Carbon nanoparticles versus patent blue dye for detection of sentinel lymph node in patients with early breast cancer

Mahmoud R. M. Elsebaai, Mohamed A. H. Shehab, Dina M. Hanafy, Karim F. Abd Al Moaty

General Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence to Mahmoud R. M. Elsebaai, MSc, General Surgery, Faculty of Medicine, Ain Shams University, 32 mohamed ibrahim, taqsim omar ibn el khattab, el salam 1st destrict, Cairo 11788, Egypt.
Tel: 01001145740;
e-mail: hoodasebaai@gmail.com

Received: 11 December 2023
Revised: 24 December 2023
Accepted: 24 December 2023
Published: 22 March 2024

The Egyptian Journal of Surgery 2024, 43:485–492

Background
Sentinel lymph nodes biopsy (SLNB) has replaced axillary lymph node dissection (ALND) in a considerable percentage of patients with early-stage breast cancer which was a great advance in preventing many surgical complications and enhancing their health welfare. Although there are different sentinel lymph nodes (SLNs) tracers with different identification rates, there is no agreement about the idealistic method.

Aim
The study was designed to compare carbon nanoparticles and patent blue v dye regarding SLNs detection rate, number of SLNs, time of detection, metastatic SLNs, cost, and safety in patients with early breast cancer and clinically node-negative axilla.

Patients and methods
A total of 40 patients with axillary lymph node-negative early-stage breast cancer patients were divided into two groups and subjected to carbon nanoparticles and patent blue V dye in group A and group B, respectively. Patients who were pregnant or lactating had node-positive axilla (N1-3) or metastatic breast cancer (M1) or had neoadjuvant chemotherapy were excluded.

Results
The mean age was 48.3±9.5 and 47 ±8.9, while the mean BMI of 33.3±4.8 and 32.834±4.862, the SLN detection rates were 95% and 90% in groups A and B, respectively. A total of 128 sentinel lymph nodes (SLNs) were removed from patients in the two groups (65 with Carbon Nanoparticles and 63 with patent blue dye). The mean number of SLNs was 3.4±0.7 (range, 2–5) and 3.5±1.2 (range, 2–7), mean time of SLNs detection was 13.5±4.5 (range, 7–22) and 12.7 ± 3.6 (range, 7–18 min) between group A and B, respectively.

Conclusion
There is no significant difference between carbon nanoparticles and patent blue dye regarding axillary SLNs in early breast cancer regarding identification rate, number of SLNs, time of detection, metastatic SLNs, cost, and safety with slight preference to carbon nanoparticles regarding postoperative skin staining and Egyptian market availability.

Keywords:
carbon nanoparticles, patent blue V dye, sentinel lymph nodes

Egyptian J Surgery 43:485–492

1110-1121

Introduction

An essential component of breast cancer management, axillary lymph node dissection (ALND) has significant implications for accurate staging, prognosis, and treatment guidance.

But this also leads to several adverse effects, including insensibility on the adduction side of the upper limb, shoulder joint movement restriction, and upper limb lymphedema. According to data, less than 30% of ALN were found to be metastatic in clinical stages I and II breast cancer patients [1]. In patients with axillary negative lymph nodes, ALND is considered to be an over treatment, it is unable to raise the overall survival rates or extend the duration of disease-free life. Moreover, it might impair the function and quality of life and result in many other postoperative problems [2].

Recently, sentinel lymph node biopsy (SLNB) has replaced ALND in a sizable portion of patients with early-stage breast cancer which was a great advance in enhancing their health welfare.

At present time, SLNB can be done by the injection of indocyanine green (ICG), radioactive colloid, blue dye,

or both. Blue dye (68–86%), radioisotope (86–99%), combination method (89–97%), and ICG (73.8–99%) all have different identification rates [3,4]. Although these methods have high rates of sentinel lymph node (SLN) identification, there is no agreement about the idealistic method [5]. Radiation exposure and the scarce supply and high expense of radio colloids are some of the issues raised by the radioactive colloid approach [6]. Because of their very small diameters, blue dye, and ICG, both allow passage through the SLNs to higher-level nodes, leading to the inaccurate identification of sentinel nodes [7,8]. Furthermore, to perform the ICG method in the operating room, certain equipment is needed [9]. Nevertheless, there have been reports of blue dye-related side effects, including skin and fat necrosis, allergic responses, localized inflammation, and skin discoloration.

