Original Article

Impact of margin width on local recurrence after breast conservative surgery following neoadjuvant chemotherapy

Walid Akmal[1], Omar Z. Youssef[1], Neveen S. Tahoun[2], Ahmed Rabea[3], Tamer M. Manie[1], Mohamed Elmahdy[4]

[1]Department of Surgical Oncology, National Cancer Institute, Cairo University, Egypt.

[2]Department of Pathology, National Cancer Institute, Cairo University, Egypt.

[3]Department of Medical Oncology, National Cancer Institute, Cairo University, Egypt

[4]Department of Surgical Oncology, Nasser Institute Hospital for Research and Treatment, Cairo, Egypt

Email: handesayali11@gmail.com

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Abstract

Background: The main goal of BCS after NAC is complete excision of the tumor with clear margin, however, no clear definition of what constitutes a clear margin has been proposed. An additional challenge for surgeons is the extent of resection especially in good responders to NAC. The aim of this study was to determine the impact of margin width on local recurrence after breast conservative surgery for patients who responded to neoadjuvant chemotherapy. Patients and Methods: This study is a prospective observational cohort study conducted at the National Cancer Institute, Cairo university, Egypt. The study included 75 Egyptian female breast cancer patients who responded to NAC and then assigned to BCS in the period from October 2019 till October 2020. Patients were assessed with regular appointments at the outpatient clinics up to 2 years follow up after surgery.

Results: The mean age was 43.8±9.5 years and 65.3 % of patients were in the premenopausal status. All patients (75 cases) had either cT2 or cT3 disease. Clinical nodal disease (cN1-3) was found in 68 patients (90.7%). Radiologic complete response was seen in 31 patients (41.3%). Most patients (85.3%) had a least circumferential margin of more than 2 mm. Positive nodal involvement was confirmed in 22 patients (29.3%). Over 70% of patients had ypT stage 1c or 2 and over 60 % of patients had ypN stage 0. By the end of follow up, four patients developed local recurrence. The unadjusted local recurrence rate was 5.3% and cumulative local recurrence free survival of the whole studied group at 36 months was 94.6%. The least circumferential resection margin (2mm) had no impact on local recurrence free survival.

Conclusion: Margin after NAC and BCS is safe according to ‘‘no ink on tumor’’ guideline and we emphasize the resection of the clipped area in cases of cCR and/or rCR, however, further studies with larger sample size and longer duration of follow up are required to mitigate the local recurrence after BCS following NAC.

Keywords: Breast, chemotherapy, recurrence, survival, tumor.

1. INTRODUCTION

There is an ongoing debate regarding what constitutes an adequate negative margin among NAC-BCS patients. The SSO/ASCO/ASTRO consensus statement defines an adequate margin in upfront surgery group as ‘‘no ink on tumor’’ but does not include patients receiving NAC [1]. Neoadjuvant chemotherapy for breast cancer patients has led to high rates of clinical response and thus a more conservative approach for breast surgery [2]. The main goals of neoadjuvant systemic therapy are to improve surgical options and to acquire early information on response of the tumor, as good responders are surrogates of good prognosis. More recently, indications for NST have evolved to recognize its critical role in guiding subsequent therapy, particularly in HER2+ and TNBC [3, 4]. The main challenge for surgeons performing BCS after NAC is determining the presence and extent of the residual lesion, especially in good responders to NAC [5]. The partial response to NST may influence the surgical planning. The honeycomb (swiss cheese) pattern is problematic as the residual carcinoma presents as multiple scattered foci over a tumor bed, whereas the concentric (onion peel) pattern represents a uniform response to NST [6]. Radiologic complete response is the presence of a marking clip overlying a normal breast parenchyma or an architectural distortion pattern in sonomammography (clip sign) [7]. It has been documented that pathologic complete response is a

prognostic marker for breast ca ncer patients after NAC, however, clinical, and radiologic complete response complicates the surgery because it is difficult to locate the original site of the primary tumor [8]. The gold standard of good pathological assessment is the identification of the area that best correlates with clinical and radiological findings in the NAC-BCS patients [9]. Although to our knowledge there are no differences regarding survival outcomes for patients receiving NAC versus adjuvant chemotherapy, however, in case of BCS after NAC, there were 6 factors that contributed to both local recurrence and locoregional recurrence: 1) clinical/radiologic T3 to T4 tumor at the time of diagnosis; 2) positive lymph nodes at the time of diagnosis; 3) the presence of ER negative disease; 4) the presence of >3 pathologically positive lymph nodes; 5) the absence of pCR in the breast after NAC; and 6) the absence of pCR in the axilla after NAC [10].

