar/comlex sclerosing lesions: a clinicopathologic correlation study from a single instution. Ann Diagn Pathol 2015; 19: 24-28. (PMID: 25578683) [Crossref]
6. King TA, Scharfenberg JC, Smetherman DH, Farkas EA, Bolton JS, Fuhrman GM. A Better Understanding of the Term Radial Scar. The American Journal of Surgery 2000; 180: 428-433. (PMID: 11182392) [Crossref]
7. Andacoğlu O, Shakir KA, Teh YC, Bonaventure M, Ozbek U, Anello M, et al. Rationale of Exicisional biopsy after the diagnosis of benign radial scar on core biopsy A single instituonal outcome analysis. Am J Clin Oncol 2013; 31: 7-11. (PMID: 22134516) [Crossref]
8. Berg JC, Visscher DW, Vierkant RA, Pankratz VS, Maloney SD, Lewis JT, et al. Breast cancer risk in women with radial scars in benign breast biopsies. Breast Cancer Res Treat 2008; 108: 167-174. (PMID: 18297395) [Crossref]
9. Fenoglio C, Lattes R. Sclerosing papillary proliferations in the female breast: A benign lesion often mistaken for carcinoma. Cancer 1974; 33: 691-700. (PMID: 4815573) [Crossref]
10. Hamprel H. Strahlige narben und obliterierende mastopathie. Beitrage zur pathologischen histologie der mamma. XI. Virchows Arch. Anat. Histopathol 1975; 369: 55-68. [Crossref]
11. Bianchi S, Giannotti E, Vanzi E, Marziali M, Abdulcabir D, Boeri C, et al. Radial scar without associated atypical epithelial proliferation on image- guided 14 gauge needle core biopsy: Analysis of 49 cases from a single- centre and review of the literature. Breast 2012; 21: 159-164. (PMID: 21944431) [Crossref]
12. Opric D, Fajdic J, Hrgovic Z, Granic M, Milosevic Z. Radial scar of the breast - a confusing lesion. Adv Med Sci 2007; 52: 257-261. (PMID: 18217429) [Crossref]
13. Egyed Z, Pentek Z, Jaray B, Kulka J, Svastics E, Kas J, et al. Radial scar-significant diagnostic challenge. Pathol Oncol Res 2008; 14: 123-129. (PMID: 18409019) [Crossref]
14. Bunting DM, Steel JR, Holgate CS, Watkins RM. Long term follow-up and risk of breast cancer after a radial scar or complex sclerosing lesion has been identified in a benign open breast biopsy. Eur J Surg Oncol 2011; 37: 709-713. (PMID: 21684716) [Crossref]
15. Tabar L, Dean PB. Stellate lesions. In: Tabar L, Dean PB, editors. Teaching atlas of mammography New York: Thieme Verlag;1985. p:87-136. [Crossref]

16. Alleva DQ, Smetherman DH, Farr GH Jr, Cederbom GJ. Radial scar of the breast: radiologic-pathologic correlation in 22 cases. Radiographics 1999; 19: S27-S35. (PMID: 10517441) [Crossref]

17. Cawson JN, Nickson C, Evans J, Kavanagh AM. Variation in mammographic appereance between projections of small breast cancers compared wiht radial scars. J Med Imaging and Radiation Oncology 2010; 54: 415-420. (PMID: 20958939) [Crossref]

18. Cohen MA, Newell MS. Radial Scars of the Breast Encountered at Core Biopsy: Review of Histologic, Imaging, and Management Considerations. AJR Am J Roentgenol 2017; 209: 1168-1177. (PMID: 28813198) [Crossref]

19. Jacobs TW, Byrne C, Colditz G, Connolly JL, Schnitt S. Radial Scars in Benign Breast-Biopsy Specimens and the Risk of Breast Cancer. N Engl J Med 1999; 340: 430-436. (PMID: 9971867) [Crossref]

20. Manfrin E, Remo A, Falsirollo F, Reghellin D, Bonetti F. Risk of neoplastic transformation in asymptomatic radial scar. Analysis of 117 cases. Breast Cancer Research and Treatment 2008; 107: 371-377. (PMID: 17457669) [Crossref]

21. Morgan C, Shah ZA, Hamilton R, Wang J, Spigel J, DeLeon W, et al. The radial scar of the breast diagnosed at core needle biopsy. Proc (Bayl Univ Med Cent) 2012; 25: 3-5. (PMID: 22275773) [Crossref]

22. Myers J, Walls AL. Atypical Breast Hiperplasia. In: Stat Pearls (internet) Treasure Island (FL): StatPearls Publishing; 2021. [Crossref]

23. Osborn G, Wilton F, Stevens G, Vaughan-Williams E, Gower-Thomes K. A review of needle core biopsy diagnosed radial scars in the Welsh Breast Screening Programme. Ann R Coll Surg Engl 2011; 93: 123-126. [Crossref]

24. Kalife ET, Lourence AP, Baird GL, Wang Y. Clinical and radiological follow-up study biopsy diagnosis of radial scar/radial sclerosin lesion without other atypia. Breast J 2016; 22: 1-8. (PMID: 27540716) [Crossref]

25. Donaldson AR, Sieck L, Booth CN, Calhoun BC. Radial scar diagnosed on breast core biopsy: Frequency of atypia and carcinoma on excision and implication for management. Breast 2016; 30: 201-207. (PMID: 27371970) [Crossref]

26. Kim EMH, Hanking A, Cassity J, McDonald D, White B, Rowberry R, et al. Isolaterd radial scar diagnosis by core- needle biopsy: Is surgical excision necesasary? Springerplus 2016; 5: 1-7. (PMID: 27047724) [Crossref]

Original Article

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# Nipple Sparing Goldilocks Mastectomy, A New Modification of the Original Technique

Ahmed Setit, Khaled Bela, Ashraf Khater, Islam Elzahaby, Amr Hossam, Emad Hamed
Department of Surgery, Oncology Center, Mansoura University Faculty of Medicine, Mansoura, Egypt

**ABSTRACT**

**Objective:** Although Goldilocks mastectomy offers good aesthetic outcomes. Removal of the nipple-areolar complex (NAC) often has a negative psychological impact. The objective of this study was to assess the feasibility and esthetic outcome of this technique with salvage of the NAC using a dermal pedicle.

**Materials and Methods:** The study included female patients suffering from breast carcinoma with large and or ptotic breast. Patients were offered Goldilocks mastectomy. Those who were unfit for anesthesia, those with locally advanced or metastatic disease or those refusing the procedure were excluded.

**Results:** Fifteen female patients (18 breasts) with a mean age of 51.6 years underwent Goldilocks breast reconstruction with a trial of NAC preservation. The mean body mass index was 39.1 kg/m2. More than half (56%) were cup C, while 44% were cup D. Seven cases (46.7%) showed grade II ptosis and 8 (53.3%) were grade III. The mean operative time was 168 minutes (range 130–240 minutes). NAC ischemic changes were noted in five cases; two (11%) were partial while three (17%) were total. Two cases (11%) suffered from flap loss and one of them was total. No locoregional recurrence or distant metastases were observed.

**Conclusion:** The Goldilocks mastectomy with nipple preservation is an appealing and feasible option for a certain group of patients who have large-sized and/or ptotic breasts. Nevertheless, it is a time-consuming technique with relatively higher rates of flap and NAC complications. Further, studies are required with a larger number of cases and longer follow-up.

**Keywords:** Goldilocks mastectomy, breast reconstruction, nipple areola complex

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**Key Points**

- Goldilocks mastectomy
- Breast reconstruction
- Nipple areola complex

## Introduction

Skin- and nipple-sparing mastectomies are challenging procedures, especially in large and ptotic breasted-women due to the resulting redundant skin flaps (1). The Goldilocks mastectomy was designed to make use of the redundant lower pole skin and subcutaneous fat to recreate a breast mound without a prosthetic implant or autologous tissue transfer. The main challenge for this technique was preservation of the nipple areolar complex (NAC) due to the relocated upper areolar border to the newly created inframammary crease and the placement of the lower areolar border under the upper pole which interferes with blood supply of the NAC (2). Although NAC preservation was described with Goldilocks mastectomy in the form of skin graft with success (3, 4), NAC sparing is still questionable. To the best of our knowledge, there are few studies investigating the possibility of NAC preservation with Goldilocks mastectomy (5). This work was designed to evaluate the feasibility of NAC sparing during the Goldilocks mastectomy.

## Materials and Methods

### Patients

The study was conducted in the period from February 2019 to February 2022. Fifteen consecutive patients with breast carcinoma who were offered Goldilocks mastectomy were included in the study. Patients with large-sized and or ptotic breasts who were not candidates for breast conserving surgery (BCS) were included. Patients who

Corresponding Author:
Ashraf Khater; dr.ashrafkhater@yahoo.com

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refused the procedure or those with history of breast surgery that might interfere with vascularity of the skin flaps were excluded. All patients were diagnosed through the symptomatic and screening service in the oncology institute. All patients were informed about the expected advantages and risks of the procedure, with the possibility of nipple necrosis and written consents were obtained. The study obtained the required approval from the local ethical committee.

