Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

Predictive Factors for Local Relapse in Breast Cancer Patients after Surgery
Breast Cancer Surgery and Local Relapse

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ABSTRACT

Background and objectives: We aimed to identify the possible risk factors that may affect local relapse after conservative surgery or modified radical mastectomy for breast cancer.

Methods: We conducted a retrospective observational study of breast cancer patients treated with conservative surgery or modified radical mastectomy between 2012 and 2019. All analyses were undertaken using Statistical Package for the Social Sciences (SPSS) version 23.0.

Results: A total of 70 women were included in our study. Of them, 29 women were ≥50, and 22 women had a tumor size of ≥20. Negative lymph node involvement was noted in 54 women (77.1%) and multifocality in 33 women (47.1%). The commonest histological type was ductal (87.1%). Positive estrogen, progesterone, and HER2 receptors were reported in 84%, 70%, and 6%, respectively. Local relapse occurred in only sevenpatients (10%); 6 patients had it in the first 24 months. The mean time for recurrence-free was 47.06 ± 22.92 months (range= 9 to 79 months). There was a statistically significant association between local relapse and tumor size (p= 0.029), clinical lymph node involvement (p= 0.043), multifocality (p= 0.046), neoadjuvant chemotherapy (p= 0.028), metastasis (p= 0.019), and positive margins (p= 0.006). There was a statistically significant relationship between local relapse and estrogen, progesterone, and HER2 receptors (all $p<0.05$).

Conclusion: A proper monitoring of breast cancer patients is critical to prevent local relapse after surgical operations. Determining the risk factors may provide a proper management plan, good clinical outcome, and therefore preventing tumor recurrence.

Keywords:breast cancer;local relapse; predictive; recurrence; surgery

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer-related death in women. Early diagnosis of breast cancer is challenging because it evolves silently and is discovered during the routine examination, or it may present with a palpable breast mass, breast shape or size changes, or nipple discharge (1,2).

Local relapse is a serious complication that occurs after the surgical removal of breast cancer. Its incidence varies between 3% to 15%, mostly in the first follow-up years, and it is associated with poor prognosis and reduced overall survival. The local relapse after mastectomy significantly increases mortality rate and distant metastasis (3). Previous literature has highlighted the factors that would affect the local relapse; these factors included the (a) patient age, (b)previous surgery performed and surgical technique used in the second intervention,(c) size and multifocality of the tumor, (d) histological grade and immunohistochemical characteristics, (e)lymph nodes (LNs) involvement and lymphovascular infiltration margin involvement (f) neoadjuvant therapy and metastasis (3–9). Therefore studying and investigating these factors may help in choosing the appropriate treatment option for each case as well as

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decrease the mortality rate (10,11).We conducted this retrospective study to identify the possible risk factors that may affect local relapse through the follow-up of 70 patients who were treated with conservative surgery or modified radical mastectomy.

METHODS

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting our study (12). The study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Zagazig University, Egypt (Approval number: ZU-IRB#5697/19-11-2019).

We conducted this retrospective cohort study at the Surgical Oncology Unit at Zagazig University Hospitals, Egypt, within the period from 2012 to 2019.We included data of all female patients of any age treated with conservative surgery or modified radical mastectomy for breast cancer during the study period. We excluded data of male patients or female patients with missing data.

Routinely in our institution, all patients are subjected to (1) complete history taking, (2) demographic data including name, age, residence, occupation, marital status, particular habits of medical importance, and menstrual history, (3) full local and general clinical examination including both axillae for any clinical palpable axillary lymph nodes (LNs), (4) mammography and ultrasound of present breast, (5) FNAC or Tru-cut biopsy from breast mass, (6) routine laboratory investigations including complete blood picture, coagulation profile, liver function test, kidney function test, and viral markers, (7) plain X-ray chest and CT chest if needed, and (8) abdominal ultrasonography & CT abdomen & pelvis if needed.

We determined a cut point of 50 years regarding the patients' age because of its relationship with menopause and the associated hormonal changes. Moreover, the tumor size of ≥ 2 cm and the histological grade have been reported to enhance the recurrence rate of breast cancer. Therefore, these parameters were considered to differentiate the studied population. Hormonal receptors (estrogen receptor (ER) and progesterone receptor (PR)) of a value >5% were considered positive. The HER2 was reported based on the crosses in the immunohistochemical study (>3 was positive, 2 was considered undetermined, and 1 was negative). In the case of "undetermined", an in-situ hybridization assay was conducted to assess the positivity or negativity (14–16). We defined the patients' disease-free interval as well as the relationship between local relapse and other variables.

