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Assessment of safety margins in breast cancer conserving surgeries after peritumoral carbon particles injection and intraoperative specimen radiography compared to frozen section pathology

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Abstract

Breast cancer is the most diagnosed malignancy and the second common cause of cancer-related death in women worldwide. Breast-conserving surgery (BCS) plus radiation therapy, also known as breast-conserving therapy (BCT), is recommended in early-stage cases. Evaluation of safety margins in breast conserving surgery by preoperative peritumoral carbon injection and intraoperative specimen radiography compared to frozen section pathology This study was conducted at Kasr Al-Ainy teaching Hospitals, Faculty of Medicine, Cairo University between 1st January 2021 and 1st January 2022. The study included 140 Female patients aged between 20 -70 years old with breast cancer who are candidate for breast conserving surgery. There is significant correlation between specimen radiography and free margins identified by paraffin section which support this method of intraoperative margins assessment as it could detect true free margins in 61 patients 98.4% of all free margins With added preoperative peritumoral carbon injection in group A, frozen section pathology examination of safety margins showed significant relation with also free margins identified by paraffin pathology where there are 98.5 true negative margins of all negative margins. Peritumoral carbon particles injection provides better visual feedback for surgeon to achieve effective excision with safety margins. It is safe and helpful to improve results of specimen radiography and frozen section in margins assessment and decrease intraoperative and postoperative re-excision rates especially in early breast cancer cases. Specimen radiography is a reliable method for identifying free surgical margins in breast conserving surgeries.

Keywords: Specimen radiography, Frozen section pathology, Carbon particles injection, Breast conserving surgery.

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1. Introduction

Breast cancer is the most diagnosed malignancy worldwide where more than 2.26 million new cases diagnosed in 2020. In Egypt, breast cancer is the most common malignancy in women, accounting for 38.8% of cancers in this population. For long, mastectomy had been the standard of management of breast cancer surgeries. Nowadays, with the recent advances in diagnostic and therapeutic techniques breast conservative surgeries are being safely offered to the majority of patients [1-2]. Early-stage diagnosis of breast cancer increases the chances of survival and, therefore, reduces mortality rates. Breast-conserving surgery (BCS) plus radiation therapy, also known as breast-conserving therapy (BCT), is recommended for individuals diagnosed with early or localized breast cancer [3]. The backbone of breast conserving surgery is oncological safety. Margin status has been linked directly to local and distant recurrence. Therefore, effort must be made to attain tumor free resection margins without resecting too much healthy breast parenchyma around the tumors [4]. Many tumor localization and margin status assessment techniques have been discussed in literature. None were proven to be substantially superior to others. Our prospective single center study assesses the value of preoperative ultrasound guided carbon localization of margins of resection and intraoperative specimen radiography in comparison to frozen section pathology, in terms of evaluating the margins safety [5]. This work aimed to evaluate safety margins in breast conserving surgery by preoperative peritumoral carbon injection and intraoperative specimen radiography compared to frozen section pathology.

2. Patients and Methods

This study was conducted at Kasr Al-Ainy teaching Hospitals, Faculty of Medicine, Cairo University between 1st January 2021 and 1st January 2022. The study protocol was reviewed and permitted by the institutional research and ethics committee. This study includes 140 Female patients aged between 20 -70 years old with breast cancer who are candidate for breast conserving surgery

2.1. Inclusion criteria

Early-stage breast cancer cT_{1-2} candidate for breast conserving surgery and post neoadjuvant breast cancer cases who turned cT_{1-2} post neoadjuvant and candidate for breast conserving surgery.

