Evaluation of the efficacy and safety of ultrasound guided injection of carbon nanoparticles as a preoperative localizing tool of non-palpable breast cancer and sentinel lymph nodes detection

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Objective
This study aimed to measure the efficacy of using carbon nanoparticles in the preoperative localization of early breast cancer (BC) cases as well as in the detection of sentinel lymph nodes in Egypt. In addition, the purpose of the study was to determine whether the efficacy of carbon nanoparticles outweighs their high price and additional shipping fees.

Material and methods
The current pilot study enrolled 16 early BC patients, particularly those eligible for breast-conserving surgery. All patients underwent standardized injection techniques. The operating surgeons provided comprehensive intraoperative findings and postoperative histopathological reports of the excised tissues.

Results
After neoadjuvant chemotherapy (NAC), downstaging of the study subjects was achieved until reaching the TNM stage of T1N1M0 and T1N0M0 in 2 cases (12.5%) and 14 cases (87.5%), respectively. Ultrasound-guided injection of carbon nanoparticles was done, followed by surgical excision on the same day or the day after injection. Eleven patients had positive mass lesions preoperatively, with a mean tumoral size of less than 1 cm in maximum dimension. Moreover, 6 out of the 11 patients showed positive black staining intraoperatively with an accuracy of 68.75%. Postoperative histopathological examination (the gold standard) of axillary specimens revealed that 3 out of 16 of the study population have positive tumor-infiltrated lymph nodes. However, only 2 of these cases demonstrated intra-operative black staining, with the black dye's positive and negative predictive values of staining being 100% and 92.2%, respectively.

Conclusions
Preoperative carbon nanoparticle suspension injection is a safe and effective method for adequate tumoral localization in BC patients. Nevertheless, this pilot study did not provide strong evidence for the adequacy of sentinel lymph node detection due to the small sample size, high cost, and extra shipping fees of the carbon nanoparticles.

Keywords:
axillary clearance, breast-conserving surgery, carbon nanoparticles, early breast cancer, preoperative localization

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List of abbreviations: MRM, modified radicle mastectomy; NAC, neoadjuvant chemotherapy; ROLL, radio-guided occult lesion localization; RSL, radioactive seed localization; US, ultrasound

Introduction

Breast cancer (BC) has become the most prevalent cancer among women worldwide, with a high mortality rate. Therefore, screening programs and women's awareness campaigns are required for early detection in order to reduce elevated mortality rates [1].

Currently, breast-conserving surgery is considered the standard surgical treatment option for women with early BC due to its comparable long-term survival rate compared to MRM, yielding an acceptable cosmetic outcome and low morbidity [2].

Preoperative localization of small non-palpable lesions and their draining lymph nodes is an outcome-defining step for an accurate estimation of the true tumor outlines and adequate surgical lesional excision without excessive, unnecessary resection of healthy tissues, resulting in improved cosmetic outcomes. Wire placement has been the standard technique for

preoperative breast lesion localization. Recent research focuses on newly developed techniques compared to wire placement, such as intralesional clip insertion prior to chemotherapy administration, intraoperative ultrasound, radio-guided occult lesion localization (ROLL), radioactive seed localization (RSL), and most recently, carbon nanoparticles injection [2,3].

Carbon nanoparticle injection is currently utilized extensively in the localization of thyroid, breast, and stomach tumors. In preoperative breast tumor localization, carbon nanoparticle suspension is injected perilesional under ultrasound guidance. Carbon nanoparticles are designed with a specifically larger diameter that facilitates their uptake by lymphatics but not by the blood capillaries [4,5].

Neoadjuvant chemotherapy is one of the significant steps in the treatment protocol for women with BC. It contributes to making the management plan more conserving and less physically and psychologically acceptable. After neoadjuvant chemotherapy, carbon nanoparticle injection has been shown to be an effective preoperative localization tool for patients with BC [6].

Methods

Aim of the study

The current pilot study aimed to measure the efficacy of using carbon nanoparticles in the preoperative localization of early breast cancer (BC) cases as well as in the detection of sentinel lymph nodes in Egypt.