2. PATIENTS AND METHODS

The aim of this study was to determine the impact of margin width on local recurrence after breast conservative surgery for patients who responded to neoadjuvant chemotherapy. This study included 75 Egyptian female breast cancer patients who had a clinical and radiologic response to neoadjuvant chemotherapy; whether locally advanced breast cancer or early cT2 and/or cN1 triple negative / Her 2 positive breast cancer. Patients were assessed by the multidisciplinary team at the National Cancer Institute: including a surgical oncologist, medical oncologist, radiation oncologist and interventional radiologist.

Investigations included full labs, bilateral sonomammography, contrast enhanced sonomammography or magnetic resonance imaging. The type of imaging modality in the post-neoadjuvant setting was according to pre-neoadjuvant breast imaging. Tumor marking with ultrasound guided clip and/or clips (for multifocal tumors), before initiation of neoadjuvant chemotherapy, was followed by ultrasound guided wire localization (for impalpable cases), after completion of neoadjuvant chemotherapy.

Patients were assigned to breast conservative surgery combined with intraoperative frozen section. Also, specimen orientation was done; for marking circumferential margins, and specimen radiography; for documentation of clip(s) and tumor localization (Figure 1) . Patients were assessed clinically and radiologically, after completion of their course of radiotherapy, with regular appointments at the outpatient clinics up to 2 years follow up after surgery.

Clip marking | Wire localization | Wire guided excision

Specimen orientation | Specimen radiography | Specimen frozen section

Figure 1: Case study for wire guided excision after a good response to neoadjuvant therapy

Statistical analysis was done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean, median, and range. Qualitative data were expressed as number, frequency, and percentage. Survival analysis was done using Kaplan-Meier method. A p-value < 0.05 was considered significant.

3. RESULTS

The mean age was 43.8±9.5 years and 65.3 % of patients were in the premenopausal status (Figure 2). Multifocal breast tumors were present in 11 patients (14.7%). All patients (75 cases) had either cT2 or cT3 disease. Clinical nodal disease (cN1-3) was found in 68 patients (90.7%). Most patients (92 %) had either stage IIB or IIIA disease. The most common histological type was invasive duct carcinoma (94.7%). Luminal B was the most encountered molecular subtype in 42 patients (56%), followed by triple negative breast cancer in 18 patients (Figure 3). The main type of surgical procedure was wire guided excision, performed in 36 patients (48%) (Figure 4) and 68 patients (90.7%) had axillary lymph node dissection.