Utilized extensively in the field of cancer detection and treatment, carbon nanoparticles are synthetic tracers created by carefully modifying tiny activated carbon particles with an average diameter of 150 nm [10]. Recently, there has been a lot of concern in them, in regard to their possible use in lymphatic mapping. Because of their small size and permeability, carbon nanoparticles preferentially enter lymphatic channels rather than blood capillaries. When injected into the surrounding tissues of the tumor, Macrophages quickly absorb carbon nanoparticles, which then enter lymphatics toward the SLNs and pigment them black. SLNs in colorectal and thyroid malignancies can be found using this approach, which makes necessary labeling of tumor-draining lymph nodes easier [11,12].

Because carbon nanoparticles have limited entrance to the blood circulation, they do not cause any harmful side effects in humans. due to its significant attraction to the lymphatic system and safety. It has been utilized recently with a 98.3% identification rate for SLND [13].

Ptent blue V dye is a synthetic dye belonging to the triarylmethane group. It is sometimes referred to as food additive E131, acid blue 3, and disulphine blue [14].

Prior to being used in cannulation for lymphography, patent blue V has long been used in medical practice to detect lymphatic veins. SLNB is a more recent approach that has been established as part of the staging protocol for patients with early-stage breast cancer [1]. The procedure is done by injecting patent blue V intradermally into the involved breast. The dye is absorbed by the lymphatic vessels, causing the SLN to become blue-stained, which makes it possible for it to be located and biopsied. SLNB has been a common practice in the management of breast cancer [15] and is now being employed in the management of cervical carcinoma [16] and cutaneous melanoma [16,17].

Aim

We contrast the methods of identifying SLNs in early-stage breast cancer with clinically negative axilla using either carbon nanoparticles or patent blue dye. we will evaluate the detection rate, number of SLNs, time of detection, SLNs metastases, cost, and safety for each.

Patients and methods

This was a prospective study. It included 40 patients with early breast carcinoma who attended to the breast surgery clinic in Al Demerdash hospital and Ain-Shams University specialized hospital (ASUSH) eligible for SLNB from March 2022 to March 2023.

The study was accredited by the Research ethics Committee, General surgery department, Ain Shams University. There were 40 female patients involved in our study and were recruited into two groups each group involved 20 patients by randomization method generated by (random.org).

All patients received information about surgical technique and risks of the operation and other treatment options. All patients participated in this study after signing an informed consent and medical photography consent.

Inclusion criteria were being female patient aged up to 75 years old, with early breast cancer (T1-2, N0, M0). ALN should have been clinically and radiologically negative with no previous Axillary surgery or radiotherapy. Excluded patients were those who were pregnant or lactating or had node positive axilla (N1-3) or metastatic breast cancer (M1) or had neoadjuvant chemotherapy, hormonal therapy or targeted therapy or had multicentric breast cancer.

All patients were subjected to triple assessment (clinical assessment, radiological assessment, and core needle biopsy), after confirming the diagnosis of breast cancer. Metastatic and preoperative workup were done. All cases were discussed in the multidisciplinary team meeting held weekly at breast unit, Al-Demer-dash hospital, Ain-Shams University which included breast surgery, oncology, radiology, and pathology specialities

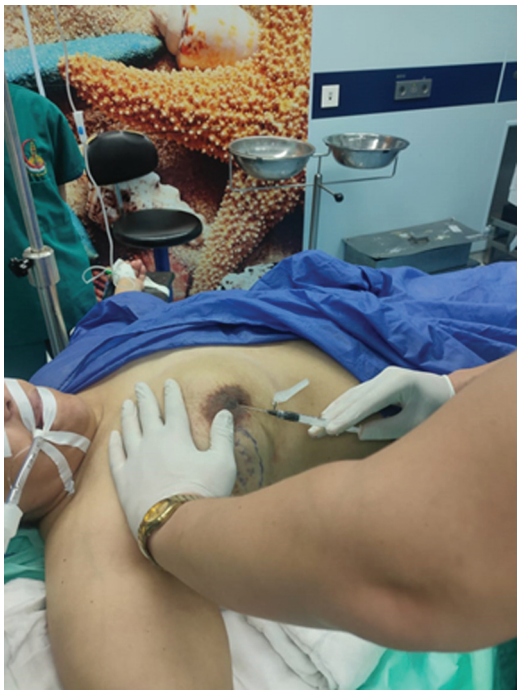
where surgical decision was taken. All involved surgeons were well trained on SLNB procedures.