2.2. Exclusion criteria

Inflammatory breast cancer (cT4d) and Multicentric breast cancer

2.3. Methods of the Study

Female patients presented at specialized outpatient breast clinic, (many of whom were referred to breast unit by the national screening program). After thorough history taking and meticulous clinical examination, patients had a breast Sonomammography, MRI or Contrast Enhanced Mammography (CESM). Those who were found to be BIRADS 4 or 5 were sent to the breast unit in radiology department for an ultrasound guided core needle biopsy. For patients with pathologically proven breast cancer metastatic workup in the form of chest X-ray and abdominal ultrasound were examined. Thoracoabdominal CT scans were performed for cases needed neoadjuvant theraby. A well-established breast cancer specific multidisciplinary team (MDT) mange all cases. MDT comprises breast surgeons, oncologists, pathologists and radiologists. Female patients with breast cancer were called to be examined by MDT, where a tailored treatment strategy is planned. Those who were planned for breast conserving surgery either upfront or post neoadjuvant treatment were included in our study. Patient who was candidate for breast conserving surgery randomized into two groups:

2.3.1. Group A

Group A included 70 patients. For these patients; preoperative ultrasound guided carbon particles injection was performed under local anesthesia around tumor. Carbon particles were injected the day before the operation at four points, 1 cm superior, inferior, medial and lateral to the main mass. Sterile suspended carbon particles diluted with saline solution; 1 cm of Black Eye™ ink synthetized by THE STANDARD CO., LTD was diluted to 20 cm saline then 5 cm of diluted ink was injected at four points around the lump under ultrasound guidance using a wide bore needle, creating multiple black trails one centimeter wider than the margins of the tumor by continuous infusion on withdrawal of the needle. Care should be taken to avoid too deep injection for fear of chest wall injuries and too superficial injection which is known to cause a long-lasting tattooing of the skin, in cases where the injection entry points might not be excised. Surgical resection of mass was guided by the black carbon tattoo ensuring proper safety margins. Lateral, medial, superior and inferior. Posteriorly, the breast parenchyma was resected down to the pectoral fascia and cutaneously a skin ellipse over the mass was resected or 1 cm safety margin in case no skin were excised. Specimen sent for intraoperative frozen section pathology examination. Intraoperative decision was decided upon frozen section pathology opinion after histopathological assessment; either excision of further margins or wait for paraffin study result. Finally, specimen sent for paraffin section examination.

2.3.2. Group B

Include 70 patients. In these patients; resection of mass performed by traditional intraoperative palpation. One-centimeter gross safety margins radially and superficially (in cases where no skin excision was needed) and all breast parenchyma deeply down to the pectoral fascia were resected in all cases to ensure a properly adequate posterior margin. Excision was guided by tactile palpation and visual feedback, Marking the specimen by threads (Lateral; long thread - Superior; short thread -Deep; double thread), specimen sent for frozen section pathology then to be confirmed by final paraffin pathology examination, Intraoperative decision was decided upon frozen section pathology opinion after histopathological assessment; either excision of further margins or wait for paraffin study result and Finally, specimen sent for paraffin section examination.

2.4. Statistical analysis of data

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test (Chan, 2003a). For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 (Chan, 2003b). Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic efficacy were calculated as described by (Galen, 1980). P-values less than 0.05 were considered as statistically significant**.**

3. Results and discussion

Breast cancer is the most common type of cancer among women in developing countries. It represents 25% of all female cancers. Mastectomy was the management of choice in breast cancer for a long time; nowadays, increased patients' awareness, ongoing screening campaigns, enhanced imaging modalities and systemic treatment has led to the fact that breast conserving surgeries can be safely offered to most women with breast cancer. several follow-up studies showed comparable disease-free and almost same survival rates between patients undergoing mastectomy and breast conserving surgeries [6-7]. In this pilot study, preoperative peritumoral carbon nanoparticles injection added on to improve accuracy of intraoperative specimen radiography and frozen section examination results in assessment of safety margins in breast conserving surgeries. Carbon nanoparticles used in this study has many advantages in comparison with blue dyes, India ink and charcoal suspension.