All analyses were undertaken using Statistical Package for the Social Sciences (SPSS) software version 23.0. Qualitative data were represented as frequency and percentages, while the quantitative data were represented as mean ± standard deviation (SD). Differences between continuous variables were tested using a student t-test or Mann-Whitney test as appropriate. The Chi-square test was used to assess the difference and association of qualitative variables. Risk ratio (RR) was used to compare the risk that a disease would occur among individuals who have a particular characteristic or who have been expressed to a risk factor to the disease would occur in individuals who lack the characteristic or have not been exposed. For all the above-mentioned statistical tests, the significance threshold was fixed at 5% (P-value).

Results

1.1 Characteristics of the studypopulation

Seventy women were included in our study. About 58.6% of the included patients aged less than 50, and 68.6% had tumor size <20. Most of the included women had negative LNs involvement (77.1%), ductal histological type (87.1%), carcinoma in situ (64.3%) with no lymphovascular involvement (74.3%). About 84%, 70%, and 6% had positive ER, PR, and HER2, respectively. Metastasis and positive margins were reported in seven and 10 patients out of the 70 patients. The distribution of the studied patients according to demographic and disease-specific characteristics is shown in **Table 1.**

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Table (1) Distribution of the studied patients according to demographic and disease-specific characteristics

		n= 70 (%)
Age	<50 years	41 (58.6)
	≥ 50 years	29 (41.4)
Tumor size	<20	48 (68.6)
	≥ 20	22 (31.4)
Clinical **LNs** involvement	Positive	16 (22.9)
	Negative	54 (77.1)
Multifocality	Yes	33 (47.1)
	No	37 (52.9)
Neoadjuvant chemotherapy	Yes	22 (31.4)
	No	48 (68.6)
Histological type	Ductal	61 (87.1)
	Lobular	9 (12.9)
Carcinoma in situ	Yes	45 (64.3)
	No	25 (35.7)
Lymphovascular involvement	Yes	18 (25.7)
	No	52 (74.3)
Histological grade	<G2	18 (25.7)
	≥G2	52 (74.3)
Metastasis	Present	7 (10)
	Absent	63 (90)
Positive margins	Present	10 (14.3)
	Absent	60 (85.7)
Estrogen receptor	Positive	59 (84.3)
	Negative	11 (15.7)
Progesterone receptor	Positive	49 (70)
	Negative	21 (30)
HER2	Positive	4 (5.7)
	Negative	66 (94.3)

1.2 local relapse

Seven patients (10%) had a local relapse; of them, six patients experienced it in the first 24 months. The recurrence-free period ranged from 9 to 79 months, with a mean of 47.06 months **(Table 2).**

Table (2) Distribution of the studied patients according to the occurrence of local relapse and survival

		n= 70 (%)
Local relapse	Yes	7 (10)
	No	63 (90)
Relapse	< 24 months	6 (85.7)
	≥ 24 months	1 (14.3)
Survival (months)	Mean ± SD	47.057 ± 22.916
	Range	9 to 79

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1.2.1. The relationship between local relapse and baseline patient characteristics

There is a statistically non-significant relationship between the occurrence of local relapse and age, histological type, lymphovascular involvement, presence of ductal carcinoma in situ, or histological grade (all p>0.05). There is a statistically significant relationship between local relapse and tumor size (p= 0.029), clinical LNsinvolvement (p= 0.043), multifocality (p= 0.046), neoadjuvant chemotherapy (p= 0.028), metastasis (p= 0.019), and positive margins (p= 0.006). Tumor size ≥20, positive LNs, multifocality, neoadjuvant chemotherapy, metastasis, and positive margins increased the risk of relapse by 2.65, 4.5, 6.73, 5.46, 11.1, and 12.67 folds, respectively **(Table 3).**

Table (3) The relationship between local relapse and baseline patient characteristics