After induction of general anesthesia and patient positioning in supine position with abducted arm, sterilization of the operative site and draping were done. Intradermal peri-areolar placement of 1 ml of Carbon nanoparticles suspension in group A (Fig. 1) and 2 ml of patent blue v dye in group B (Fig. 2), then massaging breast for 5–10 min to facilitate drawing the dye up into lymph vessels and its retention by lymph node (Fig. 3), incision of axillary skin, inspection of the axilla for black stained lymph nodes in group A (Fig. 4) and for blue stained lymph nodes in group B (Fig. 5). Then, SLNB was sent for frozen section. If negative, no further axillary surgery was done. If positive, level I and II axillary clearance was done.

After obtaining SLNS, breast surgery which was conservative breast surgery for the whole 40 patients done according to the decision of multidisciplinary team and patient desire. Wound closure and covering then recovery of the patient from anesthesia. All specimen were sent for histopathological examination through paraffin embedded section.

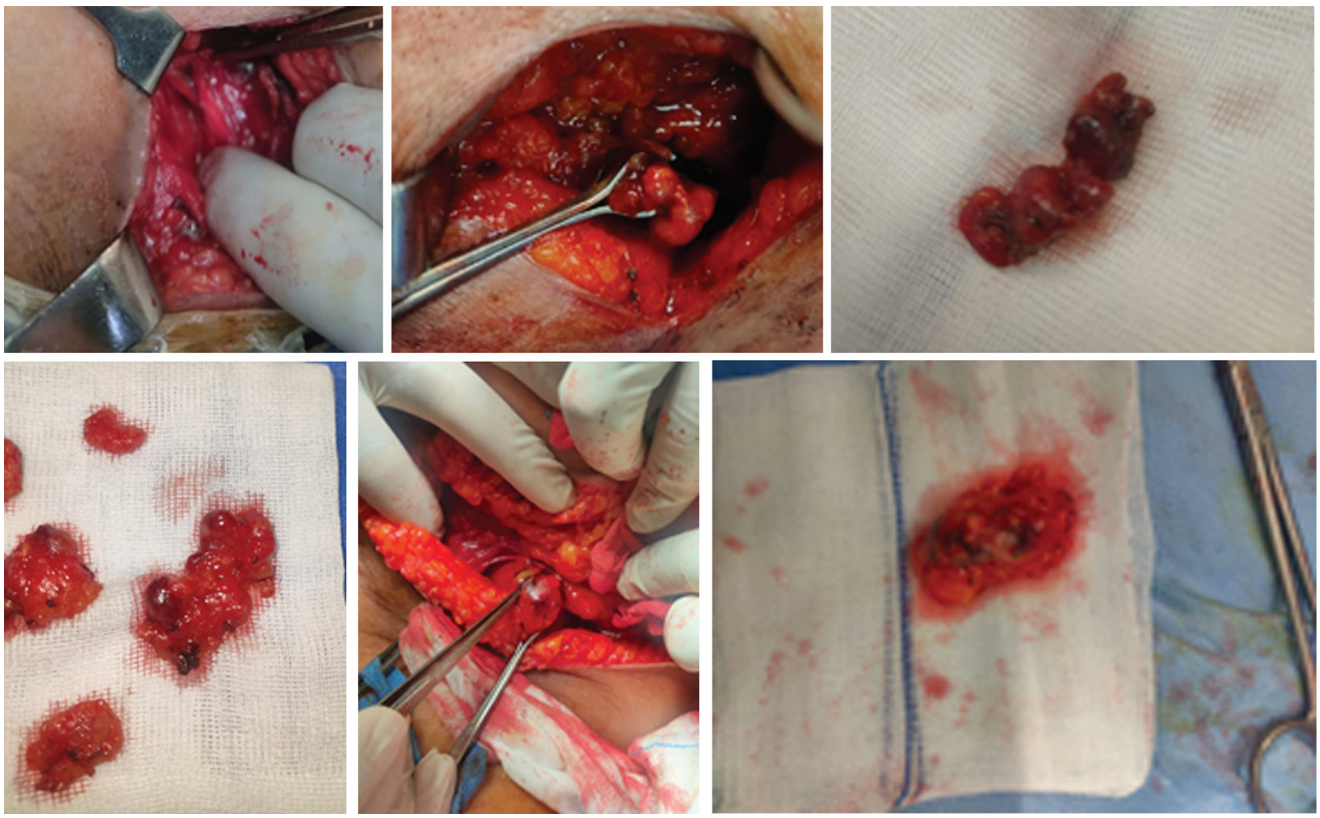
The collected data was recorded, tabulated and coded using Excel 365, Microsoft Corporation, USA. Then