Blue dyes easily disperse in breast tissue after injection and stain axillary lymph node while carbon particles are heavy particles taken by phagocytes and fixed in tissues. It can't easily disperse and could stay in injected area for months. Using India ink in marking may cause localized and generalized allergic reaction while carbon nanoparticles is purified particles that cause minimal allergy. Charcoal suspension has major disadvantage of blockage of syringe during injection; bigger particles that could aggregate and block the syringe (150 microns) which is not present with carbon nanoparticles injection (60-100 nano). The stability of carbon marking over time is one of its strengths. Carbon is particulate and not water soluble, it stays within the track. In addition, these carbon particles get phagocytosed and thus marking these tracks for long periods of time. This is especially useful if surgery is delayed for days after injecting the carbon. Graham et al., compared specimen radiography results with histological examination and found that positive predictive value, 98% and negative predictive value, 32% versus 37.5% and 98.39% respectively in our study [8]. Few studies discussed the effectiveness of specimen radiography method in assessment of safety margins; retrospective study was done at the Basel University Hospital Breast Center where assessment of safety margins done by specimen radiography and results were; accuracy, sensitivity and specificity 60%, 60%, and 60%, respectively versus 91.4%,75% and 92.4% in group A in our study [9]. Layfield et al reported that use of intraoperative specimen radiography for palpable breast cancer led to a reduction in the mean specimen weight without increasing re-excision rates and was associated with improved cosmesis [10]. 182 patients with breast cancer who underwent intraoperative specimen radiography after BCS at the Ajou University Hospital. This Study illustrated the value of intraoperative specimen radiography in determining the margin status of excised palpable or nonpalpable breast lesions. Additionally, the level of agreement between the radiologic and final pathologic interpretations of margin status was analyzed. This study suggests that specimen radiography can be useful in assessing margin status [11]. A recent study evaluated the diagnostic accuracy of intraoperative specimen radiography on margin level in patients treated with neoadjuvant chemotherapy. Study included 174 cases receiving breast conserving surgery (BCS) after neoadjuvant chemotherapy where specimen radiography results compared to paraffin pathological examination which served as the gold standard for evaluation. specimen radiography results in schaefgan et al study in comparison to our study results in group A in post neoadjuvant cases were sensitivity of 19.2%, versus 75% a specificity of 89.2% versus 77.78%, a positive predictive value of 7.7% versus 42.86%, and a negative predictive value of 95.9% versus 93.33% [12]. Specimen radiography is still important in order to document the removal of calcifications and the tumor. Benefits of specimen radiography for margin assessment include relatively accessible devices and, when compared to frozen section pathology, less economic impact and faster results (5-10 min). Garcia et al discussed meta-analysis study, which includes 9 studies related to frozen section, evaluated the accuracy of intraoperative technique for margin assessment and reported sensitivity of 86% versus 25% in our study and specificity of 91% versus 88.7% in group A of our study. Study conducted in Oncology Center Mansoura University, where the data of 219 patients with breast cancer, who were managed by breast conserving surgery with intraoperative frozen section analysis of the safety margins, was analyzed. Results: The intraoperative frozen section analysis of safety margin was negative from the start in 183 (83.6%) patients, while it was positive in 36 patients (16.4%). Intraoperative decision of margin re-excision was applied for 29 patients (13.2%) in order to reach negative margin versus (12.9%) in group B of our study. The postoperative paraffin results were typical with intraoperative frozen section analysis results in 216 patients (98.6%) [14]. Neoadjuvant therapy had a good advantage of improving the chance of breast conserving surgeries but on the other hand, it confuses the margins assessment by resulting fibrosis.all patients in group A who recalled for another operation for reexcision were presented initially post neoadjuvant while 3 out of 8 patients in group B who recalled for reexcision presented post neoadjuvant. All early breast cancer patients in group A didn't need post-operative recall for reexcision with only 5 patients in group B. There was no significant difference between both groups in operative time, post-operative pain, seroma formation, wound infection, and hospital stay which was only 1 day in both groups. There were only 2 cases with wound infection and 1 case of seroma formation in group A versus 3 case of wound infection and 2 cases of seroma formation in group B.