Parameter	Local relapse		test		RR (95% CI)
	Yes	No	χ^2	p	
	n= 7 (%)	N= 63(%)			
Age:					
<50 years	5 (71.4)	36 (57.1)	0.53	0.467	1.88 (0.32 to 10.4)
≥50 **years**	2 (28.6)	27 (42.9)			
Tumor size:					
<20	**2 (28.6)**	**46 (73)**	**Fisher**	**0.029***	**2.65 (1.42 to 4.92)**
≥20	**5 (71.4)**	**17 (27)**			
Clinical LNs involvement:					
Positive	**4 (57.1)**	**19 (19)**	**Fisher**	**0.043***	**4.5 (1.12 to 18.05)**
Negative	**3 (42.9)**	**51 (81)**			
Multifocality:					
Yes	**6 (85.7)**	**27 (42.9)**	**Fisher**	**0.046***	**6.73 (0.91 to 70.42)**
No	**1 (14.3)**	**36 (57.1)**			
Neoadjuvant chemotherapy:					
Yes	**5 (71.4)**	**17 (27)**	**Fisher**	**0.028***	**5.46 (1.15 to 25.96)**
No	**2 (28.6)**	**46 (73)**			
Histological type:					
Ductal	6 (85.7)	55 (87.3)	Fisher	>0.999	0.87 (0.09 to 8.22)
Lobular	1 (14.3)	8 (12.7)			
Carcinoma in situ:					
Yes	4 (57.1)	41 (65.1)	Fisher	0.694	0.72 (0.09 to 8.22)
No	3 (42.9)	22 (34.9)			
Lymphovascular involvement:					
Yes	3 (42.9)	15 (23.8)	Fisher	0.363	2.17 (0.54 to 8.77)
No	4 (57.1)	48 (76.2)			
Histological grade:					
<G2	1 (14.3)	17 (27)	Fisher	0.668	0.48 (0.06 to 3.73).
≥G2	6 (85.7)	46 (73)			

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Metastasis:					
Present	**3 (42.9)**	**4 (6.3)**	**Fisher**	**0.019***	**11.1 (1.82 to 67.41)**
Absent	**4 (57.1)**	**59 (93.7)**			
Positive margins:					
Present	**4 (57.1)**	**6 (9.5)**	**Fisher**	**0.006***	**12.67 (2.28 to 70.53)**
Absent	**3 (42.9)**	**57 (90.5)**			

χ2= Chi square test; RR= Relative risk; CI= confidence interval; *p<0.05 is statistically significant

1.2.2. The relation between local relapse and hormonal receptors

There is a statistically significant relationship between local relapse and ER, PR, and HER2 (all p<0.05). Negative PR, ER, and positive HER2 increasedthe relapse risk by 22.81, 5.14, and 12.2 folds, respectively **(Table 4).**

Table (4) The relation between local relapse and hormonal receptors

Parameter		**Local relapse**		**test**		**RR (95% CI)**
		Yes	No	χ2	P	
		n= 7 (%)	n= 63(%)			
ER:	**Positive**	3 (42.9)	56 (88.9)	Fisher	0.01*	5.14 (1.99 to 13.28)
	Negative	4 (57.1)	7 (11.1)			
PR:	**Positive**	2 (28.6)	47 (74.6)	Fisher	0.022*	2.81 (1.5 to 5.29)
	Negative	5 (71.4)	16 (25.4)			
HER2:	**Positive**	2 (28.6)	2 (3.2)	Fisher	0.047*	12.2 (1.4 to 105.96)
	Negative	5 (71.4)	61 (96.8)			

χ2= Chi square test; RR= Relative risk; CI= confidence interval; *p<0.05 is statistically significant

Discussion

Our study identified the critical factors that affect local relapse through the follow-up of 70 patients treated with conservative surgery or modified radical mastectomy. The local relapse occurred in 7 patients (10%). In six patients, the local relapse occurred during 24 months. In 2014, Hastings et al. conducted a study on patients with T1 N0 stage with no nodal involvement; the authors documented that the local relapse rate was 3.2% (17). In another recent study, the local relapse rate was higher in the first three years (4.6%), and about half of the patients are likely to get the disease in further point (18). The recurrence rate can also reach a higher incidence of up to 10% in triple-negative patients, which is an aggressive form of breast cancer (19). In a phase-3 clinical trial after 20 years of follow-up, the ipsilateral relapse rate was 16.4% in patients treated by breast irradiation with boost and 12% in patients without boost (20). Therefore, the local relapse rate is deemed acceptable in our study regarding the follow-up period and other risk factors.