Figure 1



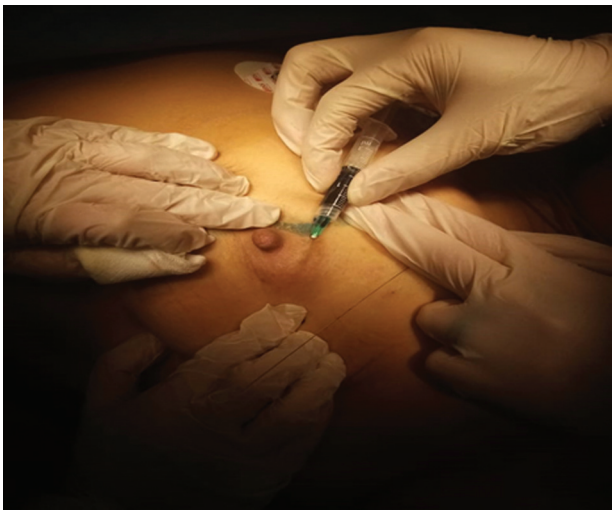
Peri-areolar intradermal injection of carbon nanoparticles.

Figure 2



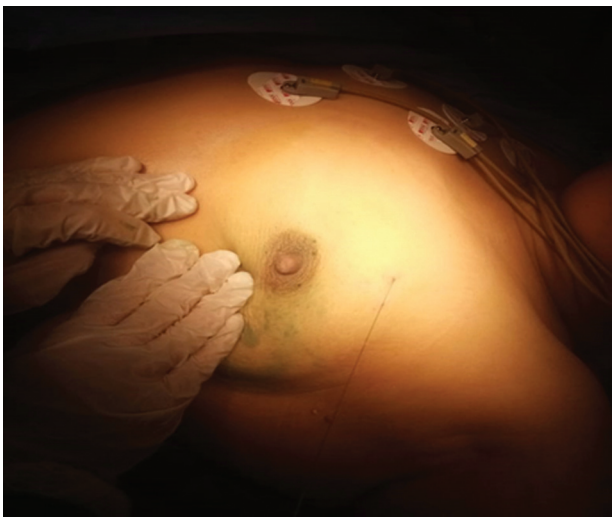
Peri-areolar intradermal injection of patent blue dye.

Figure 3



Breast massaging after patent blue dye injection.

Figure 4



Intraoperative identification of black stained Sentinel lymph nodes 15 min after carbon nanoparticles injection in 3 of our cases.

data was statistically interpreted using the Statistical Package for Social Sciences, IBM SPSS Statistics, version 28.0, IBM Corporation, USA.

Results

Patients and tumour characteristics

Some information about the patients and the pathological results are disclosed in Table 1.

In total of 40 patients divided into two study groups each includes 20 patients. The mean age was 48.3±9.5 and 47 ±8.9, while mean BMI of 33.3±4.8 and 32.834 ±4.862 in group A and group B, respectively.