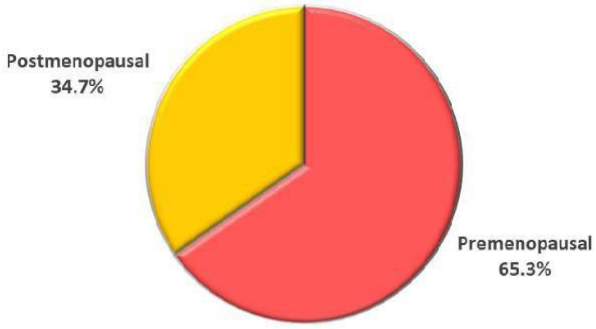

Figure 2: Menopausal status of the studied group

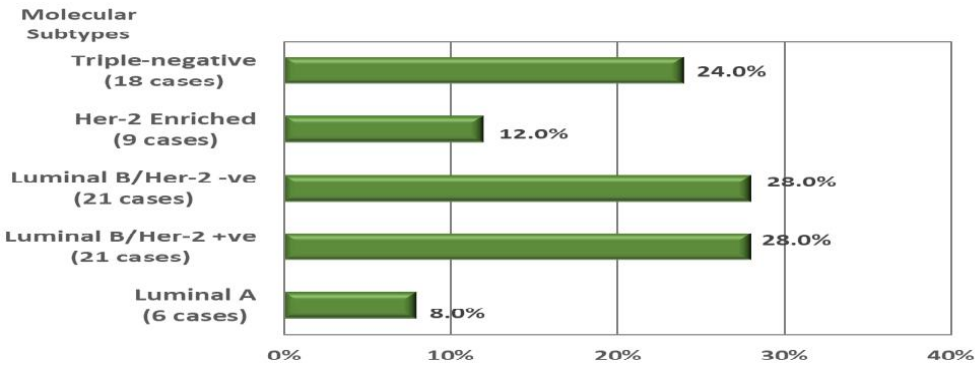

Figure 3: Molecular subtypes of the studied group

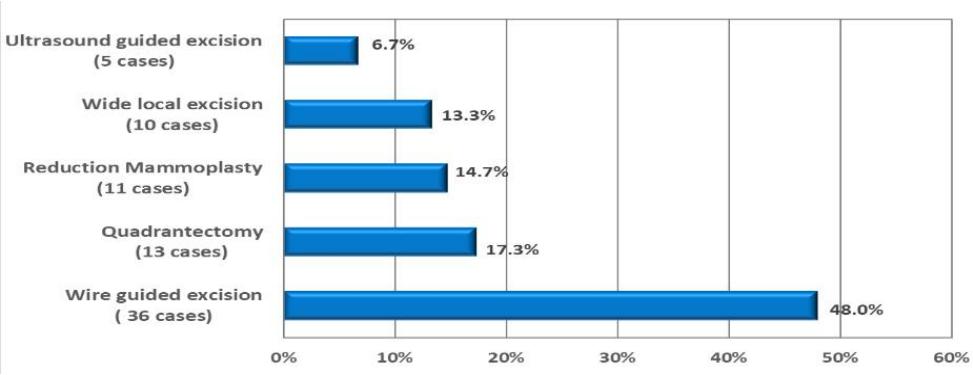

Figure 4: The type of surgical procedure performed in the studied group

Table 1: Pre-treatment characteristics of the studied group

		Number	Percentage (%)
Whole Group		**75**	**100**
Age (years)	< 50	50	66.7
	≥ 50	25	33.3
Multifocality	Yes	11	14.7
	No	64	85.3
cTNM			
cT	cT2	45	60.0
	cT3	30	40.0
cN	cN0	7	9.3
	cN1	59	78.7
	cN2	8	10.7
	cN3	1	1.3
Tumor Stage	IIA	5	6.7
	IIB	35	46.7
	IIIA	34	45.3
	IIIC	1	1.3
Tumor Type	Invasive ductal carcinoma	71	94.7
	Invasive lobular carcinoma	1	1.3
	Undifferentiated carcinoma	2	2.7
	Mucinous carcinoma	1	1.3
Tumor Grade	G I	3	4.0
	G II	41	54.7
	G III	31	41.3
Molecular Subtype	Luminal A	6	8.0
	Luminal B/Her-2 +ve	21	28.0
	Luminal B/Her-2 -ve	21	28.0
	Her-2 Enriched	9	12.0
	Triple-negative	18	24.0

Legend: cTNM; Clinical tumor staging, Her-2; Human epidermal growth factor receptor 2

Table 2: Post-treatment outcome of the studied group

		Number	Percentage (%)
Whole Group		**75**	**100**
Radiologic Response	rCR	31	41.3
	rPR	44	58.7
Least Circumferential Margin (mm)	10 (1-25)*****		
	≤ 2	11	14.7
	> 2	64	85.3
Lymph Nodes	12 (3-25)*****		
Positive	+ve	22	29.3
Negative	-ve	53	70.6
Ductal Carcinoma In Situ	Yes	17	22.7
	No	58	77.3
Lymphovascular Invasion	Yes	13	17.3
	No	62	82.7
ypTNM			
ypT	ypT0	5	6.7
	ypT1a	3	4.0
	ypT1b	9	12.0
	ypT1c	16	21.3
	ypT2	39	52.0
	ypT3	3	4.0
ypN	ypN0	46	61.3
	ypN0(sn)	7	9.3
	ypN1a	17	22.7
	ypN2a	3	4.0
	ypN3a	2	2.7