Of the studied risk factors, nine factors showed a significantly increased risk of local relapse. These factors include tumor size, LNsinvolved, multifocality presence, neoadjuvant chemotherapy, metastasis, presence of positive margins, negative ER, negative PR, and positive HER2. Previous literature reported that tumor size is the most crucial increasing risk factor of local relapse (15). Besides, in the case of axillary part involvement, the relapse risk would increase (21). A tumor sized of more than 2 cm increases local relapse risk (18). In the only invasive tumor, tumor size may show no effect on the local relapse rate (22). However, Elsayed et al. documented an increased risk of distant recurrence (23). Another critical risk factor that significantly increases the risk of local relapse is clinical LNs (18,23,24).

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On the other hand, other studies reported no significant increased risk (22,25). However, Vooged et al. reported an increased risk in only distant, not local relapse, while Elsayed et al. reported an increased risk for both local and distant relapse (23,25). It is advisable to use adjuvant therapy as endocrine therapy or chemotherapy after breast surgery to decrease both local and distant relapse (25,26). ER, PR, and HER2 are important biomarkers that affect breast cancer prognosis and hormonal treatment response (27). Local relapse rate increases in patients with triple hormonal negative receptors, patients with negative ER and PR, and patients with positive HER2 rather than other receptor combinations (28). This is the same reported in Shahriari-Ahmadi et al., who documented an increased relapse risk with negative ER, PR, and positive HER2 with specifically ER in the early stages of breast cancer, which agrees with our results (29). The absence of PR can be a predictive risk of recurrence even if ER is present (30). Investigating hormonal receptors types are necessary to determine the treatment plan as HER2 positive female have an increased risk of distal relapse if they did not initiate hormonal therapy (31). Moreover, Mannel et al. suggested choosing the adjuvant therapy also according to the present hormonal receptors in metastatic LNs not only in the primary tumor as it is found that there can be a discordant between nodal hormonal receptors and primary tumor receptors, which can lead to treatment failure (32,33).

Marginal involvement significantly increases the recurrence rate, as presented in our study and documented in the literature (18,34). At the edge of the tumor, Ki67% is highly concentrated, increasing aggravation of cancer and increasing local relapse risk (35). This is why the American Society for Radiation Oncology defined the free margin as no tumor in ink, which is more accurate to decide marginal involvement (35). However, some studies showed no significant increased risk of local relapse as reported in Voogd et al., which can be due to the radiation used to eradicate cancer cells and not use ink to decide the margins' involvement. However, there is a significant relation with distant relapse explained by an increasing aggravation of cancer, as previously mentioned (25).

Multifocality makes it more challenging in intra-ductal breast cancer to complete the tumor's resection, which requests more interventions to obtain free margin and may increase local relapse (18,36,37). It is also the same mechanism in lobular breast cancer; however, it is more challenging to manage (38). Metastasis also has a role in increasing relapse rate as reported in Tejera Hernández et al., 2019 which shows that 45% of local relapse patients had metastasis while only 6% of patients with no local relapse had metastasis; nevertheless, more studies are warranted to study its relation to local relapse (18).

Neo-adjuvant chemotherapy also may increase the local relapse rate (18). Although neoadjuvant chemotherapy can destroy breast cancer cells, a meta-analysis of randomized control trials comparing neoadjuvant chemotherapy and postoperative adjuvant chemotherapy finds a more significant increased risk of neo-adjuvant chemotherapy than adjuvant chemotherapy after 15 years (39). This can be because of the significantly increased incidence of breast conservation surgery in neo-adjuvant chemotherapy patients; however, no increased risk is observed in distant relapse or death (39). Therefore, further research studies are needed to understand this effect.

Despite the significance of the studied risk factors in increasing local relapse, some weak points should be considered. Our study investigates the effect of local relapse after surgical intervention of breast cancer (breast conservative surgery or mastectomy), without specific determination of local relapse or factors affecting it in each surgical procedure. Moreover, our study design is a retrospective cohort design that may increase selective and recall biases (40). Therefore, the results should be taken with caution.

