# Detection of sentinel lymph node using carbon nano-particles in patients with early breast cancer

Mostafa Nagy[a], Ahmed G. Eldin[a], Karim Fahmy[a], Mohamed Elshinawi[a,b]

[a]Department of Surgery, Faculty of Medicine, Ain Shams University, Cairo, [b]Galala University, Suez, Egypt

Correspondence to Mostafa Nagy, MSc, Department of Surgery, Faculty of Medicine, Ain Shams University, Cairo 11835, Egypt. Tel: +20 01096870455; E-mail: mostafa_nagy218@hotmail.com

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**Introduction**
Management in breast cancer is heading toward less invasive approaches with high survival and low recurrence rates. Axillary lymph node dissection (ALND) has a high morbidity on breast cancer patients; on the other hand, sentinel lymph node biopsy (SLNB) overcomes such morbidity with comparable survival and recurrence rates. In this study, the authors aim to assess diagnostic accuracy of carbon nanoparticles (CN) in SLNB in patients with early breast cancer.

**Patients and methods**
From November 2020 to March 2022, patients with early breast cancer and clinically and radiologically free axillary lymph nodes who had SLN detection using CNs followed by ALND were included. Patients who received neoadjuvant chemotherapy, are pregnant, or refused consent were excluded.

**Results**
In this study, 30 patients with clinically node-negative early breast cancer patients were investigated using CN for SLN mapping. Mean age of our participants was 49.2±5.8. CN technique had a sensitivity of 100% (95% confidence interval: 80.49–100), specificity of 92.3% (95% confidence interval: 63.9–99.8), positive predictive value of 94.4%, negative predictive value of 100%, and false-negative rate=0%. The summary receiver-operating characteristics of CN showed excellent diagnostic performance with area under the curve of 0.962 ($P$=0.0001).

**Conclusion**
SLN mapping using proper technique is vital to avoid recurrence and promote survival and decrease morbidity without need for ALND. CN had excellent sensitivity and specificity with low false-negative rate.

**Keywords:**
cancer breast, carbon nanoparticles, sentinel lymph node

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## Introduction

Axillary lymph node dissection (ALND) is an important part of breast cancer surgery, which has important values for correct staging, prognosis, and guiding treatment. However, this also causes many complications, such as upper limb lymphedema, shoulder joint movement disorder, numbness of the adduction side of the upper limb, and other symptoms. Data have shown that the metastasis rate of the axillary lymph node of breast cancer in clinical stages I and II was less than 30% [1].

For axillary lymph node-negative patients, ALND cannot improve the overall survival rate and prolong disease-free survival time. Furthermore, it may lead to postoperative complications and affect patient's quality of life. Moreover, it is also an excessive treatment [2].

In recent years, with the application of sentinel lymph node biopsy (SLNB) technology, ALND has been avoided in a considerable proportion of patients in the early stage of breast cancer, which improved the quality of life of patients.

Currently, SLNB is dependent on injection of blue dye, radioactive colloid, the combination of both, or indocyanine green (ICG). The identification rates vary with blue dye (68–86%), radioisotope (86–99%), combined technique (89–97%), and ICG (73.8–99%) [3, 4]. Despite high rates of sentinel lymph node (SLN) detection with these techniques, there is no general consensus about the optimal technique.

Carbon nanoparticles (CNs) are a synthetic tracer via the specific modification of small activated carbon particles with an average diameter of 150 nm, which is widely used in the field of cancer diagnosis and therapy [5]. They have received considerable interest in recent years, especially with respect to their potential utilization of lymphatic mapping. CNs selectively enter the lymphatic vessels rather than blood capillaries due to the molecular size and permeability. Upon injection into the tissues around the tumor, CNs are rapidly engulfed by macrophages and then pass through the lymphatic vessels to the SLNs, thus staining them black. This technique facilitates the vital staining of tumor-draining lymph nodes, and has been applied in the detection of SLNs in colorectal, gastric, and thyroid cancers [6–9].

CNs have no toxic side effects on the human body due to less access to the blood circulation. Because of safety and strong affinity for the lymphatic system, recently it has been used for SLN detection with identification rate of 98.3%. Therefore, the feasibility of CNs for the identification of SLNs in early breast cancer must be investigated. In our pilot study, the diagnostic accuracy of SLN detection using CNs is assessed.

## Patients and methods

In this prospective pilot study, 30 patients with early breast cancer were recruited. Patients had SLN detection using CNs followed by ALND at Breast Surgery Unit at Ain Shams University Hospitals from November 2020 to March 2022.