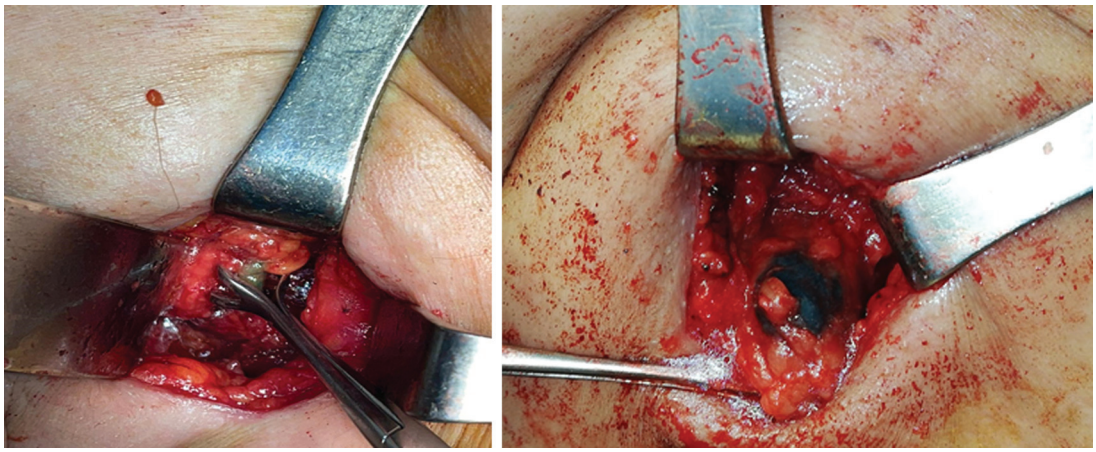
Ten patients among group A were found to have medical comorbidities. Three patients have diabetes mellitus, six patients have hypertension, and one patient has ischemic heart disease. They are matched with another seven patients in group B to have medical comorbidities. Two patients have diabetes mellitus, three patients have hypertension, two patients have ischemic heart disease.

There is nonsignificant difference between the two groups regarding menstrual status.

Tumour characteristics

The tumour characteristics are outlined in Table 2, which included tumour size, stage, histological type and molecular subtypes. The tumour size is evaluated along the longest diameter of the tumour mass by ultrasonography. The mean tumour size was 24.5 ±12.7 and 22.9±13 mm in group A and B in order. There was no evidence of lymph nodes affection or distant metastasis in either group. There was no statistically noteworthy difference between both groups results.

Figure 5



Intraoperative identification of the blue-stained Sentinel lymph node 15 min after Patent blue dye injection in two of our cases.

Table 1 Patient parameters and characteristics

	Group		T-Test	
	Group A	Group B	t	*P*-value
Age				
Range	32–67	35–68	0.444	0.659
Mean ±SD	48.350±9.522	47.050±8.976		
Weight				
Range	61–103	65–107	0.230	0.820
Mean ±SD	83.550±11.208	82.700±12.179		
Height				
Range	148–170	150–172	–0.245	0.808
Mean ±SD	158.350±5.733	158.800±5.881		
BMI				
Range	26.49–44	25.39–43.4	0.360	0.721
Mean ±SD	33.386±4.826	32.834±4.862		
Chi-Square	***N* (%)**	***N* (%)**	**X^2**	***P*-value**
Hypertension				
No	14 (70.00)	17 (85.00)	1.290	0.256
Yes	6 (30.00)	3 (15.00)		
Diabetes mellitus				
No	17 (85.00)	18 (90.00)	0.229	0.633
Yes	3 (15.00)	2 (10.00)		
Cardiac				
No	19 (95.00)	18 (90.00)	0.360	0.548
Yes	1 (5.00)	2 (10.00)		
Menstrual status				
Premenopause	12 (60.00)	10 (50.00)	0.404	0.525
Postmenopause	8 (40.00)	10 (50.00)		

Table 2 Tumour characteristics

	Group		T-Test	
	Group A	Group B	T	*P*-value
Tumour size (mm)				
Range	5–48	3–48	0.404	0.688
Mean ±SD	24.550±12.788	22.900±13.018		
Chi-Square	***N* (%)**	***N* (%)**	**X^2**	***P*-value**
Tumour Stage				
TIS	1 (5.00)	2 (10.00)	0.582	0.748
T1	12 (60.00)	10 (50.00)		
T2	7 (35.00)	8 (40.00)		
Histological Type				
DCIS	3 (15.00)	2 (10.00)	1.177	0.555
IDC	13 (65.00)	16 (80.00)		
ILC	4 (20.00)	2 (10.00)		
Molecular subtypes				
Luminal A	13 (65.00)	16 (80.00)	1.453	0.484
Luminal B	4 (20.00)	3 (15.00)		
Basal cell like or triple negative	3 (15.00)	1 (5.00)		
Estrogen Receptors				
Negative	2 (10.00)	1 (5.00)	0.360	0.548
Positive	18 (90.00)	19 (95.00)		
Progesterone Receptors				
Negative	6 (30.00)	3 (15.00)	1.290	0.256
Positive	14 (70.00)	17 (85.00)		
HER 2 Receptors				
Negative	19 (95.00)	17 (85.00)	1.111	0.292
Positive	1 (5.00)	3 (15.00)		