In conclusion, after a surgical operation, proper monitoring of breast cancer patients is critical as local relapse is suspected in the first few years. Tumor and patients' characteristics as multifocality, LNs involvement, marginal involvement, hormonal receptors, metastasis, neo-adjuvant chemotherapy, and tumor size affect the local relapse; therefore, determining these factors may help in good management, selecting specific treatment for each case, good clinical outcome, and therefore preventing local relapse.

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REFERENCES

1. Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. Local Cancer Recurrence: The Realities, Challenges, and Opportunities for New Therapies. CA: a cancer journal for clinicians. 2018;68(6):488–505.
2. Narod SA. Personalised medicine and population health: breast and ovarian cancer. Human genetics. 2018 Oct;137(10):769–78.
3. Engelhardt EG, Garvelink MM, de Haes J (Hanneke) CJM, van der Hoeven JJM, Smets EMA, Pieterse AH, et al. Predicting and Communicating the Risk of Recurrence and Death in Women With Early-Stage Breast Cancer: A Systematic Review of Risk Prediction Models. Journal of Clinical Oncology. 2014 Nov;32(3):238–50.
4. Martin AM, Weber BL. Genetic and hormonal risk factors in breast cancer. Journal of the National Cancer Institute. 2000.
5. Roué T, Labbé S, Belliardo S, Plenet J, Douine M, Nacher M. Predictive Factors of the Survival of Women With Invasive Breast Cancer in French Guiana: The Burden of Health Inequalities. Clinical Breast Cancer. 2016;
6. Akinyemiju T, Wiener H, Pisu M. Cancer-related risk factors and incidence of major cancers by race, gender and region; analysis of the NIH-AARP diet and health study. BMC Cancer. 2017;
7. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K. Population-attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncology. 2017;
8. Tamimi RM, Spiegelman D, Smith-Warner SA, Wang M, Pazaris M, Willett WC, et al. Population attributable risk of modifiable and nonmodifiable breast cancer risk factors in postmenopausal breast cancer. American Journal of Epidemiology. 2016;
9. Dai X, Xiang L, Li T, Bai Z. Cancer hallmarks, biomarkers and breast cancer molecular subtypes. Journal of Cancer. 2016.
10. Henry NL, Somerfield MR, Abramson VG, Ismaila N, Allison KH, Anders CK, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: Update of the ASCO endorsement of the cancer care Ontario guideline. Journal of Clinical Oncology. 2019;
11. Henry NL, Somerfield MR, Abramson VG, Allison KH, Anders CK, Chingos DT, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: American society of clinical oncology endorsement of cancer care Ontario guideline recommendations. Journal of Clinical Oncology. 2016;34(19):2303–11.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of clinical epidemiology. 2008 Apr;61(4):344–9.
13. Declaration of Helsinki (1964). BMJ. 1996 Dec;313(7070):1448–9.
14. Bosma SCJ, Van Der Leij F, Van Werkhoven E, Bartelink H, Wesseling J, Linn S, et al. Very low local recurrence rates after breast-conserving therapy: Analysis of 8485 patients treated over a 28-year period. Breast Cancer Research and Treatment. 2016;
15. Fei F, Messina C, Slaets L, Chakiba C, Cameron D, Bogaerts J, et al. Tumour size is the only predictive factor of distant recurrence after pathological complete response to neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancers: A sub-study of EORTC 10994/BIG 1-00 phase III trial. European Journal of Cancer. 2015;51(3):301–9.
16. Lester SC, Bose S, Chen YY, Connolly JL, De Baca ME, Fitzgibbons PL, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Archives of Pathology and Laboratory Medicine. 2009.
17. Hastings J, Iganej S, Huang C, Huang R, Slezak J. Risk Factors for Locoregional Recurrence After Mastectomy in Stage T1 N0 Breast Cancer: American Journal of Clinical Oncology. 2014