Legend: rCR; radiologic complete response, rPR; radiologic partial response, sn; sentinel node, ypTNM; Post neoadjuvant pathologic staging

The majority of patients (49 cases) received neoadjuvant chemotherapy (AC / Taxol), while the remaining patients (26 cases) received neoadjuvant chemotherapy and targeted therapy (AC / Taxol + Herceptin). All patients (75 cases) received post operative radiation therapy, 27 cases received adjuvant hormonal therapy alone (6 cases were luminal A and 21 cases were luminal B HER-2 negative), 21 cases received adjuvant herceptin and hormonal therapy (luminal B HER-2 positive), 8 cases received adjuvant herceptin alone (HER -2 Enriched), and 19 cases were kept under follow up (18 cases were triple-negative and 1 case was HER-2 Enriched but unfortunately had a herceptin induced cardiotoxicity). Radiologic complete response was seen in 31 patients (41.3%). Most patients (85.3%) had a least circumferential margin of more than 2 mm. Positive nodal involvement was confirmed in 22 patients (29.3%). Over 70% of patients had ypT stage 1c or 2 (Figure 5) and over 60 % of patients had ypN stage 0 (Figure 6).

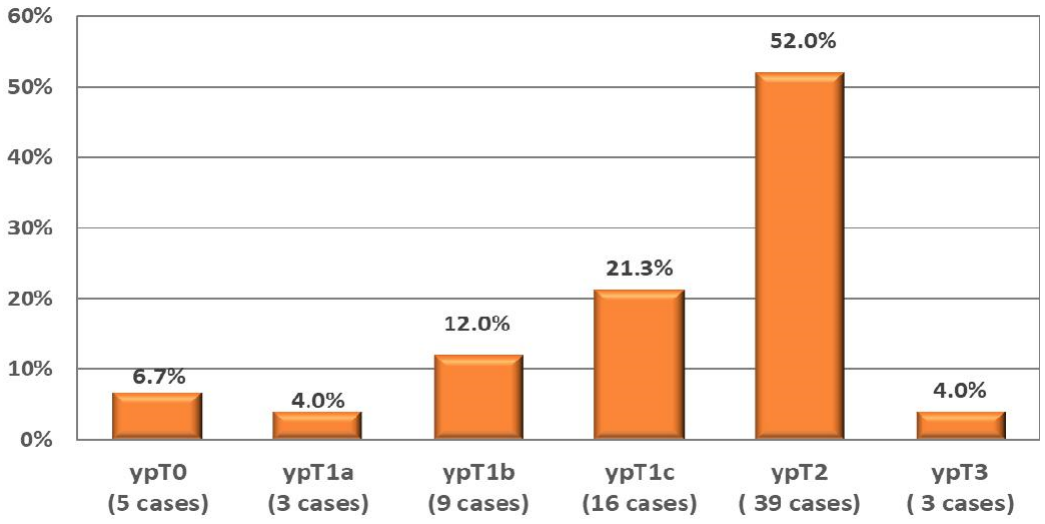

Figure 5: The post neoadjuvant pathologic T stage of the studied group

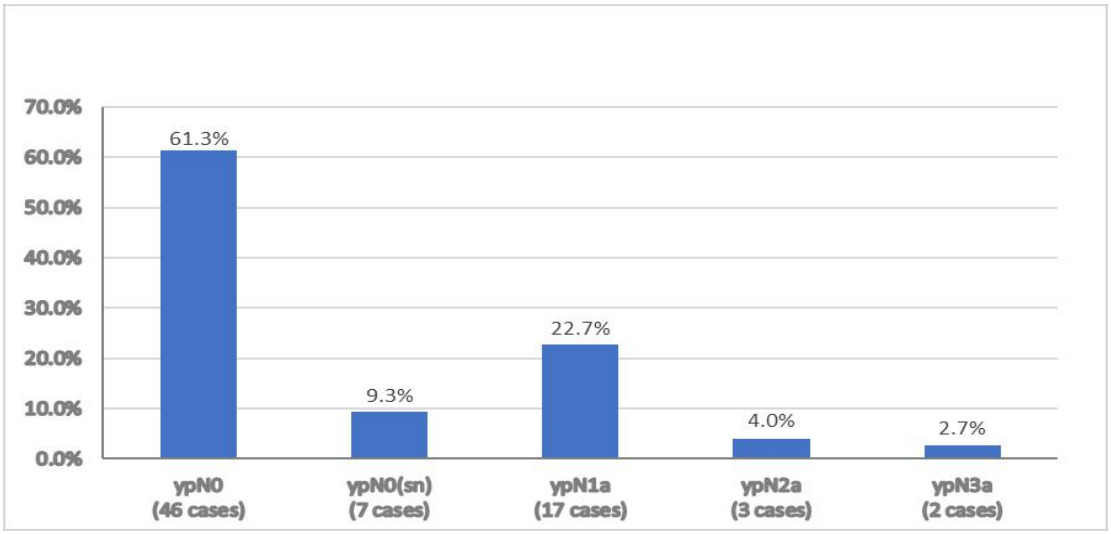

Figure 6: The post neoadjuvant pathologic N stage of the studied group

Table 3: Factors affecting local recurrence free survival in the studied group

Factors	N	n events	Survival at 3 years (%)	p-value
Whole Group	**75**	**4**	**94.6**	
Age				0.707
< 50 years	50	3	93.9	
≥ 50 years	25	1	96.0	
Multifocality				0.510
Yes	11	1	90.9	
No	64	3	95.3	
cTNM				
cT				0.685

cT2	45	2	95.6	
cT3	30	2	93.1	
cN				0.609
cN0	7	0	100	
cN1	59	3	94.9	
cN2, 3	9	1	88.9	
Tumor Stage				0.254
Stage II	40	1	97.5	
Stage III	35	3	91.3	
Tumor Type				0.630