Ethical consideration

(1) FMASU REC with Assurance number FWA 000017585.
(2) A detailed explanation of the procedure to the patient.
(3) Informed consent was obtained from all patients.

Patients and methods

This is a single-arm prospective study conducted at the ultrasound clinic and interventional radiology unit in El Demerdash Hospital during the period from late 2020 to early 2022

Inclusion criteria

(1) Patients with non-palpable breast masses (accidentally discovered in the national BC campaign).
(2) Proven BC via biopsy
(3) Patient with early-stage BC and eligible for breast-conserving surgery
(4) No mass lesions post-chemotherapy but with pre-applied clips guiding carbon nanoparticles injection.

Exclusion criteria

(1) Patients who refused to participate in the study.
(2) Advanced stage BC, metastasizing or locally advanced.
(3) Inflammatory BC.
(4) Patients who opted for a radical mastectomy as a surgical option.

Carbon nanoparticle suspension injection was performed on the day of operation or one day prior to the scheduled surgery using a high-resolution ultrasound machine with a 6–15 MHz superficial linear transducer. The procedure duration was approximately 5 min

Patients were in a supine position, exposing the breast side containing the targeted lesion with the abduction of the related upper limb placed over the head. An extensive ultrasound examination was performed by an experienced breast radiologist in order to identify tumor location and plan the perilesional carbon nanoparticle injection. If there was no mass lesion, carbon nanoparticle suspension was injected guided by the pre-applied clips and previous/initial sonomammographic studies performed earlier. The area of interest was sterilized with betadine.

A bleb was created by injecting 3 cm of local anesthetic (lidocaine 1%) subcutaneously at the penetration site by a syringe. A suspension of carbon nanoparticles with a size range of 120–150 nm suspension was prepared on set and mixed with distilled water at a ratio of (1:1). The suspension was then slowly injected perilesional at four points, superficial and deep on both medial and lateral sides of the lesion borders. A drop of prepared suspension is injected intradermally after the procedure termination creating a cutaneous stained focus to guide the surgical site of penetration with an attached detailed diagram of the lesion and its relationship to the overlying skin, chest wall, and site of penetration.

The breast radiologist in charge guided the surgeon to the lesion of interest intraoperatively, using the black staining and the detailed diagram. The results of frozen section analysis were collected and reported with an emphasis on adequate margins free of tumor on the

excised specimen and the presence of tumor cells in the axillary lymph nodes.

Seroma formation, an unsatisfactory cosmetic outcome, and wound infection are potential postoperative complications that must be addressed. Postoperative ultrasound and complementary Doppler examination for regional residual tumors are best initially performed three months postoperatively.

Statistical analysis

Data entry for statistical analysis was performed using a Microsoft Excel Spreadsheet. SPSS Statistics for Windows was used to perform tabulation and statistical analysis.

Results

This study included 16 patients with early-stage BC who received neoadjuvant chemotherapy. The range of ages was 30-71 years, with a mean age of 48.38±13.85 years. Additionally, 68.8% of the study population (11 patients) had positive mass lesions, with a mean tumor size of 9.23±4.02 (range 3.5–15 mm), whereas 31.2% (5 patients) had negative mass lesions with a complete sonographic resolution of the lesion yet showed breast clips. All patients were pathologically proven invasive BC; only 2 (12.5%) showed focal lymphovascular invasion.

Carbon nanoparticle suspension was injected preoperatively, and the patient underwent conservative breast surgery. The majority of patients (62.5%) showed no gross uptake of carbon nanoparticles by the breast tissues intraoperatively, and only 6 patients (37.5% of the study sample) showed positive black staining. Histopathological examination of resected tissues revealed adequate tumor-free margins.

Regardless of their preoperative LN status, all our study participants were scheduled for axillary LN dissection after intraoperative inspection and examination of the axilla by the naked eye searching for any black-stained LNs. Axillary LNs were then sent for a paraffin section and histopathological examination.