**Surgical technique**

Preoperative marking was performed in the standing position using a Wise pattern (Figure 1A). The NAC was reduced to a 42-mm diameter and left intact as the keyhole pattern is de-epithelialized (Figure 1A). When creating the circum-areolar incision, we took great care in order not to divide the thicker fibrous dermal layer with a full-thickness incision to protect the subdermal vascular plexus. De-epithelization and tissue dissection was done using tumescent infiltration and scissor dissection (Figure 1B). The tumescent fluid was a mixture of lidocaine 2% in a total maximum dose of 20 mg/kg, adrenaline in a dose of 2 mg 1/1.000, sodium bicarbonate which is diluted in saline then injected at the subdermal and subcutaneous tissue till it becomes tense, edematous, and swollen to facilitate the de-epithelialization process. The standard mastectomy flap was created via the lateral pillar of the keyhole pattern (Figure 2A). The plane was created at the gross interface of the parenchyma and subdermal fat by infiltration of tumescent fluid with delicate scissor dissection, avoiding injury of the subdermal vascular plexus (Figure 2B). The breast was elevated from the chest wall and sent for pathological evaluation. The skin flaps represent the entire skin envelop of the breast with the de-epithelialized keyhole portion containing the NAC. When necessary, sentinel lymph node biopsy and/or axillary dissection was carried out through the same incisions. Once the supply of the most distal portion of the flaps and NAC was adequate (Figure 3A). The NAC was transposed to the previously marked position with tailoring sutures while the medial and lateral vertical limbs of the keyhole were approximated (Figure 3B). The de-epithelialized fasciocutaneous flaps were folded to provide volume. Adjustments were made with the patient in the

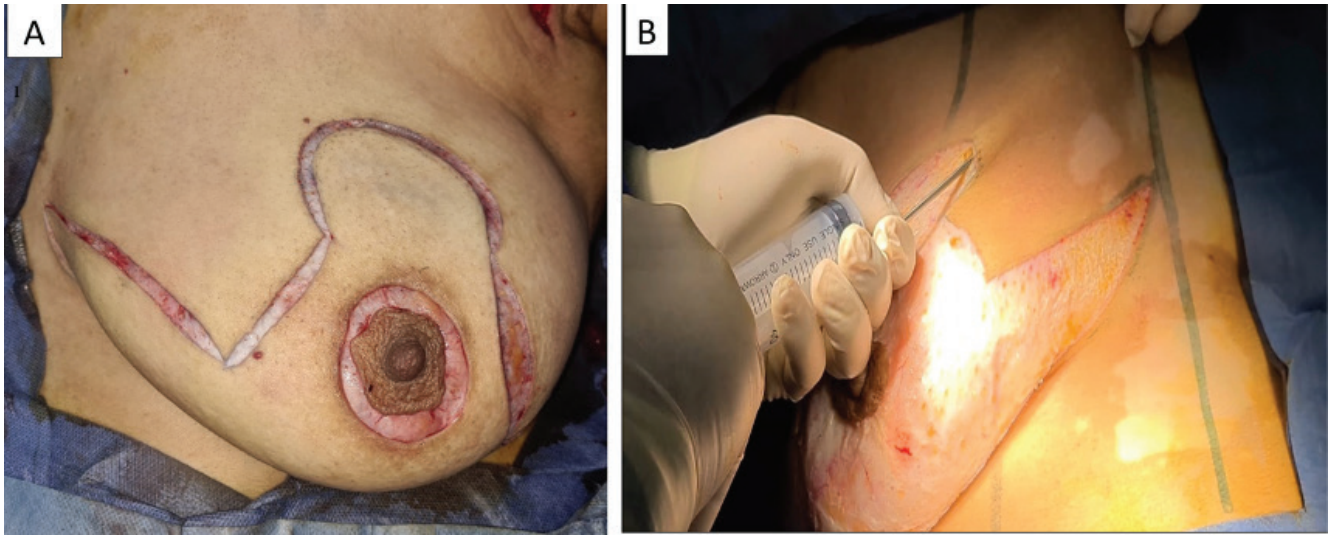


**Figure 1.** A. Intraoperative: marking the wise pattern + circum-areolar incision. B. Subcutaneous tumescent fluid infiltration

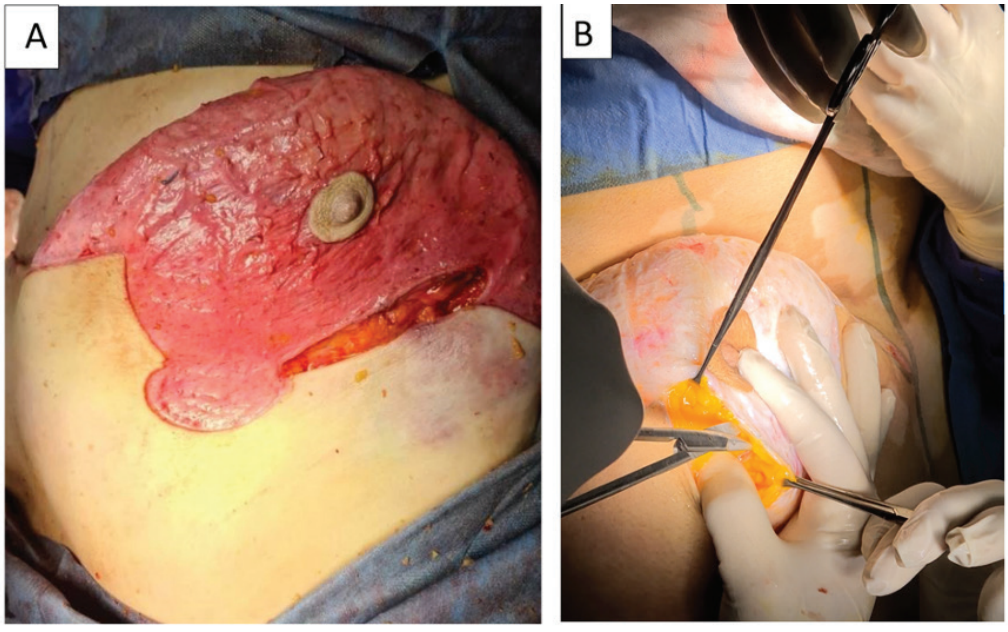


**Figure 2.** A. Mastectomy via lateral pillar of keyhole pattern. B. Scissor dissection through mastectomy flap plane

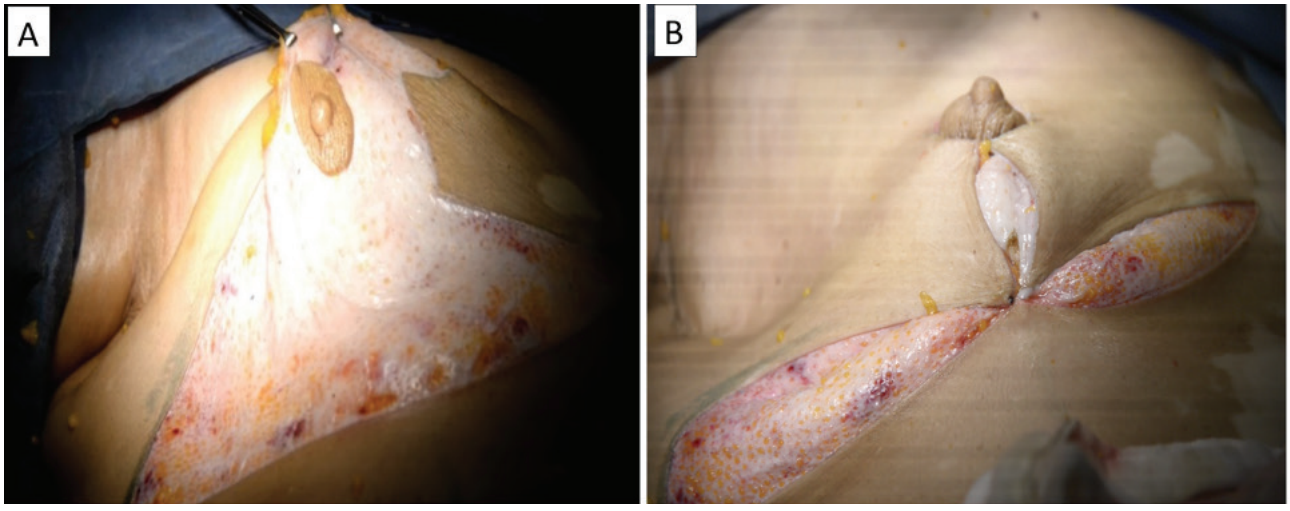


**Figure 3.** A. The de-epithelialized keyhole containing NAC. B. Closure of the upper envelope over the lower de-epithelialized dermal flap

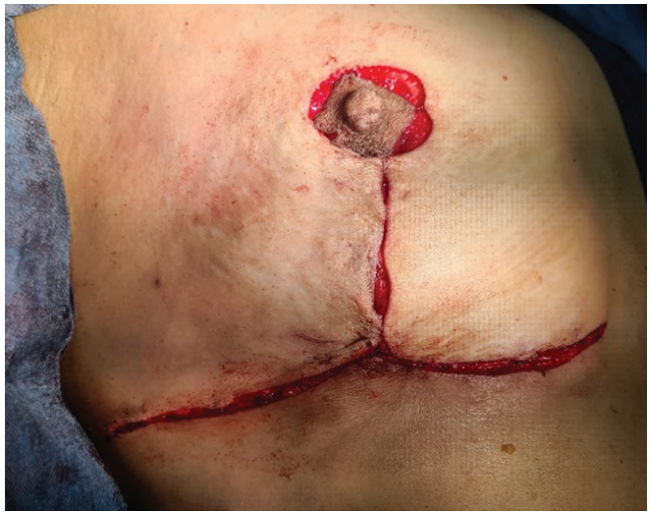

**Figure 4.** Inverted T shape closure with the patient in sitting position

sitting position. When the configuration was satisfactory, the tailoring sutures were removed, drains were placed, and the dermal closure was accomplished (Figure 4).