Patients included were pathologically confirmed breast cancer patients (Tis/T1/T2 N0 M0) and clinically and radiologically free axillary lymph nodes. Patients who received neoadjuvant chemotherapy, were pregnant, or refused consent were excluded.

Approval was obtained from the Ethics' Review Committee at Ain Shams University. Informed consent was obtained from all participants. Preoperative data collection included clinicopathological data as tumor site, sex, tumor pathology, hormone receptor status, and TNM classification. Postoperative data included morbidity and mortality.

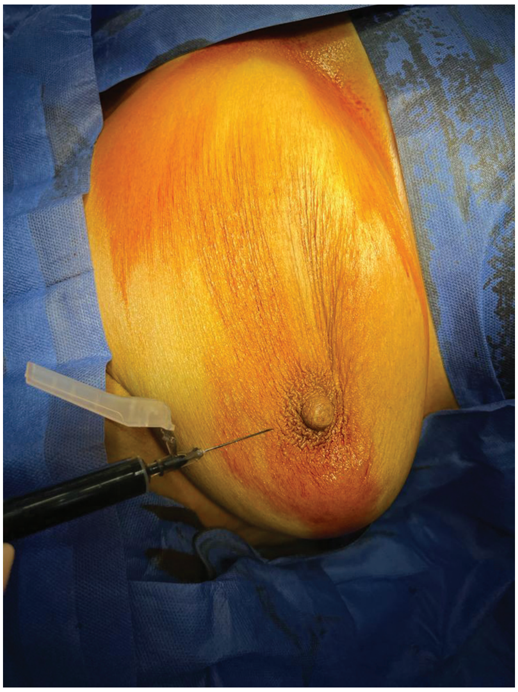
### Surgical technique

CNs 120–150 nm (purchased from The National Research Centre, Egypt) were prepared on a set mixed with distilled water with a ratio 1 : 1.. The average amount of 1-ml solution using a 16-gauge needle was injected intradermally into the retroareolar region 10–15 min before surgery (Fig. 1). The whole breast was massaged for about 5 min to facilitate the absorption of CN into the lymph vessels. Then, the axilla was inspected for black-stained SLNs (Figs 2 and 3). After SLN biopsy, all patients had ALND. All these SLNs were sent with the whole axilla for detailed pathological examination by paraffin fixation processing. ALND findings were used to validate SLN biopsy results.

### Statistical method

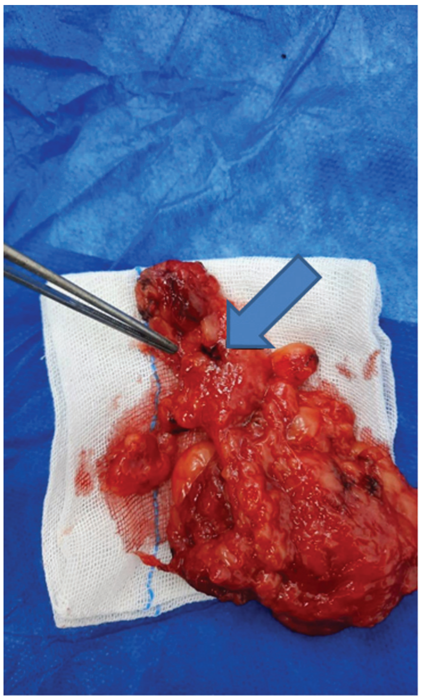
Data were collected and analyzed using SPSS version 26 (Chicago, USA). Sensitivity, specificity, accuracy,

**Figure 1**



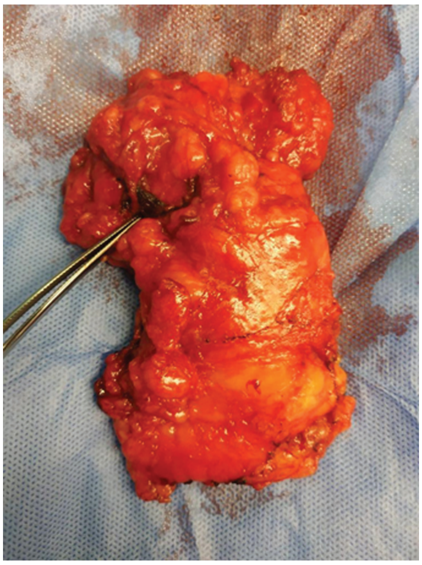
Injection of carbon nanoparticle into retroareolar area.