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

Nov;37(5):486–91.
18. Tejera Hernández AA, Vega Benítez VM, Rocca Cardenas JC, Gutiérrez Giner MI, Díaz Chico JC, Hernández Hernández JR. Factors predicting local relapse and survival in patients treated with surgery for breast cancer. Asian Journal of Surgery. 2019 Nov;42(7):755–60.
19. Pogoda K, Niwińska A, Murawska M, Pieńkowski T. Analysis of pattern, time and risk factors influencing recurrence in triple-negative breast cancer patients. Medical Oncology. 2013 Nov;30(1):388.
20. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. The Lancet Oncology. 2015 Nov;16(1):47–56.
21. Houvenaeghel G, Classe JM, Garbay JR, Giard S, Cohen M, Faure C, et al. Survival impact and predictive factors of axillary recurrence after sentinel biopsy. European Journal of Cancer. 2016;58:73–82.
22. Fredriksson I, Liljegren G, Palm-Sjövall M, Arnesson L-G, Emdin SO, Fornander T, et al. Risk factors for local recurrence after breast-conserving surgery: Local recurrence after breast-conserving surgery. British Journal of Surgery. 2003 Nov;90(9):1093–102.
23. Elsayed M, Alhussini M, Basha A, Awad AT. Analysis of loco-regional and distant recurrences in breast cancer after conservative surgery. World Journal of Surgical Oncology. 2016 Nov;14(1):144.
24. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet (London, England). 2005;366(9503):2087–106.
25. Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al. Differences in Risk Factors for Local and Distant Recurrence After Breast-Conserving Therapy or Mastectomy for Stage I and II Breast Cancer: Pooled Results of Two Large European Randomized Trials. Journal of Clinical Oncology. 2001 Nov;19(6):1688–97.
26. Ziogas D, Roukos DH. Genetics and personal genomics for personalized breast cancer surgery: progress and challenges in research and clinical practice. Annals of Surgical Oncology. 2009;16(7):1771–82.
27. Esteva FJ, Hortobagyi GN. Prognostic molecular markers in early breast cancer. Breast Cancer Research. 2004 Nov;6(3):109.
28. Kyndi M, Sørensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J, et al. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2008;26(9):1419–26.
29. Shahriari-Ahmadi A, Arabi M, Payandeh M, Sadeghi M. The recurrence frequency of breast cancer and its prognostic factors in Iranian patients. International Journal of Applied and Basic Medical Research. 2017 Nov;7(1):40.
30. Bogina G, Lunardi G, Coati F, Zamboni G, Gori S, Bortesi L, et al. Progesterone receptor status and clinical outcome in breast cancer patients with estrogen receptor-positive locoregional recurrence. Tumori. 2015;101(4):398–403.
31. Ishitobi M, Okuno J, Kittaka N, Nakayama T, Koyama H, Tamaki Y. Distant Recurrence Risk after Late Ipsilateral Breast Tumor Recurrence: Results of a Retrospective, Single-Institution Study. Oncology. 2015;89(5):269–74.
32. Mannell A. An overview of risk factors for recurrent breast cancer. 2017;55:6.
33. Aitken SJ, Thomas JS, Langdon SP, Harrison DJ, Faratian D. Quantitative analysis of changes in ER, PR and HER2 expression in primary breast cancer and paired nodal metastases. Annals of Oncology. 2010 Nov;21(6):1254–61.
34. Schnitt SJ, Abner A, Gelman R, Connolly JL, Recht A, Duda RB, et al. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

with breast-conserving surgery and radiation therapy. Cancer. 1994;74(6):1746–51.
35. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. International Journal of Radiation Oncology, Biology, Physics. 2014;88(3):553–64.
36. Klein J, Kong I, Paszat L, Nofech-Mozes S, Hanna W, Thiruchelvam D, et al. Close or positive resection margins are not associated with an increased risk of chest wall recurrence in women with DCIS treated by mastectomy: a population-based analysis. SpringerPlus. 2015;4:335.
37. Zhang X, Dai H, Liu B, Song F, Chen K. Predictors for local invasive recurrence of ductal carcinoma in situ of the breast: a meta-analysis. European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP). 2016;25(1):19–28.
38. Rezai M, Kraemer S, Kimmig R, Kern P. Breast conservative surgery and local recurrence. Breast (Edinburgh, Scotland). 2015;24 Suppl 2:S100-107.
39. Asselain B, Barlow W, Bartlett J, Bergh J, Bergsten-Nordström E, Bliss J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. The Lancet Oncology. 2018 Nov;19(1):27–39.
40. Sedgwick P. Retrospective cohort studies: Advantages and disadvantages. BMJ (Online). 2014;348(February).