### Follow-up

The follow-up schedule was weekly in the first month, then every three months after that for 15 months. Patients were assessed physically to detect early postoperative complications, including infection, hematoma, seroma, wound problems, flap loss and NAC congestion or ischemia. The aesthetic outcome was assessed by independent surgeons during the postoperative follow-up and images were judged by a panel of three surgeons. The aesthetic results were estimated on a 5-points scale (excellent: 5, good: 4, fair: 3, poor: 2, bad: 1) depending on multiple parameters, including volume symmetry, shape of breast mound, symmetry of NAC and post-irradiation changes. Delay in adjuvant therapy, local recurrence or distant metastasis were recorded.

## Results

Between February 2020 and February 2022, a total of 15 female patients (18 breasts) with breast cancer with large sized and or ptosed breasts were offered Goldilocks mastectomy with nipple preservation. Three cases went for bilateral nipple sparing goldilocks mastectomy. Median follow-up was 15 months (range 3–24 months). Table 1 shows patient and tumor characteristics. The mean age was 51.6 years old (range 33 to 70 years; Table 1). The mean body mass index (BMI) was 39.1 kg/m$^2$. Five patients were recorded with medical co-morbidities (three were diabetic and hypertensive). Four patients had a history of neoadjuvant therapy and 11 patients proceeded for upfront surgery. Eight patients received adjuvant radiotherapy. Table 2 shows the operative details. The mean operative time was 168 minutes (ranging from 130 to 240 minutes). The mean estimated blood loss was 110 cc (50–250 cc) with no intraoperative blood transfusion. Regarding complications (Table 3), two cases (11%) suffered from wound gaping, neither of whom was diabetic. Both were managed by refashioning and closure under local anesthesia. NAC ischemic changes occurred in five cases; two (11%) were managed by medical treatment and frequent dressing using heparin-soaked gauze, and they completely recovered. However, three cases (17%) suffered from total NAC loss and underwent NAC amputation. Two cases (11%) suffered from flap loss. One of them exhibited total flap loss, and it was managed by flap amputation and immediate closure under general anesthesia. The other case showed partial flap loss and underwent debridement and closure (Figure 5). Seroma developed in one case (5.5%), and this was managed by tube drain insertion under local anesthesia, as aspiration by wide pore needle failed to control the condition. One case (5.5%) suffered from superficial skin necrosis, and this was managed by topical ointments, dressing and medications until complete resolution. No cases suffered from fat necrosis during the follow-up period.

### Esthetic Outcome

Seven (40%) patients were scored as excellent, four (22%) as good, and three (16%) as satisfactory. Two patients (11%) were scored as poor and other two (11%) as very poor (Table 4).

### Oncologic Outcome

There was a median follow-up period of 15 (1–24) months, during which no loco-regional recurrences or distant metastasis were recorded.

## Discussion and Conclusion

The Goldilocks procedure has increased in popularity since its original description in 2012 as an alternative for immediate breast reconstruction, particularly for obese women who are not candidates for traditional prosthetic or autologous reconstruction (1, 4). The aim

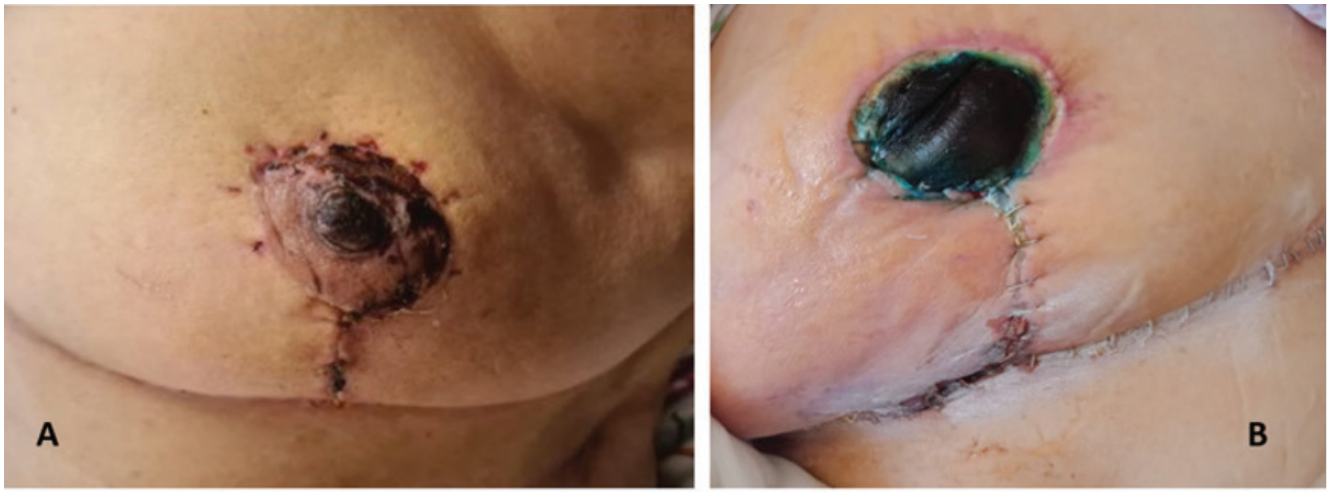


**Figure 5.** NAC necrosis; A partial, B: complete

Table 1. Patients and tumor characteristics

| Item | Number (percentage)/mean (range) |
|---|---|
| Mean age (range) | 51.6±0.5 (33–70) |
| Body mass index (BMI) | 39.1±0.75 (31–46) |
| Smoking history | 0 |
| Diabetes | 3 (20%) |
| Hypertension | 3 (20%) |
| Cup size | |
| Cup C | 56% |
| Cup D | 44% |
| Degree of Ptosis | |
| Grade 2 | 7 (46.7%) |
| Grade 3 | 8 (53.3%) |
| Neoadjuvant chemotherapy | 4 (26.7%) |
| Adjuvant radiotherapy | 8 (53.3%) |
| Tumor Histology | |
| Invasive duct carcinoma (IDC) | 9 cases (50%) |
| Invasive lobular carcinoma | 6 cases (%33) |
| Invasive cribriform carcinoma | 1 case (6%) |
| Ductal carcinoma *in situ* | 2 cases (11%). |
| Luminal Type | |
| Luminal A | 10 (56%) |
| Luminal B | 8 (44%) |
| Triple Negative | 0 |
| Stage* | |
| 0 | 2 (11%) |
| IA | 2 (11%) |
| IIA | 4 (22%) |
| IIB | 5 (28%) |
| IIIA | 2 (11%) |
| IIIB | 1 (6%) |
| IIIC | 2 (11%) |
| Follow-up period | 15 months (1–24) |

* According AJCC pathological staging the highest percentage of cases 28% was with stage IIB

Table 2. Operative details

| Item | Number (percentage)/ mean (range) |
|---|---|
| Mean operative time | 168 minutes (130 to 240 minutes) |
| Mean estimated blood loss | 110 mL (50–250 mL) |
| mean weight of the excised breast tissue (including the tumor) | 1110 grams (760–1550 grams) |
| Mean gross tumor size | 5.7 cm (2–12 cm) |

Table 3. Post-operative complications

| Complication | Total number | Percentage |
|---|---|---|
| Wound gap | 2 | 11% |
| Seroma | 1 | 5.5% |
| NAC ischemic changes | | |
| Partial loss | 2 | (11%) |
| Total loss (with subsequent amputation) | 3 | (17%) |
| Flap loss | | |
| Partial loss | 1 | (5.6%) |
| Total loss | 1 | (5.6%) |
| Superficial skin necrosis | 1 | 5.5% |

of this technique was to reconstruct a breast mound exclusively from the cutaneous mastectomy flap tissue. To achieve a more aesthetically acceptable result, certain modifications have been made, such as free nipple grafting, simultaneous addition of the LICAP perforator flap, usage of this technique as a bridge for implant-based breast reconstruction or fat grafting (5, 6). In 2018, Richardson and Aronowitz (5) published a case report for bilateral Goldilocks mastectomy with *in situ* NAC preservation using a dermal pedicled flap. To our knowledge,