Two patients enrolled in this study were stage N1 (showing only ipsilateral axillary lymph node metastasis), and they showed positive intraoperative black staining. The remainder of the study population (14 patients) exhibited no gross stains visible to the naked eye and had no clinical staging prior to surgery.

Postoperative histopathology examination revealed tumor-infiltrated LNs in 3 out of 16 cases, with overall positive and negative predictive values of carbon nanoparticle injection for tumor-infiltrated axillary lymph nodes detection 100% and 92.2%, respectively, as shown in Table 1.

Discussion

Carbon nanoparticle injection has been utilized in preoperative localization of breast, thyroid, and certain gastrointestinal malignancies, along with the tracing of affected lymphatics [7].

BC is the most prevalent malignancy affecting women worldwide. Early detection and proper management of BC, particularly in node-negative stages, increase the 5-year survival rate by replacing aggressive breast radical surgeries and axillary lymph node clearance with less invasive procedures and sentinel lymph node biopsy [1]. The national screening campaign for breast cancer played a crucial role in the early detection of the disease.

This prospective single-arm pilot study is designed to determine the feasibility, safety, and accuracy of preoperative perilesional carbon nanoparticle injection in early-stage cases of BC. It aims to localize and roughly estimate the perilesional invaded apparently healthy tissue, providing a rough estimate of the actual tumor extension and the detection of draining axillary lymph node affection. Therefore, it preserves as much healthy breast tissue as possible for cosmetic purposes, avoiding unnecessary axillary lymph node clearance.

All patients underwent conservative breast surgery and had tumor-free margins at the intraoperative frozen section, and all axillary specimens were sent for paraffin examination.

Table 1 Significance of nodal black staining (sensitivity and specificity) in correlation to the gold standard histopathological examination of nodal affection

	Histopathological postoperative				
Black stained LN	Negative LNs No. (%)	Positive LNs No. (%)	Test value*	*P*-value	significance
Negative	13 (100%)	1 (33.3%)	9.905	0.002	HS
Positive	0 (0.0%)	2 (66.7%)			

P-value >0.05: Nonsignificant (NS); *P*-value <0.05: Significant (S); *P*-value <0.01: highly significant (HS). *: Chi-square test.

Ultrasound-guided perilesional injection of carbon nanoparticle suspension is performed with a technical success rate of 100%. Positive gross uptake of black dye was noted intraoperatively with an accuracy of 68.75% and a p-value of 0.037, as depicted in Table 2. No signs of residual tumorous tissue or recurrence were detected postoperatively in our cases.

In 2014, Yanyan Jiang *et al.* correlated the effectiveness of carbon suspension utilization in early-stage BC localization with the completion of physical, laboratory, and investigations, including sonomammography, to detect local recurrence and distant metastases, which were negative throughout the duration of the study. In addition, neither a recurrence nor distant metastasis was reported in their study [8].

In our study, using carbon nanoparticle suspension to detect axillary lymph nodes has a sensitivity and negative predictive value NPV of 66.7% and 92.9%, respectively. In contrast, Liulu Zhang reported that the sensitivity and NPV of carbon nanoparticle use in his study were 95.5% [5].

Another study by Xiufeng Wu in 2014 revealed that the sensitivity and NPV of carbon nanoparticle suspension were 88.9 and 94.9%, respectively, in affected axillary lymph node staining [9].

A systematic review and meta-analysis compared the results of 33 studies about carbon nanoparticle injection in sentinel lymph node mapping in BC patients. All the included studies reported high sensitivity of carbon nanoparticles of an average of 91 to 95% [9].

With the exception of injection-related pain, none of our patients experienced severe or life-threatening side effects from carbon nanoparticles injection at the time of injection, shortly after injection, or during the early postoperative follow-up (up to six months postoperatively). The breast surgeon reported that all members of the study population had satisfactory cosmetic outcomes following breast surgery.

Illustrative case

A 62-year-old female patient with pathologically proven left-sided invasive ductal carcinoma underwent preoperative neoadjuvant chemotherapy and was scheduled for breast-conserving surgery.

Under ultrasound guidance, we injected 2 ml of carbon nanoparticle suspension perilesional, as demonstrated in Fig. 1a, b.