Invasive ductal carcinoma	71	4	94.3	
Other types	4	0	100	
Tumor Grade				0.717
G I or II	44	2	95.5	
G III	31	2	93.4	
Molecular Subtype				0.709
Luminal A	6	1	83.3	
Luminal B/Her-2 +ve	21	1	95.2	
Luminal B/Her-2 -ve	21	1	95.0	
Her-2 Enriched	9	0	100	
Triple-negative	18	1	94.4	
Radiologic Response				0.505
rCR	31	1	96.8	
rPR	44	3	93.1	
Least Circumferential Margin				**0.399**
≤ 2 mm	**11**	**0**	**100**	
> 2 mm	**64**	**4**	**93.7**	
Factors	**N**	**n events**	**Survival at 3 years (%)**	**p-value**
Lymph Nodes				0.053
Positive	22	3	87.0	
Negative	53	1	98.1	
Ductal Carcinoma In Situ				0.909
Yes	17	1	94.1	
No	58	3	94.8	
Lymphovascular Invasion				0.707
Yes	13	1	92.3	
No	62	3	95.2	
ypTNM				
ypT				**< 0.001**
ypT0	**5**	**2**	**60.0**	
ypT1	**28**	**0**	**100**	
ypT2, 3	**42**	**2**	**95.1**	
ypN				**0.042**
ypN0	**52**	**1**	**98.1**	

ypN1a	**17**	**3**	**82.4**
ypN2a, 3a	**5**	**0**	**100**

Legend: cTNM; Clinical tumor staging, Her-2; Human epidermal growth factor receptor 2, rCR; radiologic complete response, rPR; radiologic partial response, sn; sentinel node, ypTNM; Post neoadjuvant pathologic staging

The median follow up period was 30.2 months By the end of follow up, four patients developed local recurrence (1 case was Luminal A, 1 case was Luminal B/Her-2 +ve, 1 case was Luminal B/Her-2 -ve, and 1 case was TNBC). The unadjusted local recurrence rate was 5.3% and cumulative local recurrence free survival of the whole studied group at 36 months was 94.6%. The least circumferential resection margin (2mm) had no impact on local recurrence free survival. The only factors that affected LRFS were the ypT stage ($p < 0.001$) and ypN stage ($p=0.042$). However, the local recurrence free survival analysis for ypT0 was worse compared to ypT1-3 which could be explained by the phenomenon of "pCR paradox".