Figure 1: Ultrasound guided carbon particles injection.

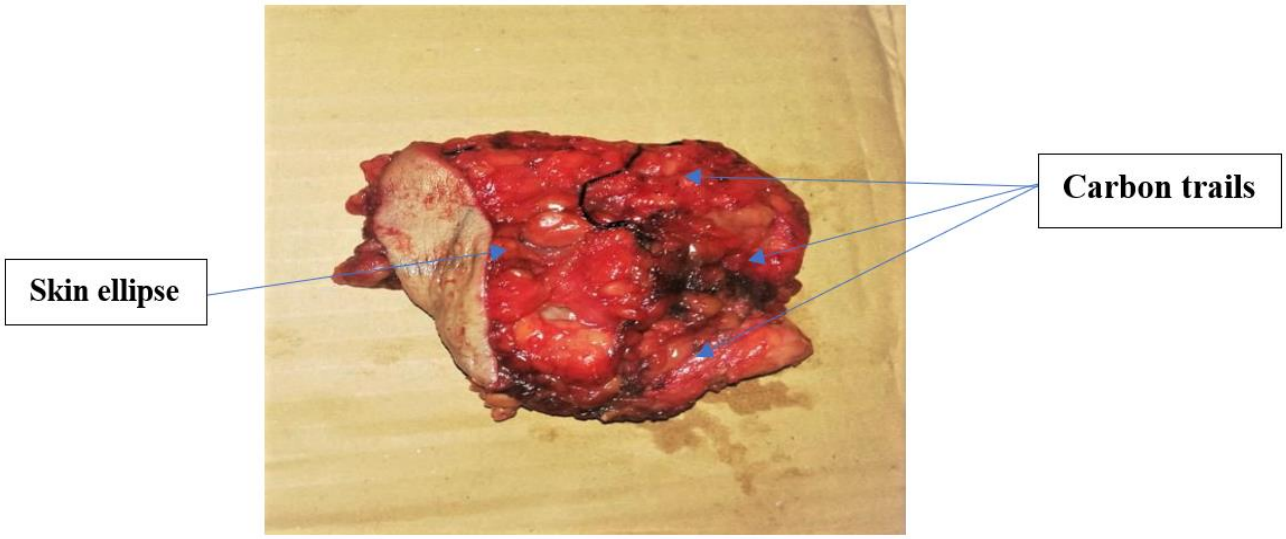

Figure 2: Excised mass with skin ellipse and carbon trails identified.

Marking the specimen by threads (Lateral; long thread - Superior; short thread -Deep; double thread).