Table 3 Sentinel lymph node detection by different methods

	Group		Chi-Square	
	Group A *N* (%)	Group B *N* (%)	X^2	*P*-value
Detection sentinel lymph node				
No	1 (5.00)	2 (10.00)	0.360	0.548
Yes	19 (95.00)	18 (90.00)		
Metastatic SLNS				
No	16 (84.21)	14 (77.78)	0.249	0.618
Yes	3 (15.79)	4 (22.22)		
T-Test			**T**	***P*-value**
Number of detected SLNS				
Range	2–5	2–7	−0.397	0.694
Mean ±SD	3.421±0.769	3.556±1.247		
Time of detection of SLNS (min)				
Range	7–22	7–18	0.587	0.561
Mean ±SD	13.579±4.538	12.778±3.687		

Table 4 Complication of using carbon nanoparticles and patent blue dye in sentinel lymph nodes detection in early breast cancer

	Group		Chi-Square	
Postoperative Complication	Group A *N* (%)	Group B *N* (%)	X^2	*P*-value
No complication	16 (80.00)	17 (85.00)	1.364	0.506
Skin staining	1 (5.00)	3 (15.00)		
Wound seroma	1 (5.00)	2 (10.00)		

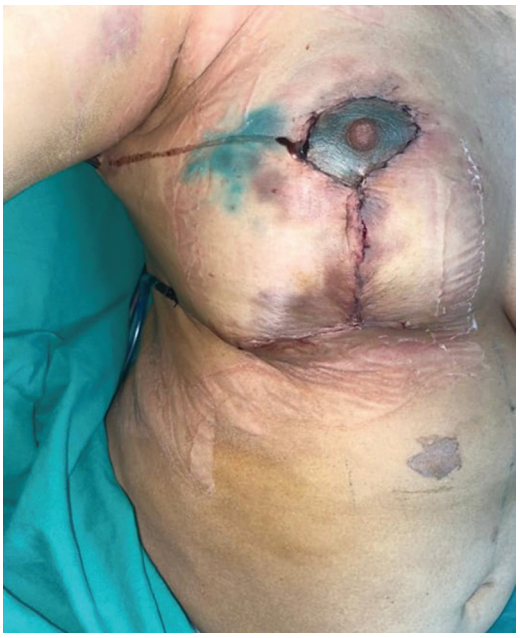
The detection rates of the two groups are shown in Table 3. The SLN detection rates were 95% and 90% in group A and B, respectively. Nineteen patients out of the 20 patients in the carbon nano-particles group showed black stained nodes, and 18 patients out of 20 patients in the patent blue dye group had their SLNs successfully stained blue after skin and subdermal fat incision. A total of 128 SLNs were removed from patients in the two groups (65 with carbon nanoparticles and 63 with patent blue dye). The mean number of SLNs was 3.4±0.7 (range, 2–5) and 3.5±1.2 (range, 2–7) in group A and B, respectively.

Mean time of SLNS detection was 13.5±4.5 (range, 7–22) and 12.7± 3.6 (range, 7–18 min) between group A and B, respectively.

There were 1 patient in group A where there were no black stained lymph nodes and two patients in group B where there were no blue stained lymph nodes after skin and subdermal fat incision. Those three patients underwent cherry picking of palpable ALN. SLN was positive in three patients (15.7%) in group A and four (22.2%) patients in group B. Axillary dissection was done in those seven patients.

During the follow-up period, one patient in group A and two patients in group B developed wound seroma which was managed conservatively and successfully during postoperative follow-up. And one patient in group A and three patients in group B developed skin staining (Table 4, Fig. 6).

Figure 6



Skin staining after patent blue dye injection.

Discussion

The prognosis of patients with breast cancer, adjuvant therapy selection, and breast cancer staging are all significantly influenced by the ALN. In patients with early-stage breast cancer, SLNB is a common technique for ALN staging and is able to precisely predict the existence of ALN metastases [18]. This preserves the function of the afflicted upper limb, lowers the incidence of surgical problems, shields patients with early-stage axillary lymph node-negative breast cancer from the necessity for ALND, and enhances health well-being for the patients [18].

Sensitive, easy to use, safe, and affordable should all be features of the ideal sentinel lymph node tracer.

The motive for this study is to assess and contrast the efficacy of two tracers, patent blue dye and carbon nanoparticles, in identifying SLNs in patients with early-stage breast cancer who have negative ALNs both radiologically and clinically.