4. DISCUSSION

There is no data supporting a positive effect of NAC on tumor free margins. This could be due to a variety of factors; 1) Lack of prospective controlled studies with no consensus on the margin width after NAC and BCS, 2) Difficulty to estimate a non-concentric residual disease after tumor downstaging. As a result, macroscopic evaluation of the original location and extent of residual disease is complicated. It goes without saying that clip marking before NAC is essential to identify the residual tumor or tumor bed and achieve clear margins after BCS [5].

In our study, the median follow up period was 30.2 months. By the end of follow up, four patients developed local recurrence. The unadjusted local recurrence rate was 5.3% and cumulative local recurrence free survival of the whole studied group at 36 months was 94.6% which is comparable to a previous study by Choi, Laws [11]; in which the unadjusted local recurrence rate was 3.9% and 5 year LRFS was 96.3%. The least circumferential resection margin (2mm) had no impact on local recurrence free survival.

Several studies highlighted that margin width after neoadjuvant chemotherapy and breast conservative surgery had no impact on LRFS; Choi, Laws [11] reported that there was no association between margin width and LRFS. Hormone receptor negative subtype, lack of pCR, and positive pathologic nodal status were associated with inferior outcomes in terms of survival. Lin, Lin [12] presumed that a margin of ''no ink on tumor'' maybe sufficient for breast cancer patients treated with NAC and BCS, and it is not necessary for re-excision if least surgical margin is < 1mm. Wimmer, Bolliger [13] emphasized that there is no difference regarding LRFS in close, wide, or unknown margins (after pCR) in NAC-BCS patients and also emphasized the resection of the clipped area in cases of pCR. Mrdutt, Heerdt [1] concluded that a margin greater than 2 mm did not improve the local control in patients undergoing breast conservation following NAC. However, pathologic features and tumor biology, not margin width, were associated with IBTR in NAC-BCS patients.

The main point of strength in our study is that the cumulative local recurrence free survival of the whole studied group at 36 months was 94.6%. LR rates are low after NAC and BCS. As a result, what constitute to be the least margins for surgeons performing BCS should be defined as ''no ink on tumor'' since most surgeons tend to achieve larger margins which comprise the cosmetic outcome of breast conservation in NAC-BCS patients.

Our study has some limitations, which must be taken into consideration when interpreting our findings, namely, a small sample size (75 cases) and a relatively short period of follow up (median follow up = 30.2 months). The local recurrence free survival analysis for ypT0 was worse compared to ypT1-3 which could be explained by the phenomenon of "pCR paradox".

All attempts should be made to undergo BCS in patients receiving NAC, whether in locally advanced breast cancer or early cT2 and/or cN1 triple negative / Her 2 positive breast cancer, unless there are contraindications for breast conservation. All patients undergoing NAC and BCS should be included in prospective trials with larger sample size and longer duration of follow up for better evaluation of the added benefits and drawbacks. There is an increase in both prognostic and predictive markers obtained from both prospective and retrospective studies that will allow clinicians to customize an individualized treatment approach. However, further studies will be necessary to potentially change the guidelines regarding the treatment offered for the locoregional control of breast cancer patients.

5. CONCLUSION

In our study, The least circumferential resection margin (2mm) had no impact on local recurrence free survival. Accordingly, margin of excision after neoadjuvant chemotherapy and breast conservative surgery is safe according to ‘‘no ink on tumor’’ guideline and we emphasize the resection of the clipped area in cases of cCR and/or rCR. We recommend further studies with larger sample size and longer duration of follow up to mitigate the local recurrence after breast conservative surgery following neoadjuvant chemotherapy. Also, to maximize the oncological or cosmetic outcomes and minimize the local recurrence rates, there are essential steps to be followed as; accurate staging before and after NAC, clip placement to be followed by wire localization in case of cCR and/or rCR, modern oncoplastic techniques that allow more options for surgical resections without affecting the oncological or cosmetic outcomes, and finally intraoperative radiologic and pathologic assessment of the breast surgical specimens.