The breast mass exhibited positive uptake of the black dye, and discrete black-stained foci could be identified in the axillary specimen, as depicted in Fig. 2a, b.

Limitation of our study

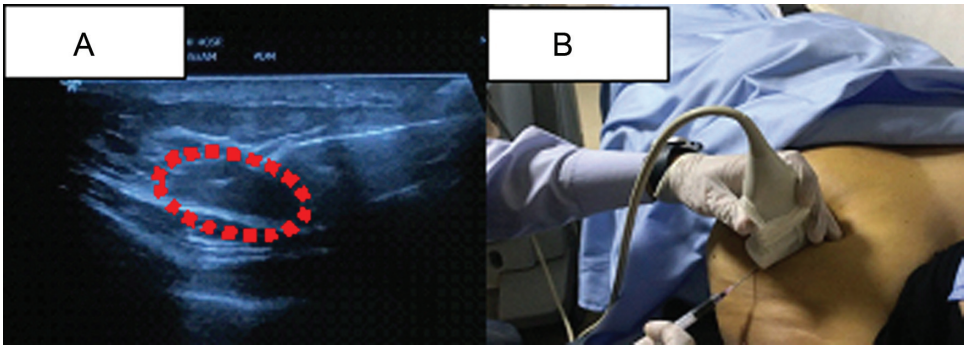
Despite its advantages, this black dye has some limitations, such as high cost, shipping fees, and the black color that can be mistaken intraoperatively with cauterized spots near the mass/lymph node stained that

Table 2 Significance and accuracy of carbon nanoparticle injection in black staining of tumoral tissue intraoperatively

Parameter	TP	TN	FP	FN	Accuracy	Sensitivity	Specificity	PPV	NPV
Black stained	2	13	0	1	93.8%	66.7%	100.0%	100%	92.9%

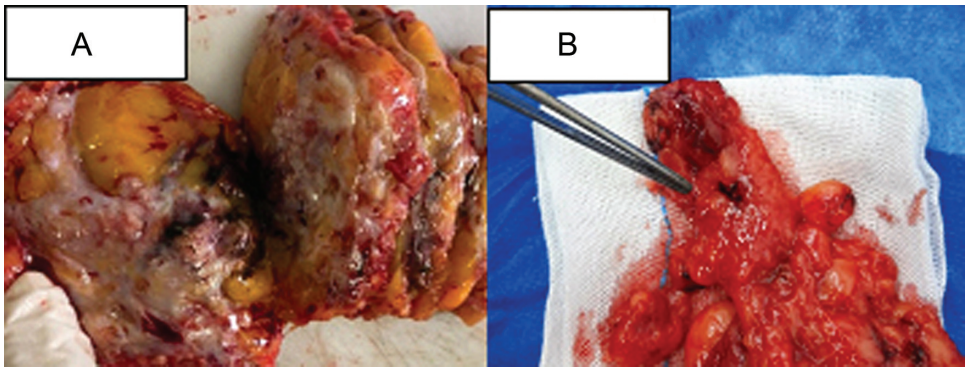
FN, false negative; FP, false positive; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

Fig. 1



A and B: ultrasound-guided perilesional injection of carbon nanoparticle suspension.

Fig. 2



A: The excised breast tissue. B: The axillary specimen.

are as small as the cauterized focus. Carbon suspension injections may also clump, causing lymphatic obstruction and impeding normal lymphatic drainage, thereby increasing false-negative results of lymph node inflammation.

Due to the high cost and shipping fees of carbon nanoparticles, this study included a small number of patients, which is another limitation. Therefore, it is recommended that more studies with a larger number of patients be conducted in our country in order to achieve more accurate and reliable results.

Conclusions

Preoperative carbon nanoparticle suspension injection is a safe and effective method for adequate tumoral localization in patients with breast cancer. However, this pilot study did not provide strong evidence for the adequacy of sentinel lymph node detection due to the small number of patients assigned to this study as well as the high cost and additional shipping fees of the carbon nanoparticles.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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