Table 4. Cosmetic outcome evaluation

| Score | Number | Percent |
|---|---|---|
| 1 Very poor | 2 | 11% |
| 2 Poor | 2 | 11% |
| 3 Satisfactory | 3 | 16% |
| 4 Good | 4 | 22% |
| 5 Excellent | 7 | 40% |
| Total | 18 | 100 |

this is the first case series in which the Goldilocks technique has been utilized for autologous reconstruction with *in situ* NAC preservation. Fifteen patients (18 breasts) with large-sized (CUP C and D) ptotic breasts who were not eligible for or refused BCS and other oncoplastic techniques. Counselling about a contralateral procedure to improve the overall symmetry was performed. Three cases underwent contralateral inferior pedicled reduction. One case underwent a modified radical mastectomy 15 years previously without reconstruction. Three cases went for bilateral, nipple-sparing Goldilocks mastectomy and eight cases refused contralateral symmetrization (7). Our BMI is relatively higher than the study of Heather Richardson in 2012 (sample of 32 women with a mean BMI 30.3 kg/m$^2$ and range 18–51.9 kg/m$^2$ (4). The mean age was 51.6 years with a range of 33–70 years. The older patients had greater appreciation for this technique, and they were satisfied with the outcome (8). One third of our patients had comorbidities, like hypertension and diabetes. In other studies, this ratio was 50% (9). The mean operative time was 168 minutes ranging for 120–240 minutes, which is longer than the initial technique of Goldilocks (its mean operative time was 120 minutes). This may be due to the time taken for NAC preservation. Regarding complications, two cases (11%) suffered from wound gaping, and they were managed by refashioning and suturing under local anesthesia. There was one case of seroma, which was managed by insertion of a tube drain under local anesthesia when frequent aspiration failed to resolve the condition. There were no cases of hematoma. One of the most important advantages of this technique is preservation and maintenance of nipple protrusion, which is lost in most cases with nipple grafting which may also suffer from hypopigmentation (9). NAC ischemic changes was noted in five cases; two (11%) were managed by medical treatment and frequent dressing using heparin-soaked gauze, and both totally improved. In three cases (17%), there was a NAC loss, and they underwent NAC amputation. Two cases (11%) suffered from flap loss, one of them was total, and it was managed by flap amputation and primary closure while the other was partial, and it underwent debridement and refashioning. One case (5.5%) suffered from superficial skin necrosis and infection, and it was managed by local ointments, dressing and medical treatment till complete resolution. No cases suffered from fat necrosis during the follow-up period. This matches with most of the complication rates in the literature; Davies et al. (10) reported a rate of 17.2% major complications, 23%minor and 61% of patients who had no complications. In our study, we faced the primary disadvantage of Goldilocks procedure, which was the limited window for glandular resection. This problem was solved by glandular resection from both pillars of the skin flaps.

The Goldilocks mastectomy with nipple preservation is an appealing and feasible option for a certain group of patients who have large-sized and/or ptotic breasts. Nevertheless, it is a time-consuming technique with relatively higher rates of flap and NAC complications. Further, studies are required with a larger number of cases and longer follow-up.

**Ethics Committee Approval:** The study obtained the required approval from the local ethical committee (Medical Research Ethics Committee Institutional Review Board – approval number: MS.20.10.11, date: 05.01.2021).

**Informed Consent:** Written consents were obtained.

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### Authorship Contributions

Surgical and Medical Practices: A.S., K.B., A.K., I.E., A.H., E.H.; Concept: A.S., K.B.; Design: A.S., A.K.; Data Collection or Processing: A.S., K.B., A.K.; Analysis or Interpretation: A.S., K.B., A.K.; Literature Search: A.S., K.B., A.K., A.H.; Writing: A.S., K.B., A.K., I.E., A.H., E.H.

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## References

1. Zavala KJ, Kwon JG, Han HH, Kim EK, Eom JS. The Goldilocks technique: An alternative method to construct a breast mound after prosthetic breast reconstruction failure. Arch Plast Surg 2019; 46: 475-479. (PMID: 31042862) [Crossref]
2. Oliver JD, Chaudhry A, Vyas KS, Manrique OJ, Martinez-Jorge J. Aesthetic Goldilocks mastectomy and breast reconstruction: promoting its use in the ideal candidate. Gland Surg 2018; 7: 493-495. (PMID: 30505771) [Crossref]
3. Chaudhry A, Oliver JD, Vyas KS, Alsubaie SA, Manrique OJ, Martinez-Jorge J. Outcomes analysis of Goldilocks mastectomy and breast reconstruction: A single institution experience of 96 cases. J Surg Oncol 2019; 119: 1047-1052. (PMID: 30950070) [Crossref]
4. Richardson H, Ma G. The Goldilocks mastectomy. Int J Surg 2012; 10: 522-526. (PMID: 22892093) [Crossref]
5. Richardson H, Aronowitz JA. Goldilocks Mastectomy with Bilateral In Situ Nipple Preservation Via Dermal Pedicle. Plast Reconstr Surg Glob Open 2018; 6: e1748. (PMID: 29876184) [Crossref]
6. De Biasio F, Zingaretti N, Mura S, Fin A, Riccio M, Parodi PC. A new method of salvaging nipple projection after secondary nipple reconstruction using locoregional flap. Indian J Plast Surg 2017; 50: 107-108. (PMID: 28615822) [Crossref]
7. Schwartz Jean-Claude D, Skowronski Piotr P. Total single-stage autologous breast reconstruction with free nipple grafts. Plast Reconstr Surg 2015; 3: e587. (PMID: 26894012) [Crossref]
8. Zeeneldin AA, Ramadan M, Gaber AA, Taha FM. Clinico-pathological features of breast carcinoma in elderly Egyptian patients: a comparison with the non-elderly using population-based data. J Egypt Natl Canc Inst 2013; 25: 5-11. (PMID: 23499201) [Crossref]
9. Manrique OJ, Kuruoglu D, Yan M, Bustos SS, Boughey JC, Harless CA, et al. Immediate Breast Reconstruction Using the Goldilocks Procedure: A Balance between More Surgery and Patient Satisfaction. Plast Reconstr Surg 2022; 149: 801-809. (PMID: 35103645) [Crossref]
10. Davies K, Allan L, Roblin P, Ross D, Farhadi J. Factors affecting post-operative complications following skin sparing mastectomy with immediate breast reconstruction. Breast 2011; 20: 21-25. (PMID: 20619645) [Crossref]

**Original Article**

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# Impact of COVID-19 on Breast Cancer Management in a Multiethnic Middle-Income Asian Country Setting

Ng Jing Hui[1], See Mee Hoong[2], Tneoh Jia Min[2], Teh Mei Sze[2], Mahmoud Danaee[3], Nur Shahirah Abdul Latiff[1], Abigail Ashwini Murali[1], Lee Lee Lai[4]

[1]Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
[2]Breast Surgery Unit, Department of Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
[3]Centre for Epidemiology and Evidence-Based Practice, Department of Social and Preventive Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
[4]Nursing Science Department, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

**ABSTRACT**

**Objective:** Coronavirus disease-2019 (COVID-19) has caused hospitals to suspend routine procedures. As the world recovers, there is concern that the outcome of many diseases has been impaired. This study aimed to assess the impact of the pandemic on breast cancer demography, clinicopathological characteristics and patient management at a teaching hospital in Kuala Lumpur, Malaysia.

**Materials and Methods:** Pre-COVID data were collected between January 1, 2019, to March 18, 2020, when a national lockdown was implemented, which caused the suspension of services at the breast clinic of University Malaya Medical Centre (UMMC). COVID data was obtained from March 2020 until June 2021.

**Results:** This study compared 374 breast cancer patients in the COVID-19 period with 382 patients in the pre-COVID period. There was no significant difference in the median (range) time to surgery between pre-COVID [45 (26.50–153.50) days] and COVID [44 (24.75–156.25) days] periods. The clinicopathological features of breast cancer showed reduction in *in situ* carcinoma and increase in Stage 4 diagnoses during the COVID period. There was a reduction in screening-detected carcinoma (9% vs. 12.3%), mastectomy followed by immediate reconstruction (5.6% vs. 14.5%) and adjuvant chemotherapy (25.8% vs. 32.9%) in the COVID period.

**Conclusion:** In this center COVID-19 caused operational changes in breast cancer management, including a reduction in reconstructive procedures and adjuvant treatment. Healthcare disruption and fear of COVID may have caused delayed diagnosis, resulting in a higher frequency of Stage 4 disease and lower proportion of *in situ* carcinoma during the pandemic. However, there was no delay in the time to surgery, reduction in surgical volume, or change in surgery types.

**Keywords:** Breast neoplasm; pandemic; therapeutic; patient

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**Key Points**

- COVID-19 had caused operational changes on breast cancer management especially in low and middle-income countries.
- We have found higher proportion of advanced breast cancer during COVID pandemic.
- However, there was no delay in duration of diagnosis to time of surgery, surgical volume and surgery types.

## Introduction

The rapid spread of Coronavirus disease-2019 (COVID-19) worldwide led to an unprecedented strain on healthcare services (1, 2). Malaysia recorded its first case among tourists on Jan 24, 2020, and thereafter, the disease began spreading rapidly among the local population (3). Subsequently, the government was forced to implement a lockdown, known as the Movement Control Order (MCO), on March 18, which restricted the movement and social life of citizens, caused non-essential businesses to close and suspended the operations of various services to mitigate the spread of COVID-19 (4). In the medical setting, healthcare operations were reviewed, and treatment was provided only to patients in urgent need of life-saving procedures (5). All non-urgent services, such as breast cancer screening and routine outpatient

**Corresponding Author:**
**See Mee Hoong; meehoong@ummc.edu.my**

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clinics, were suspended to minimize the risk of community-based transmission and prioritize manpower for COVID care. In light of this, the mortality risk and disease severity at presentation of breast cancer patients may have been affected, since the prolonged time to diagnosis and to treatment initiation may have negatively impacted outcome (6).