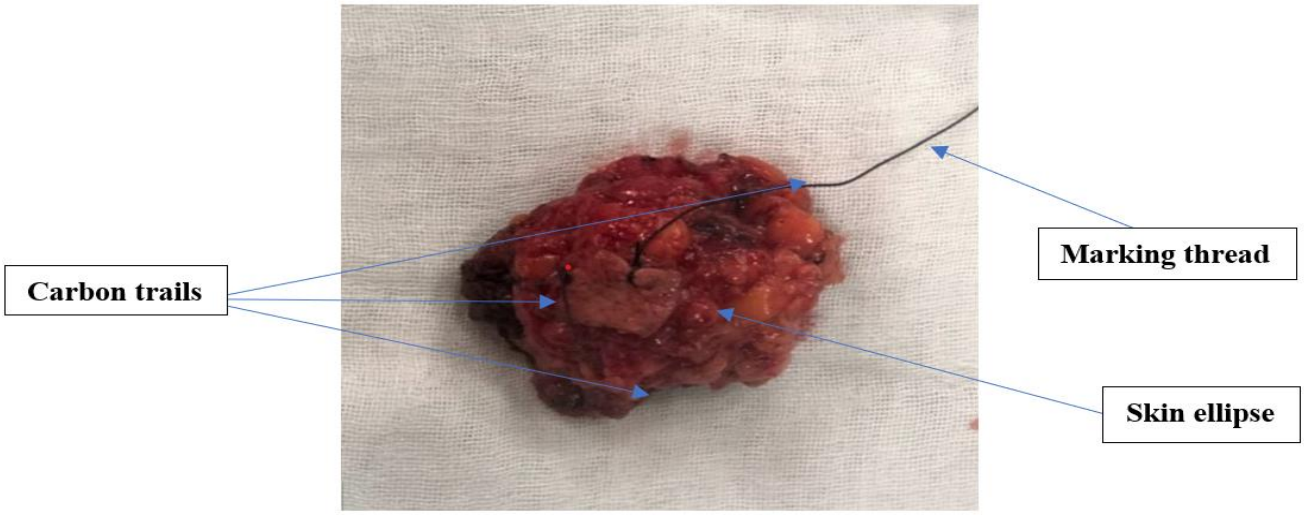

Figure 3: Excised specimen marked by threads.

Specimen was sent for specimen radiography to assess the safety margins by dedicated breast radiography consultant.

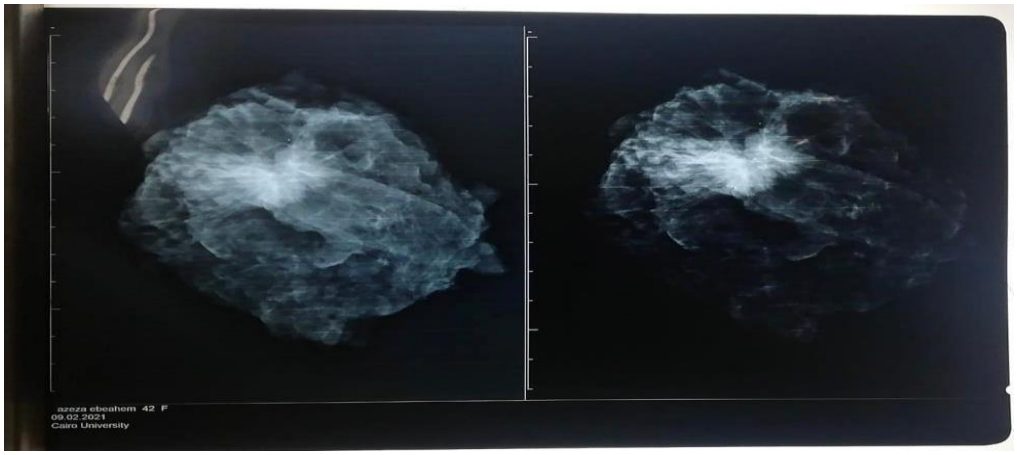

Figure 4: Intraoperative specimen radiography.

Table 1: Clinicopathological demographic data.

		Group A		Group B	
		Count	%	Count	%
Pathology	DCIS	2	2.9%	4	5.7%
	IDC G_{II}	50	71.4%	60	85.7%
	IDC G_{II} + LCIS	2	2.9%	0	0.0%
	IDC G_{III}	12	17.1%	5	7.1%
	ILC	2	2.9%	0	0.0%
	ILC G_{II}	2	2.9%	1	1.4%
IHC4	Luminal A	44	62.8%	34	48.5%
	Luminal B1	14	20.0%	26	37.1%
	Luminal B2 (Her2 +)	10	14.3%	6	8.6%
	Triple negative	0	0.0%	3	4.3%
	Her2 enriched	2	2.9%	1	1.5%
T stage	1	22	31.4%	38	54.2%
	2	48	68.6%	32	45.8%
N stage	0	40	57.1%	28	40.0%
	1	25	35.7%	33	47.1%
	2	5	7.1%	9	12.9%