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AUTHOR CONTRIBUTION

Omar Z. Youssef developed the main concept of the study. Walid Akmal performed the data collection, analysis and drafted the manuscript. Tamer M. Manie contributed to the editing and critical revision of the manuscript. All authors reviewed and approved the final draft.

CONSENT TO PARTICIPATE AND ETHICAL APPROVAL

All participating patients signed an informed consent with proper counseling about their participance in scientific research after approval of Institutional Review Board and Ethical Research Committee (IRB Review Number: 201920014.3).

DATA AND MATERIAL AVAILABILITY

All data associated with this study are present in the paper.

SOURCE OF FUND

This study has not received any external funding.

CONFLICT OF INTERST

Authors declare that there are no conflict of interests.

REFERENCES

1. Mrdutt, M., et al., Margin Width and Local Recurrence in Patients Undergoing Breast Conservation After Neoadjuvant Chemotherapy. Ann Surg Oncol, 2022. 29(1): p. 484-492.
2. Zhang, J., et al., Pathologic response rates for breast cancer stages as a predictor of outcomes in patients receiving neoadjuvant chemotherapy followed by breast-conserving surgery. Surg Oncol, 2021. 36: p. 91-98.
3. Earl, H., et al., Neoadjuvant trials in early breast cancer: pathological response at surgery and correlation to longer term outcomes - what does it all mean? BMC Med, 2015. 13: p. 234.
4. Spring, L.M., Y. Bar, and S.J. Isakoff, The Evolving Role of Neoadjuvant Therapy for Operable Breast Cancer. J Natl Compr Canc Netw, 2022. 20(6): p. 723-734.
5. Volders, J.H., et al., Breast-conserving surgery following neoadjuvant therapy-a systematic review on surgical outcomes. Breast Cancer Res Treat, 2018. 168(1): p. 1-12.
6. Cha, C., et al., Comparison of resection margin status after single or double radiopaque marker insertion for tumor localization in breast cancer patients receiving neoadjuvant chemotherapy. Breast Cancer Res Treat, 2020. 184(3): p. 797-803.

7. Makanjuola, D.I., A. Alkushi, and K. Al Anazi, Defining radiologic complete response using a correlation of presurgical ultrasound and mammographic localization findings with pathological complete response following neoadjuvant chemotherapy in breast cancer. Eur J Radiol, 2020. 130: p. 109146.
8. Shalaby, L.A.S.E.D., E.S.e.d. Khallaf, and M.M. Moussa, Clip and wire localization of locally advanced malignant breast masses in patients undergoing neoadjuvant chemotherapy and breast conservation therapy. Egyptian Journal of Radiology and Nuclear Medicine, 2019. 50(1).
9. Veys, I., et al., ICG fluorescence imaging as a new tool for optimization of pathological evaluation in breast cancer tumors after neoadjuvant chemotherapy. PLoS One, 2018. 13(5): p. e0197857.
10. Valachis, A., et al., Risk factors for locoregional disease recurrence after breast-conserving therapy in patients with breast cancer treated with neoadjuvant chemotherapy: An international collaboration and individual patient meta-analysis. Cancer, 2018. 124(14): p. 2923-2930.
11. Choi, J., et al., Margins in Breast-Conserving Surgery After Neoadjuvant Therapy. Ann Surg Oncol, 2018. 25(12): p. 3541-3547.
12. Lin, J., et al., Association of surgical margins with local recurrence in patients undergoing breast-conserving surgery after neoadjuvant chemotherapy. BMC Cancer, 2020. 20(1): p. 451.
13. Wimmer, K., et al., Impact of Surgical Margins in Breast Cancer After Preoperative Systemic Chemotherapy on Local Recurrence and Survival. Ann Surg Oncol, 2020. 27(5): p. 1700-1707.