The objective of this study was to evaluate whether restrictions imposed because of COVID-19 affected the surgical operations and outcome of breast cancer management at the University Malaya Medical Centre, which is a primary teaching hospital serving a suburban population in the Malaysian capital of Kuala Lumpur. The study reviewed the institution's primary treatments, surgical services and adjuvant therapy administration. In addition, the impact on initial presentation and clinicopathological characteristics of breast cancer were also investigated.

## Materials and Methods

### Study Populations and Patient Selection

This retrospective study was conducted between Jan 1, 2019, to March 18, 2020 (defined as the pre-COVID period), and from March 19, 2020, to December 31, 2021 (defined as COVID period) in University Malaya Medical Centre (UMMC). Electronic data records of all patients who were diagnosed in their first consultation at the institution during the study period were reviewed. In view of its retrospective nature, patients' consent was not deemed necessary for this study.

Patients who had confirmed breast carcinoma of any histological type were included. Exclusion criteria comprised those with recurrence or relapse, those who presented with benign lumps, and those who had undergone breast surgery prior to the defined periods. Timeline to surgery was defined by the number of days from the date of diagnosis to date of surgery. Types of surgery undertaken were modified radical mastectomy, simple mastectomy, breast-conserving surgery and mastectomy with reconstruction. For all the reconstructive cases included in this study, immediate reconstruction was carried out in conjunction with mastectomy in a single session.

Breast cancer staging was performed according to the 7$^{th}$ Edition of the tumour-lymph node-metastasis system (TNM classification) by the American Joint Committee on Cancer and the Union for International Cancer Control (7). However, phyllodes tumours were not graded using the TNM classification. Radiotherapy, antihormonal therapy, targeted therapy, and chemotherapy were classified as adjuvant and/or neoadjuvant therapy.

Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) positivity were determined through immunohistochemical staining. Sectioned patient biopsies on slides with >1% of tumour cells demonstrating ER nuclear staining were considered ER positive. For PR status, biopsy slides with >1% of tumour cells demonstrating PR nuclear staining were considered PR positive. If the HER/neu score was 2+, the HER-2 status was equivocal and required further testing with silver *in situ* hybridisation (SISH). HER-2 positive samples were defined as a HER/neu score of 3+ and positive SISH test, whereas HER-2 negative was defined as a score of 0 or 1+ and negative SISH test.

### Statistical Analysis

Demographic data, clinical characteristics and treatment administration in pre-COVID and COVID period patients were compared using a chi-square test for categorical data. For continuous variable analysis, normality was assessed using Kolmogorov-Smirnov test. The non-parametric continuous variables were analyzed using Mann-Whitney U tests. All analyses were performed using IBM SPSS, version 24 (IBM Corp, Armonk, NY, USA).

## Results

The study compared 374 breast cancer patients during the COVID-19 pandemic period with 382 patients during the pre-COVID period, each period spanning nine months. In the pre-COVID period, eight (2.1%) patients had bilateral breast cancer, while in the COVID period, 13 (3.5%) patients had bilateral breast cancer, resulting in a total of 398 and 387 breast cancer cases in the pre-COVID and COVID periods respectively. All patients were female, with a median age of 60 years in both groups, with a range of 51.75–70 years in the pre-COVID group and 51–69 years in the COVID group. The majority of patients comprised those of Chinese ethnicity, which made up almost half of the study population in both periods as shown in Table 1. Malays made up almost one-third of patients, followed

Table 1. Patient demographic features

| | Time period n (%) | | *p*- value | chi-square value |
|---|---|---|---|---|
| | **Pre-COVID n (%)** | **COVID n (%)** | | |
| Age, years | n = 382 | n = 374 | 0.934 | 0.832 |
| <40 | 19 (5.0) | 23 (6.1) | | |
| 40–49 | 57 (14.9) | 57 (15.2) | | |
| 50–59 | 108 (28.3) | 102 (27.3) | | |
| 60–69 | 101 (26.4) | 103 (27.5) | | |
| >70 | 97 (25.4) | 89 (23.8) | | |
| **Ethnicity** | | | **0.661** | **1.594** |
| Chinese | 190 (49.7) | 182 (48.7) | | |
| Malay | 117 (30.6) | 117 (31.3) | | |
| Indian | 68 (17.8) | 63 (16.8) | | |
| Others | 7 (1.8) | 12 (3.2) | | |
| **Nationality** | | | **0.203** | **5.945** |
| Malaysian | 376 (98.4) | 363 (97.1) | | |
| Singaporean | 1 (0.3) | 0 (0) | | |
| Indonesian | 4 (1.0) | 4 (1.1) | | |
| Filipino | 1 (0.3) | 4 (1.1) | | |
| Others | 0 (0) | 3 (0.8) | | |
| **Marital status** | | | **0.993** | **0.001** |
| Yes | 338 (88.5) | 331 (88.5) | | |
| No | 44 (11.5) | 43 (11.5) | | |

COVID: coronavirus

by Indians (around 18%) and other ethnicities (<4%). Being a government hospital, almost all patients were of Malaysian nationality (>97%), but there was a small proportion of Filipinos, Indonesians and Singaporeans (together <2%). There were no significant differences in age of diagnosis, ethnicity, nationality and marital status between pre-COVID and COVID period.

Screening-detected cases accounted for 9% of diagnoses in the COVID period, compared to 12.3% in the pre-COVID period, whereas symptomatic cases were slightly more frequent in the COVID period (91% vs. 87.7%) as shown in Table 2. The clinicopathological features of breast cancer cases, such as tumor type, grade, stage, hormone receptor (ER/PR) and HER-2 status, were similar in both groups, except for a reduction in *in situ* carcinoma and an increase in Stage 4 diagnoses during the COVID period in accordance with Table 2. Invasive ductal carcinoma was the most common tumor detected in both periods (>75%), followed by ductal carcinoma *in situ* (11–13%) and other tumor types (around 5%). Invasive lobular carcinoma (2–5%) and malignant phyllodes (<1%) were in the minority of tumor types detected in both periods. In line with the type of tumor detected, the tumor grade of patients also seemed to be quite advanced, with most having Grade 2, followed by Grade 3 disease. Grade 1 tumors made up approximately 13% of patients in both periods. The tumour type and grading results were similarly reflected in the cancer and clinical T staging, where non-invasive stage 0 and Tis patients comprised fewer than 13% in the pre-COVID period and fewer than 10% in COVID period. Most patients presented in Stage 2 or T2 of the disease. In terminal cases, there seemed to be more patients either in Stage 3 or T4. There was also a higher number of ER and PR positive patients, although the differences were not significant. However, the opposite was true for HER-2 positivity.

The median time from tumor diagnosis to surgery was 45 days (range 24.75–156.25 days) during the pandemic and 44 days (range 26.5–153.5 days) in the pre-COVID period. Interestingly, the time was not significantly different between the periods (p = 0.958).

In terms of management, most patients received upfront surgery as the primary treatment, followed by neoadjuvant systemic therapy and palliative treatment, with no significant difference between the pre-COVID and COVID as listed in Table 2. The type of surgery performed was significantly different ($p$ = 0.002), in which there is a significant reduction in the mastectomy rate followed by immediate reconstruction (5.6% vs. 14.5%) in the COVID period. However, the numbers receiving breast-conserving surgery and simple or modified radical mastectomy performed were identical in both groups. The number of patients receiving adjuvant and palliative chemotherapy was also significantly different ($p$ = 0.026). Patients who were given such treatment were more likely during the pre-COVID than the COVID period (131 vs. 103). The total number of patients who were not prescribed such treatment was higher in COVID compared with pre-COVID period (297 vs. 267). This was inevitable as chemotherapy was considered a routine clinical service and this would definitely be limited during the pandemic. There were also no significant changes in the rates of radiotherapy, hormonal therapy, targeted therapy, and axillary surgery. Furthermore, the positivity rate and pathological grouping of lymph nodes did not show significant changes between the two group. A total of 10 patients were diagnosed with COVID-19 and two succumbed to the disease. The median time from tumor diagnosis to surgery was 45 days (range 24.75–156.25 days) during the pandemic and 44 days (range 26.5–153.5days) in the pre-COVID