A dye tracer of the third generation is carbon nanoparticles. Nanotechnology produces uniformly sized carbon particles with excellent lymphatic specificity and a perfect tracer effect. Carbon nanoparticles (CNPs) have an estimated diameter of 150 nm, which makes them incapable of intrusion into blood vessels and therefore enhancing their tracing specificity. Furthermore, studies on animals have demonstrated that CNPs have no deleterious effects on the central nervous, cardiovascular, or pulmonary systems, nor are they carcinogenic or mutagenic. As a result, using carbon nanoparticles during SLNB is practical and secure [19].

According to anatomic research, the skin has a higher lymphatic density than the breast parenchyma. This indicates that tracers are removed from skin rather than parenchyma more quickly [20]. Therefore, because skin lymphatics transport blue dye more quickly and reliably than breast parenchyma, intradermal injection increases blue dye effectiveness [21]. In the current research, we injected carbon nanoparticles and patent blue intradermally for SLNB.

Skin staining at the injection site is a potential negative effect of using carbon nanoparticles or patent blue dye intradermally in SLNB. It is probable that some women may view this as a cosmetic issue. This was brought up as a possible complication when operation permission and consent was being obtained.

Sentinel lymph node identification rate for group A (patients exposed to carbon nanoparticles) was 95%, SLN metastasis was 15.7%, the mean number of harvested SLNS was 3.4. These findings are similar to those of a retrospective cohort study carried out in a single center in China, where SLN identification rate was 99.1%. Additionally, it was shown that 18.8% of individuals had sentinel lymph node metastases, with a mean of 2.9 SLNs observed.

Based on pathological results (the gold standard), the Sensitivity was 95.9%, the Specificity was 100%, the positive predictive value (PPV) was 100%, the negative predictive value (NPV) was 95.5%, and the false negative rate (FNR) was 4.1% [22].

There are several restrictions on the usage of CNSs, the most common negative effect of carbon nanoparticles is skin staining [23]. The inability of carbon nanoparticles to penetrate fat and skin makes them less visible than fluorescent tracers, such as indocyanine green. This is another drawback of carbon nanoparticles. It's interesting to note that a recent study indicates that carbon nanoparticles may be helpful as a carrier for antitumor treatment in addition to being used as lymph node tracers [24]. One patient in group A experienced a little black tint to their skin, which disappeared four weeks after surgery.

Another common SLNB dye used in Egypt is patent blue. It was tested in group B, and the results showed that the SLNs identification rate was 90%, slightly higher than the identification rate of 80% in a prospective cohort study carried out in Iran, and that the SLN metastasis was 38%, higher than the results of our study, which showed that the SLN metastasis was 22.2% [25].

Another retrospective single institution study conducted in Belgium demonstrated SLNs detection rate of 97.4% which is better than our result, metastatic lymph nodes (30.9%). The false negative rate was 4.9% and the predictive negative value was 97.7% with patent blue dye mapping method [26].

According to several research, blue skin discoloration is typical while using patent blue dye [27]. Three out of the twenty patients in group B in our research had blue skin discoloration, which went away in the six months that followed surgery. Anaphylactic reactions following the use of patent blue dyes have been observed by number of researchers [28]. Yet, no patient in our trial experienced a local inflammatory response or an allergic reaction during or after surgery. In either group, no patient had skin or fat necrosis.

We had obtained carbon nanoparticles from an Egyptian company named UNITED FOUNDATION for what equals to 32.6 USD per each gram to be diluted and used for a single case and obtained patent blue dye from Ain Shams University hospitals store which was provided to Egyptian hospitals by the Egyptian Authority for Unified Procurement which is priced at 35 USD for each dosage.

With reference to identification rate, number of SLNs, time of detection, metastatic SLNs, cost, and safety in patients with early breast cancer and clinically lymph node negative axilla, our study found no noticeable difference between carbon nanoparticles and patent blue dye in SLNs in early breast cancer.

There is limited use of carbon nanoparticles in Egypt for SLNs detection despite its acceptable identification rate, cost and safety and its local availability by national company at Egyptian market.