*DCIS: Ductal carcinoma insitu, *IDC: Invasive duct carcinoma, *ILC: Invasive lobular carcinoma, *IHC4: Immunohistochemistry, *G: Grade, *T: tumor staging *N: Lymph node stage, *Her2: Human epidermal growth factor receptor 2.
The mean age of study was 51.97 years for group A and 51.66 years for group B. patients were diagnosed with breast cancer by means of true cut core needle biopsy preoperatively, most the patients in study group had invasive duct carcinoma grade 2. Regarding immunohistochemistry in group A and group B respectively; 62.8% Vs 48.5% of patients were Luminal A, whereas 20% Vs 37.1% were luminal B_1 and 14.3% Vs 8.6% were luminal B_2 and 2.9% Vs 1.5% Her2 enriched. Most of patients in group A were T_2 68.6 % N_0 57.1% while in group B, T_1 54.2% N_1 47.1%. Regarding patient's presentation in this study, it's noted that early breast cancer cases represent 68.6% Vs 70% while post neoadjuvant patients represent 31.4% Vs 30% in group A and group B respectively.

Table 2: Correlation between specimen radiography and paraffin pathology in group A.

		Margins by specimen radiography			
		Infiltrated		Free	
		Count	%	Count	%
Margins by paraffin pathology	infiltrated	3	37.5%	1	1.6%
	free	5	62.5%	61	98.4%
	Total	8	100%	62	100%

There is significant correlation between specimen radiography and negative margins identified by paraffin section results. Specimen radiography could detect 98.4% of all free margins that identified by paraffin pathology **(P value 0.004)**. However, it only detected 37.5% of all infiltrated margins identified by paraffin pathology.

Table 3: Specimen radiography results.

Specimen radiography	Value
Sensitivity	75.00%
Specificity	92.42%
Positive Predictive Value	37.50%
Negative Predictive Value	98.39%
Accuracy	91.43%

In **group A**, specimen radiography results of identification of margins in comparison with the standard paraffin pathological technique, showed high specificity rates of 92.42%, sensitivity of 75%, positive predictive value 37.5%, negative predictive value 98.39% and accuracy 91.43%.

Table 4: Correlation between frozen and paraffin pathology results in group A.

Group A		Margins by frozen pathology			
		Infiltrated		free	
		Count	%	Count	%
Margins by paraffin pathology	infiltrated	3	60.0%	1	1.5%
	free	2	40.0%	64	98.5%
	Total	5	100%	65	100%

There is significant correlation between frozen pathology and paraffin section results regarding detection of free margins. Frozen pathology could detect 98.5% of all free margins that identified by paraffin pathology **(P value 0.001).** Also, it could identify 60% of all infiltrated margins patients. Intraoperative reexcision rate after frozen section examination in this group was 7.1%.

Table 5: Correlation between frozen and paraffin pathology results in group B.

Group B		Margins by frozen pathology			
		Infiltrated		free	
		Count	%	Count	%
Margins by paraffin pathology	infiltrated	2	22.2%	6	9.8%
	free	7	77.8%	55	90.2%
	Total	9	100%	61	100%

Frozen pathology could detect 90.2% of all free margins that identified by paraffin pathology and 22.2% of all infiltrated margins patients**.** Also, intraoperative reexcision rates after frozen section examination in this group was 12.9%.

4. Conclusions

Peritumoral carbon particles injection provides better visual feedback for surgeon to achieve effective excision with safety margins. It is safe and helpful to improve results of frozen section pathological examination in margins assessment and decrease intraoperative and postoperative reexcision rates especially in early breast cancer cases. Specimen radiography is a reliable method for identifying free surgical margins in breast conserving surgeries, especially when combined with preoperative peritumoral carbon particles injection. It showed high specificity rate and could be used in hospitals where frozen pathology is not available to decrease reexcision rate. Further studies with larger sample sizes are needed to confirm the significant advantage of this technique.

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