Table 2. Patient clinical pathological characteristics and management

| | Time period n (%) | | *p*- value | chi-square value |
|---|---|---|---|---|
| | **Pre-COVID n (%)** | **COVID n (%)** | | |
| Mode of detection | n = 398 | n = 400 | 0.129 | 2.299 |
| Screening detected | 49 (12.3) | 36 (9.0) | | |
| Symptomatic | 349 (87.7) | 364 (91.0) | | |
| **Tumour type** | | | **0.151** | **6.733** |
| Ductal carcinoma *in situ* | 54 (13.6) | 44 (11.0) | | |
| Invasive ductal carcinoma | 310 (77.9) | 303 (75.8) | | |
| Invasive lobular carcinoma | 9 (2.3) | 19 (4.8) | | |
| Phyllodes (malignant) | 4 (1.0) | 3 (0.8) | | |
| Others | 21 (5.3) | 31 (7.8) | | |
| **Tumour grade** | | | **0.281** | **2.540** |
| Grade 1 | 53 (13.5) | 47 (12.1) | | |
| Grade 2 | 197 (50.1) | 216 (55.8) | | |
| Grade 3 | 143 (36.4) | 124 (32.0) | | |
| **Breast cancer staging** | | | **0.120** | **7.308** |
| Stage 0 | 49 (12.3) | 39 (9.8) | | |
| Stage 1 | 75 (18.8) | 70 (17.5) | | |
| Stage 2 | 125 (31.4) | 147 (36.8) | | |
| Stage 3 | 101 (25.4) | 81 (20.3) | | |
| Stage 4 | 48 (12.1) | 63 (15.8) | | |
| **Clinical T** | | | **0.321** | **4.686** |
| Tis | 42 (10.6) | 34 (8.5) | | |
| T1 | 72 (18.1) | 93 (23.3) | | |
| T2 | 157 (39.4) | 141 (35.3) | | |
| T3 | 37 (9.3) | 35 (8.8) | | |
| T4 | 90 (22.6) | 97 (24.3) | | |
| **Clinical N** | | | **0.596** | **0.282** |
| N0 | 253 (63.6) | 247 (61.8) | | |
| N1-N3 | 145 (36.4) | 153 (38.3) | | |
| **Clinical M** | | | **0.132** | **2.268** |
| M0 | 350 (87.9) | 337 (84.3) | | |
| M1 | 48 (12.1) | 63 (15.8) | | |
| **ER status** | | | **0.838** | **0.042** |
| Positive | 297 (74.6) | 301 (75.3) | | |

| Table 2. Continued | | | | |
|---|---|---|---|---|
| Negative | 101 (25.4) | 99 (24.8) | | |
| **PR status** | | | **0.335** | **0.930** |
| Positive | 250 (64.8) | 264 (68.0) | | |
| Negative | 136 (35.2) | 124 (32.0) | | |
| **Her-2 status** | | | **0.540** | **0.375** |
| Positive | 85 (21.2) | 77 (23.8) | | |
| Negative | 243 (61.1) | 246 (76.3) | | |
| **Primary treatment** | | | **0.404** | **2.924** |
| Upfront surgery | 218 (54.8) | 206 (51.5) | | |
| Neoadjuvant systemic therapy | 86 (21.6) | 90 (22.5) | | |
| Palliative | 70 (17.6) | 86 (21.5) | | |
| **Types of breast cancersurgery** | | | **0.002*** | **12.816** |
| Breast conserving surgery | 75 (24.8) | 78 (27.3) | | |
| Simple mastectomy/ modifiedradical mastectomy | 184 (60.7) | 192 (67.1) | | |
| Mastectomy + reconstruction | 44 (14.5) | 16 (5.6) | | |
| **Neoadjuvant chemotherapy** | | | **0.961** | **0.002** |
| Yes | 86 (21.6) | 87 (21.8) | | |
| No | 312 (78.4) | 313 (78.3) | | |
| **Chemotherapy (adjuvant & palliative)** | | | **0.026*** | **4.941** |
| Yes | 131 (32.9) | 103 (25.8) | | |
| No | 267 (67.1) | 297 (74.3) | | |
| **Radiotherapy** | | | **0.346** | **4.473** |
| Adjuvant radiotherapy | 147 (36.9) | 145 (36.3) | | |
| IORT | 8 (2.0) | 9 (2.3) | | |
| Palliative radiotherapy | 10 (2.5) | 3 (0.8) | | |
| IORT + ERBT | 7 (1.8) | 10 (2.5) | | |
| No | 226 (56.9) | 233 (58.3) | | |
| **Hormonal therapy** | | | **0.701** | **0.147** |
| Yes | 251 (63.1) | 247 (61.8) | | |
| No | 147 (36.9) | 153 (38.3) | | |
| **Targeted therapy** | | | **0.531** | **0.393** |
| Yes | 45 (11.3) | 51 (12.8) | | |
| No | 353 (88.7) | 349 (87.3) | | |
| **Axillary surgery** | | | **0.214** | **3.087** |
| SLNB | 145 (52.3) | 138 (52.1) | | |
| Axillary dissection | 130 (46.9) | 120 (45.3) | | |
| SLNB to axillary dissection | 2 (0.7) | 7 (2.6) | | |
| **LN positivity** | | | **0.266** | **1.239** |
| Yes (N1-N3) | 105 (37.8) | 89 (33.2) | | |
| No (N0) | 173 (62.2) | 179 (66.8) | | |
| **Pathological LN** | | | **0.371** | **3.139** |
| N0 | 173 (62.2) | 179 (66.8) | | |
| N1 | 62 (22.3) | 54 (20.1) | | |
| N2 | 27 (9.7) | 27 (10.1) | | |
| N3 | 16 (5.8) | 8 (3.0) | | |
| **SLNB positivity** | | | **0.719** | **0.129** |
| SLN positive | 25 (16.9) | 27 (18.5) | | |
| SLN negative | 123 (83.1) | 119 (81.5) | | |

COVID: coronavirus; IORT: intraoperative radiation therapy; SLNB: sentinel lymph node biopsy; ERBT: external beam radiation therapy

period. Interestingly, the time was not significantly different between the periods (p = 0.958) as listed in Table 3.

## Discussion and Conclusion

The impact of operational changes in multidisciplinary breast cancer management within a large, integrated healthcare system were observed during the pandemic (8). There was an overall decrease in the number of breast cancer patients undergoing surgery as the number of procedures and admission in hospitals were reduced (9). There was also a decline in patients seeking consultation in the oncology clinic (10). However, our study showed a similar number of patients admitted to our institution in both study periods. In the present study, the "COVID period" was defined as the period of the Movement Control Order that was implemented from 18 March to 3 May 2020, and was followed by the Conditional Movement Control Order (CMCO), Recovery Movement Control Order, and Movement Control Order by states in the subsequent months with relaxed regulations. This relaxation of regulations may be a possible reason for the similar number of patients in both the pre-COVID and COVID periods. It can also be attributed to the rapid adaptation of policies to address the pandemic, which focused on identifying and managing suspicious breast lesions and cases. The median age of breast cancer patients was 60 years in both the pre-COVID and COVID groups, and the range of ages in the two periods was also similar.

The present study investigated system-wide operational changes and their likely sequelae on breast cancer management in an integrated care system. One publication had promoted the use of neoadjuvant systemic therapies to delay definitive surgery until personal protective equipment and resources to resume surgery during the pandemic became available (11). Upfront surgery was widely implemented in another institution because their facilities had the capacity to do so (12). The upfront surgery received by patients in this study included breast-conserving surgery, simple mastectomy and modified radical mastectomy. Breast conservative surgery, also known as lumpectomy or partial mastectomy, is a type of breast cancer surgery that involves removing only the cancerous tumor and a small amount of surrounding

Table 3. Patients' age and surgical wait time

| Median (range) | Pre-COVID | COVID | p-value | Mann-Whitney U value |
|---|---|---|---|---|
| Age, years | 60.00 (51.75–70.00) | 60.00 (51.00–69.00) | 0.555 | 69662.000 |
| Time to surgery | 45.00 (26.50–153.50) | 44.00 (24.75–156.25) | 0.958 | 42936.000 |

COVID: coronavirus

tissue while preserving as much of the breast as possible (13, 14). Mastectomy is a surgical procedure in which the entire breast tissue is removed. In simple mastectomy, also known as total mastectomy, the entire breast including nipple and areola are removed but not all the axillary lymph nodes while a modified radical mastectomy removes the entire breast along with the axillary lymph nodes (14). The University Malaya Medical Centre employs Clinical Practice Guideline and National Comprehensive Cancer Network (NCCN) guidelines to determine if neoadjuvant chemotherapy would be the best course of action for patients. As per the NNCN guidelines, neoadjuvant systemic therapy, including neoadjuvant chemotherapy, is recommended for women with inoperable breast cancer to attempt to convert the lesion to a resectable form (15). Additionally, a meta-analysis revealed that neoadjuvant chemotherapy resulted in a higher response rate among triple-negative and HER2-positive breast cancer patients (16). It also decreases the tumor size, making breast-conserving surgery a possible option over traditional chemotherapy (16). Our results showed similar rate of upfront surgery and neoadjuvant systemic therapy and palliative therapy during the pandemic. We hypothesize that this was due to continuation of breast care service, despite being in the midst of the pandemic (17-20).