**Figure 2**



Specimen with black-stained sentinel lymph node.

**Figure 3**



Specimen of axilla with black-stained lymph node.

false-negative rate, negative predictive value, positive predictive value, and diagnostic test performance [receiver-operating characteristics (ROC) curve] were calculated. The confidence interval (CI) was set to 95% and the margin of error accepted was set to 5%.

## Results

In this pilot study, 30 patients with clinically node-negative early breast cancer patients were investigated using CN for SLN mapping. Mean age of our participants was 49.2±5.8 .Most patients had tumor located in the upper outer quadrant 63.3% and luminal A type 73.35 breast cancers. All patients had breast-conservative surgery. Only two patients had postoperative skin discoloration that resolved within 2 months and two patients had postoperative seroma that is managed with repeated aspiration (Tables 1 and 2).

All patients had ALND after SLN mapping using CN. CN technique had a sensitivity=100% (95% CI: 80.49–100), specificity=92.3% (95% CI: 63.9–99.8), positive predictive value=94.4%, negative predictive value=100%, and false-negative rate=0% (Table 3). Table 4 shows number of LNs retrieved. Mean number of stained LNs was 3.7±0.8 with range 3–6 LNs. One hundred and 10 SLNs were stained black by CN of which 53 LNs were positive. During ALND, 263 LNs were collected of which 62 were positive for metastasis. No extranodal tumor extension is noted. The summary ROC are shown in Figure 4. CN had excellent diagnostic performance with area under the curve of 0.962 ($P$=0.0001).

**Table 1 Patients' baseline characteristics**

| Characteristics | *n* (%) |
|---|---|
| Tumor site | |
| UOQ | 19 (63.3) |
| LOQ | 2 (6.7) |
| UIQ | 4 (13.3) |
| LIQ | 2 (6.7) |
| Retroaleolar | 3 (10) |
| Pathology | |
| DCIS | 3 (10) |
| IDC | 25 (83.3) |
| ILC | 2 (6.7) |
| Hormone receptor | |
| Luminal A | 22 (73.3) |
| Luminal B | 7 (23.3) |
| TNBC | 1 (3.3) |
| Sex | |
| I | 11 (36.7) |
| II | 19 (63.3) |
| T stage | |
| Tis | 3 (10) |
| T1 | 21 (70) |
| T2 | 6 (20) |
| N0 | 30 (100) |
| M0 | 30 (100) |
| Surgery performed | |
| BCS | 30 (100) |

BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LIQ, lower inner quadrant; LOQ, lower outer quadrant; TNBC, triple negative breast cancer; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

**Table 2 Postoperative morbidity and mortality**

| Morbidity [*n* (%)] | |
|---|---|
| No | 26 (86.7) |
| Skin staining | 2 (6.7) |
| Seroma | 2 (6.7) |
| Mortality [*n* (%)] | |
| No | 30 (100) |

## Discussion

In recent decades, surgery in breast cancer had evolved toward less invasiveness and morbidity. ALND had been the standard of care in management of the axilla in clinically positive and negative axillas. However, SLNB biopsy emerged as a less invasive and less morbid choice with equal efficacy to ALND. Several techniques for SLN mapping exist, including methylene blue dye, radioisotope, and ICG fluorescence; however, the optimal modality remains challenging due to pros and cons of each of these techniques [10].

Optimal technique was thought to have high sensitivity, specificity, and accuracy with low false-negative rates, and best logistics in terms of cost, availability, and need for specific equipment.

**Table 3 Accuracy of SLN mapping using CN in early breast cancer patients**

| SLN* | ALND | | Total | |
|---|---|---|---|---|
| | Positive | Negative | | |
| Positive | 17 | 1 | 18 | PPV 94.4% |
| Negative | 0 | 12 | 12 | NPV 100% |
| Total | 17 | 13 | 30 | |
| | Sensitivity 100% (95% CI: 80.49–100) | Specificity 92.3% (95% CI: 63.9–99.8) | Accuracy 100% | |

ALND, axillary lymph node dissection; CI, confidence interval; CN, carbon nanoparticle; NPV, negative predictive value; PPV, positive predictive value; SLN, sentinel lymph node.

**Table 4 LNs removed and CN identification rate**

| | |
|---|---|
| Number of positive SLNs/ total number of stained LNs | 53/110 |
| Mean±SD/range of stained LNs by CN | 3.7±0.8/3–6 |
| CN identification rate | 100% |
| Number of positive LNs by ALND/total number of LNs excised | 62/263 |

ALND, axillary lymph node dissection; CN, carbon nanoparticle; LN, lymph node; SLN, sentinel lymph node.

In a recent network meta-analysis of 35 studies comparing different techniques for SLN detection, methylene blue dye had the highest false-negative rate 18.4% followed by radioisotope (2.6%) and ICG (0.6%) [11].

Based on our study, CN had lower false-negative rate (0%). Although radioisotope had lower false-negative rate compared with methylene blue, radioisotope had several cons, including availability, cost, need for special equipments (handheld gamma probe), and nuclear substance disposal [12].

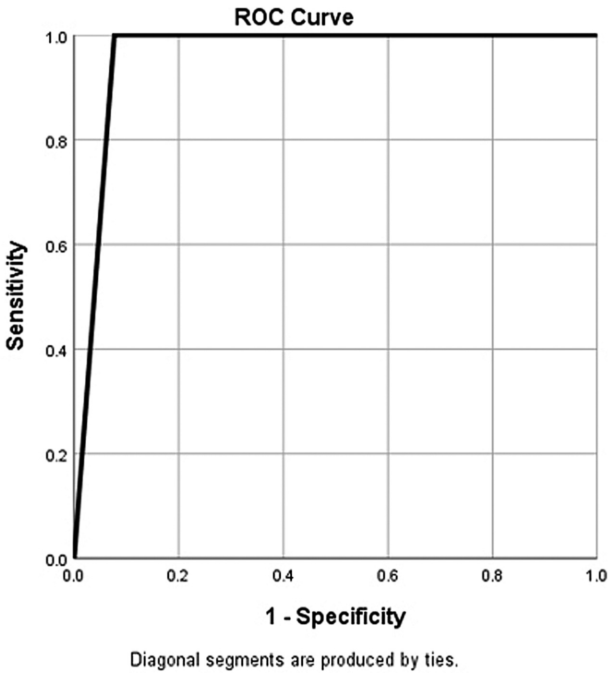
ICG is easily available and cheaper than radioisotope but requires fluorescence photodynamic eye camera. Also, ICG is associated with surgical field contamination with fluorescence if lymphatic vessels are cut accidently.

CNs have an average diameter of 150 nm to pass through lymphatic capillaries and accumulate in SLN long enough to be detected during surgery rather than diffusing quickly to other nonsentinel LNs, thereby higher false-negative rate as seen in ICG and methylene blue dye. CN are cheap, available, and do not require special intraoperative equipment [5,13].

In this study, CNs had successfully identified SLN with excellent sensitivity, specificity, false-negative rate, and area under the curve, 100, 92, 0, and 0.96%, respectively.

A study, conducted in China, investigated CN on 36 patients with clinically node-negative breast cancer

**Figure 4**




Diagnostic performance of carbon nanoparticle in sentinel lymph node mapping, receiver-operating characteristics curve.

patients as a pilot study followed by 83 patients as a prospective study.

CN had 88.9% sensitivity, 100% specificity, 11.1% false-negative rate, and 96.4% accuracy. The authors recruited another 83 patients for SLN biopsy using methylene blue. Methylene blue dye had clinically higher false-negative rate (15.8%) compared with CN yet no statistical difference was reported [13]. A recent meta-analysis of 33 studies enrolling 2171 patients with clinically node-negative breast cancer patients who underwent SLN mapping using CN had comparable results to our study. Pooled specificity, sensitivity, and ROC curve were 99, 93, and 0.98%. The authors also concluded no significant difference is detected according to dose and site of CN injection [3].

A study of 46 patients with early breast cancer had SLN status assessment using CN followed by ALND.

The results were comparable to our findings: sensitivity was 93.2%, accuracy was 97%, and false-negative rate was 6.7% [14]. In another retrospective cohort study conducted at a single center in China, 332 patients with early primary breast cancer had SLN mapping using CN. Findings were consistent with our results as the authors reported sensitivity of 95.9%, specificity of 100%, and false-negative rate of 4.1% [15].

CNs had some limitations. Black discoloration of the skin was seen postoperatively affecting cosmetic appearance. In our cohort, black skin staining was seen in two patients with complete resolution within 2 months.

## Conclusion

CNs are a promising technique for SLN mapping in clinically negative node early breast cancer patients, particularly for acceptable accuracy and superiority to other techniques in terms of cost, availability, and other logistic requirements.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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