A multicentre review of 432 patients had found delays in providing breast cancer treatment during the onset of the pandemic compared with normal treatment times (17). With governments recommending the postponement of surgeries and patients' reluctance to come to hospital due to the fear of COVID-19 infection, the average time to surgery might be expected to take longer in the pandemic cohort (11). However, the scenario in University Malaya Medical Centre (UMMC) showed no significant difference because such operations were encouraged as long as they could be performed safely. The absence of a significant difference in time to treatment between the two periods probably reflected the beneficial effects of a well-coordinated hospital in terms of medical resource re-allocation and definition of clinical priorities. Reconstruction was the treatment of choice after mastectomy. However, due to prioritization of facilities and manpower for COVID-19, many healthcare institutions had suggested keeping breast cancer surgery simple by deferring the reconstructive procedures (12). This policy was adopted in University Malaya Medical Centre (UMMC) leading to a significant drop in reconstructive procedures. This is because healthcare providers have had to divert their attention, as well as resources such as manpower, wards, and beds, to managing COVID-19 cases. As a result, longer surgeries were discouraged, and only patients who required shorter surgeries, such as skin coverings or implants, were prioritized for reconstructive procedures. In addition, reconstructive procedures involving expanders were often split into two stages to allow healthcare personnel to focus on COVID-19 management. Certain reconstructive procedures were redirected to hospitals that did not handle patients infected with COVID-19.

Delays in breast cancer diagnosis during the COVID-19 pandemic might be expected to affect oncological outcomes. There was a study that also compared breast cancer patients operated on in the COVID period with a similar cohort identified prior to the pandemic (17). This study found significantly more cases of lymph node metastasis and advanced histological grades in the COVID period patients (17). Another study detected an increase in metastatic disease in April 2020 compared with the previous year, before the pandemic began (11). There was an estimated increase of 8 to 10% in deaths due to breast cancer during the pandemic (19). However, in our study, there were no significant differences in tumor size, grade or clinical and pathological lymph node involvement between the two periods.

Research in Northern California found a higher percentage of patients presenting with symptomatic disease during the pandemic. Another study also observed a larger number of symptomatic detections and a decrease in screening detection (11). We observed a similar scenario in which symptomatic detection was slightly different between the pre-COVID and COVID periods. Fear of COVID-19 may have discouraged women from seeking routine breast cancer screening, which resulted in delayed diagnoses and more breast cancer cases being diagnosed symptomatically.

The main concern of late cancer detection was the high risk of getting a more severe diagnosis, as observed in our study. In addition, the suspension of screening services might lead to a loss of opportunity in treating pre-malignant lesions. Indeed, in a British modelling study it was shown that a 12-month delay in breast cancer diagnoses caused by the pandemic would increase the death rate by 7.9% to 9.6% after five years (22). Similarly, a Canadian model suggested that a six-month suspension of screening would result in 670 extra advanced cases and 250 additional deaths (23). Several studies predicted that there would be more patients presenting with advanced disease as a result of stage migration and possibly worse outcomes (24, 25). A recent study from a university referral hospital in northern Italy investigated this issue. They performed a retrospective single-institution review of women diagnosed with breast cancer between May and July 2020, when there was an interruption in breast cancer screening, and then fast-tracked those who had been delayed through their screening and comparing them with patients diagnosed in a similar period prior to COVID-19. They did not detect a significant difference in tumor biology, which concurred with the results of the present study. However, they did see a significant increase in locally advance stage at diagnosis (26). In University Malaya Medical Centre (UMMC), there is a slight increase in Stage 4 breast cancer cases and reduction in *in situ* breast carcinoma cases during the COVID period (22). This is most likely due to patients' reluctance to seek medical attention because of the fear of contracting COVID-19 or overwhelming the healthcare system, resulting in fewer opportunities for early detection. Furthermore, the changes in hospital policies and resources during the pandemic may have resulted in different diagnostic and treatment strategies that favored presentation with late-stage invasive carcinoma over *in situ* carcinoma.

Though our study did not focus on determining the incidence of COVID-19 among patients, only a small number (0.4%, n = 2) died due to COVID contraction in hospital, indicating that patients did not face a higher risk of COVID-19 infection when seeking treatment in hospitals. Moreover, we found out that the COVID-19 status itself did not have a significant impact on definitive treatment or surgery (6).

The main limitation of the present study was the small number of patients from a single center. Therefore, the results do not represent a general scenario, but it may be useful in helping healthcare institutions to come up with better treatment strategies as they try to adapt to the pandemic. A multicentric study with a large sample size would be needed to study the overall impact of COVID-19 on breast cancer patients and disease progression, which will also vary from country to country. More importantly, the COVID-19 pandemic, which began in March 2020, has persisted, and a longer follow-up period would be needed to assess the long-term impact on breast cancer stage migration and death rate.

COVID-19 brought operational changes in breast cancer management that have resulted in a reduction in screening-detected breast cancer cases, an increase in *de novo* Stage 4 cases, a reduction in reconstructive procedures, and a decrease in adjuvant chemotherapy. These findings are concerning because delays in screening and diagnosis can lead to more advanced cancer at diagnosis, which can negatively impact treatment outcomes and survival. The reduction in reconstructive procedures and adjuvant treatment may also affect the quality of life and long-term outcomes for breast cancer patients. Therefore, it is important to address these operational changes and their impact on breast cancer management as the pandemic persists. Patients should be encouraged to attend their outpatient appointments and screening programs once they resume.

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**Ethics Committee Approval:** The study was approved by the Medical Research Ethics Committee University of Malaya Medical Centre MECID. NO: 20211012-10689 and conformed to the Declaration of Helsinki 1975.

**Informed Consent:** Retrospective study.

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### Authorship Contributions

Concept: T.J.M., N.S.A.L., L.L.L.; Design: N.J.H., S.M.H., T.J.M.; Data Collection or Processing: N.J.H., S.M.H., T.J.M., T.M.S., M.D., N.S.A.L., A.A.M., L.L.L.; Analysis or Interpretation: N.J.H., S.M.H., T.M.S., M.D., N.S.A.L., A.A.M., L.L.L.; Literature Search: N.J.H., S.M.H., N.S.A.L., A.A.M., L.L.L.; Writing: N.J.H., S.M.H., T.J.M., T.M.S., N.S.A.L., A.A.M., L.L.L.

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## References

1. Feletto E, Grogan P, Nickson C, Smith M, Canfell K. How has COVID-19 impacted cancer screening? Adaptation of services and the future outlook in Australia. Public Helath Res Pract 2020; 30: 3042026. (PMID: 33294902) [Crossref]
2. Ng KY, Zhou S, Tan SH, Ishak ND, Goh ZZ, Chua ZY, et al. Understanding the psychological impact of COVID-19 pandemic on patients with cancer, their caregivers, and health care workers in Singapore. JCO Glob Oncol 2020; 6: 1494-1509. (PMID: 33017179) [Crossref]
3. Aziz NA, Othman J, Lugova H, Suleiman A. Malaysia's approach in handling COVID-19 onslaught: Report on the Movement Control Order (MCO) and targeted screening to reduce community infection rate and impact on public health and economy. J Infect Public Health 2020; 13: 1823-1829. (PMID: 32896496) [Crossref]
4. Shah AU, Safri SN, Thevadas R, Noordin NK, Abd Rahman A, Sekawi Z, et al. COVID-19 outbreak in Malaysia: Actions taken by the Malaysian government. Int J Infect Dis 2020; 97: 108-116. (PMID: 32497808) [Crossref]
5. Del Pilar Estevez-Diz M, Bonadio RC, Miranda VC, Carvalho JP. Management of cervical cancer patients during the COVID-19 pandemic: a challenge for developing countries. Ecancermedicalscience 2020; 14: 1060. (PMID: 32582375) [Crossref]
6. Bonadio RC, Messias AP, Moreira OA, Leis LV, Orsi BZ, Testa L, et al. Impact of the COVID-19 pandemic on breast and cervical cancer stage at diagnosis in Brazil. Ecancermedicalscience. 2021; 15: 1299. (PMID: 34824622) [Crossref]
7. Egner JR. AJCC cancer staging manual. Jama 2010; 304: 1726-1727. (PMID: 20180029) [Crossref]
8. Filipe MD, van Deukeren D, Kip M, Doeksen A, Pronk A, Verheijen PM, et al. Effect of the COVID-19 pandemic on surgical breast cancer care in the Netherlands: a multicenter retrospective cohort study. Clin Breast Cancer 2020; 20: 454-461. (PMID: 32888855) [Crossref]
9. Sheng JY, Santa-Maria CA, Mangini N, Norman H, Couzi R, Nunes R, et al. Management of breast cancer during the COVID-19 pandemic: a stage-and subtype-specific approach. JCO Oncol Pract 2020; 16: 665-674. (PMID: 32603252) [Crossref]
10. Işıklar AD, Deniz C, Soyder A, Güldoğan N, Yılmaz E, Başaran G. How Do Breast Cancer Patients Present Following COVID-19 Early Peak in a Breast Cancer Center in Turkey? Eur J Breast Health 2021; 17: 253-257. (PMID: 34263153) [Crossref]
11. Eijkelboom AH, de Munck L, Vrancken Peeters MJ, Broeders MJ, Strobbe LJ, Bos ME, et al. Impact of the COVID-19 pandemic on diagnosis, stage, and initial treatment of breast cancer in the Netherlands: a population-based study. J Hematol Oncol 2021; 14: 64. (PMID: 33865430) [Crossref]
12. Hawrot K, Shulman LN, Bleiweiss IJ, Wilkie EJ, Frosch ZA, Jankowitz RC, et al. Time to treatment initiation for breast cancer during the 2020 COVID-19 pandemic. JCO Oncol Pract 2021; 17: 534-540. (PMID: 33710914) [Crossref]
13. Breast cancer treatment (adult) (PDQ®)–patient version [Internet]. National Cancer Institute. [cited 2023Mar14]. Available from: https://www.cancer.gov/types/breast/patient/breast-treatment-pdq#_46 [Crossref]
14. Surgery for breast cancer [Internet]. Breast Cancer Treatment. [cited 2023Mar14]. Available from: https://www.cancer.org/cancer/breast-cancer/treatment/surgery-for-breast-cancer.html [Crossref]
15. National Comprehensive Cancer Network. Breast Cancer Version 1.2019:NCCN; 2019. [Crossref]
16. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and longterm clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164-172. (PMID: 24529650) [Crossref]
17. Vanni G, Tazzioli G, Pellicciaro M, Materazzo M, Paolo O, Cattadori F, et al. Delay in breast cancer treatments during the first COVID-19 lockdown. A multicentric analysis of 432 patients. Anticancer Res 2020; 40: 7119-7125. (PMID: 33288611) [Crossref]
18. Papautsky EL, Hamlish T. Patient-reported treatment delays in breast cancer care during the COVID-19 pandemic. Breast Cancer Res Treat 2020; 184: 249-254. (PMID: 32772225) [Crossref]

19. Tang A, Neeman E, Vuong B, Arasu VA, Liu R, Kuehner GE, et al. Care in the time of COVID-19: impact on the diagnosis and treatment of breast cancer in a large, integrated health care system. Breast Cancer Res Treat 2022; 191: 665-675. (PMID: 34988767) [Crossref]

20. Bartlett DL, Howe JR, Chang G, Crago A, Hogg M, Karakousis G, et al. Management of cancer surgery cases during the COVID-19 pandemic: considerations. Ann Surg Oncol 2020; 27: 1717-1720. (PMID: 32270420) [Crossref]

21. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al A. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol 2020; 21: 1023-1034. (PMID: 32702310) [Crossref]

22. Toss A, Isca C, Venturelli M, Nasso C, Ficarra G, Bellelli V, et al. Two-month stop in mammographic screening significantly impacts on breast cancer stage at diagnosis and upfront treatment in the COVID era. ESMO Open 2021; 6: 100055. (PMID: 33582382) [Crossref]

23. Yong JH, Mainprize JG, Yaffe MJ, Ruan Y, Poirier AE, Coldman A, et al. The impact of episodic screening interruption: COVID-19 and population-based cancer screening in Canada. J Med Screen 2021; 28 : 100-107. (PMID: 33241760) [Crossref]

24. Patt D, Gordan L, Diaz M, Okon T, Grady L, Harmison M, et al. Impact of COVID-19 on cancer care: how the pandemic is delaying cancer diagnosis and treatment for American seniors. JCO Clin Cancer Inform 2020; 4: 1059-1071. (PMID: 33253013) [Crossref]

25. Vuagnat P, Frelaut M, Ramtohul T, Basse C, Diakite S, Noret A, et al. COVID-19 in breast cancer patients: a cohort at the Institut Curie hospitals in the Paris area. Breast Cancer Res 2020; 22: 55. (PMID: 32460829) [Crossref]

26. Sud A, Torr B, Jones ME, Broggio J, Scott S, Loveday C, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. Lancet Oncol 2020; 21: 1035-1044. (PMID: 32702311) [Crossref]

Letter to the Editor

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# Comments to "The Randomized Controlled Study of Low-Level Laser Therapy, Kinesio-Taping and Manual Lymphatic Drainage in Patients With Stage II Breast Cancer-Related Lymphedema"

Anke Bergmann[1], Mauro Figueiredo Carvalho Andrade[2], Mirella Dias[3]

[1]Program of Clinical Epidemiology, National Cancer Institute, Rio de Janeiro, Brazil
[2]Department of Surgery, Faculty of Medicine, University of São Paulo (USP), São Paulo, Brazil
[3]Department of Physiotherapy, Faculty of Medicine, Santa Catarina State University, Florianópolis, Brazil

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We read with great interest the article published by Selcuk Yilmaz and Ayhan (1). The authors focused on a topic of utmost importance in clinical practice related to the most common and debilitating side effect of breast cancer treatment.

Currently, the gold standard approach to lymphedema patients is decongestive physical therapy, which includes manual lymphatic drainage (MLD), compressive therapy, skin care and exercises. However, other forms of adjuvant treatment have been increasingly highlighted, aiming for better therapeutic results and lower treatment related costs (2).

For that matter, the randomized clinical study performed by Selcuk Yilmaz and Ayhan (1) compared efficacy and tolerability of kinesio-taping (KT) or low-level laser therapy (LLLT) as alternatives to MLD in breast cancer survivors who developed unilateral stage II lymphedema, meaning their excess volume on the affected arm reached 5 to 20%. Patients were randomized in three groups and treated with MLD, KT or LLLT. Treatment was undertaken for three weeks, five sessions a week, and all women were oriented about self-massaging techniques, skin care and exercises. At the end of each session, the therapist applied multilayer bandaging in all groups, which was kept for 23–24 hours and supervised remedial exercises performed by the patients. After the end of the three treatment weeks, flat-knitted garments were prescribed to all patients to be worn during the maintenance phase. Outcomes were assessed immediately after treatment and up to 12 weeks of follow-up. Based on their results, the authors concluded that KT was more effective in volume reduction than MLD and that KT was as effective as LLLT.

However, we believe that some critical issues should be considered regarding their conclusions:

• Despite randomization, the MLD group presented a significant predominance of obese patients, a longer duration of swelling in months, and lesser caregiver support. Those factors are known to be related to transcription factor decoy (TFD) response (3-5). In the results published in the article, the authors did not control the influence of those variables in the statistical analysis (models of adjusted multiple regression). Therefore, the favorable outcome observed in the KT group may be due to the diverse clinical and demographic characteristics among groups and not to the intervention itself.

• Fan-cut kinesio-tape was applied using the lymphedema kinesiotaping technique of paper-off tension. The supporters of this technique argue that its beneficial effect lies in the fact that lifting the skin induces opening of initial lymph vessels and enhances fluid absorption and transport (6). In this study, patients in the KT group also had multilayer bandaging, causing this supposed skin lifting effect to be replaced by the well-established compressive effect. Therefore, edema reduction may be attributed not to the lymphatic effect of the taping, but to the overlapping compression provided by bandaging.

• LLLT was applied in the axillary and cubital areas. This technique intends to stimulate lymphatic motricity and promote lymphangiogenesis. However, these effects of LLLT are not expected to be observed in so short a follow-up (7).

**Corresponding Author:**
**Anke Bergmann; abergmann@inca.gov.br**

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In conclusion, we believe that the results obtained by Selcuk Yilmaz and Ayhan (1) emphasize the role of multilayer bandaging associated to exercises and skin care as the best therapeutic approach to breast cancer treatment related lymphedema. So, even if adjuvant therapies may be incorporated to selected patients, namely MLD alone, LLLT, KT, and others, they still need further evaluation for they do not offer better outcomes as compared to TFD.

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## References

1. Selcuk Yilmaz S, Ayhan FF. The Randomized Controlled Study of Low-Level Laser Therapy, Kinesio-Taping and Manual Lymphatic Drainage in Patients With Stage II Breast Cancer-Related Lymphedema. Eur J Breast Health 2023; 19: 34-44. (PMID: 36605467) [Crossref]
2. Bergmann A, Baiocchi JMT, de Andrade MFC. Conservative treatment of lymphedema: the state of the art. J Vasc Bras 2021; 20: e20200091. (PMID: 34777487) [Crossref]
3. Duyur Cakıt B, Pervane Vural S, Ayhan FF. Complex Decongestive Therapy in Breast Cancer-Related Lymphedema: Does Obesity Affect the Outcome Negatively? Lymphat Res Biol 2019; 17: 45-50. (PMID: 30281384) [Crossref]
4. Eyigör S, Cinar E, Caramat I, Unlu BK. Factors influencing response to lymphedema treatment in patients with breast cancer-related lymphedema. Support Care Cancer 2015; 23: 2705-2710. (PMID: 25663541) [Crossref]
5. Keskin D, Dalyan M, Ünsal-Delialioğlu S, Düzlü-Öztürk Ü. The results of the intensive phase of complete decongestive therapy and the determination of predictive factors for response to treatment in patients with breast cancer related-lymphedema. Cancer Rep (Hoboken) 2020; 3: e1225. (PMID: 32672004) [Crossref]
6. Bosman J. Lymphtaping for lymphoedema: an overview of the treatment and its uses. Br J Community Nurs 2014; Suppl: S12-S18. (PMID: 24704750) [Crossref]
7. Wang Y, Ge Y, Xing W, Liu J, Wu J, Lin H, et al. The effectiveness and safety of low-level laser therapy on breast cancer-related lymphedema: An overview and update of systematic reviews. Lasers Med Sci 2022; 37: 1389-1413. (PMID: 34779937) [Crossref]