Conclusion

Our study demonstrated no remarkable difference between the use of carbon nanoparticles and patent blue dye in SLNs detection in early stage breast cancer regarding identification rate, number of harvested nodes, time of detection, metastatic SLNs, cost and safety but there was a slight preference to carbon nanoparticles regarding postoperative skin staining and local availability. thus, carbon nanoparticles should be used on a wider scale in Egypt for detection of SLNs in early breast cancer.

Financial support and sponsorship

Nil.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

References

1 Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 220:391–398.

2 Dominguez FJ, Golshan M, Black DM. Sentinel node biopsy is important in mastectomy for ductal carcinoma in situ. Ann Surg Oncol 2008; 15:268–273.

3 Veronesi U, Paganelli G, Viale G, Galimberti V, Luini A, Zurrida S, *et al.* Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. J Natl Cancer Inst 1999; 91:368–373.

4 Martin RC, Edwards MJ, Wong SL, Tuttle TM, Carlson DJ, Brown CM, *et al.* Practical guidelines for optimal gamma probe detection of sentinel lymph nodes in breast cancer: results of a multi-institutional study. For the University of Louisville Breast Cancer Study Group. Surgery 2000; 128:139–144.

5 Tuttle TM, Zogakis TG, Dunst CM, Zera RT, Singletary SE. A review of technical aspects of sentinel lymph node identification for breast cancer. J Am Coll Surg 2002; 195:261–268.

6 Stratmann SL, McCarty TM, Kuhn JA. Radiation safety with breast sentinel node biopsy. Am J Surg. 1999; 178:454–457.

7 Rob L, Strnad P, Robova H, Charvat M, Pluta M, Schlegerova D, *et al.* Study of lymphatic mapping and sentinel node identification in early stage cervical cancer. Gynecol Oncol 2005; 98:281–288.

8 Hutteman M, Mieog JS, van der Vorst JR, Liefers GJ, Putter H, Löwik CW, *et al.* Randomized, double-blind comparison of indocyanine green with or without albumin premixing for near-infrared fluorescence imaging of sentinel lymph nodes in breast cancer patients. Breast Cancer Res Treat 2011; 127:163–170.

9 Verbeek FP, Troyan SL, Mieog JS, Liefers GJ, Moffitt LA, Rosenberg M, *et al.* Near-infrared fluorescence sentinel lymph node mapping in breast cancer: a multicenter experience. Breast Cancer Res Treat 2014; 143:333–342.

10 Modugno G, Ménard-Moyon C, Prato M, Bianco A. Carbon nanomaterials combined with metal nanoparticles for theranostic applications. Br J Pharmacol 2014; 17:975–991.

11 Yan J, Xue F, Chen H, Wu X, Zhang H, Chen G, *et al.* A multi-center study of using carbon nanoparticles to track lymph node metastasis in T1-2 colorectal cancer. Surg Endosc 2014; 28:3315–3321.

12 Hao RT, Chen J, Zhao LH, Liu C, Wang OC, Huang GL, *et al.* Sentinel lymph node biopsy using carbon nanoparticles for Chinese patients with papillary thyroid microcarcinoma. Eur J Surg Oncol 2012; 38:718–724.

13 Wu X, Lin Q, Chen G, Lu J, Zeng Y, Chen X, Yan J. Sentinel lymph node detection using carbon nanoparticles in patients with early breast cancer. PLoS ONE 2015; 10:e0135714.

14 Scherer K, Bircher AJ, Figueiredo V. Blue dyes in medicine-a confusing terminology. Contact Derm 2006; 54:231–232.

15 Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, *et al.* The sentinel node in breast cancer-a multicenter validation study. N Engl J Med 1998; 339:941–946.

16 Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, *et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992; 127:392–399.

17 Barranger E, Grahek D, Cortez A, Talbot JN, Uzan S, Darai E. Laparoscopic entinel lymph node procedure using a combination of patent blue and radioisotope in women with cervical carcinoma. Cancer 2003; 97:3003–3009.

18 Fleissig A, Fallowfield LJ, Langridge CI. Post-operative arm morbidity and quality of life. results of the almanac randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat 2006; 95:279–293.

19 Peintinger F, Reitsamer R, Stranzl H, Ralph G. Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. Br J Cancer 2003; 89:648–652.

20 Shoei H, Aboulouz S, El Lamie I. Sentinel lymph node mapping in breast carcinoma. ASJOG 2005; 2:244–254.

21 Borgstein PJ, Meijer S, Pijpers RJ, van Diest PJ. Functional lymphatic anatomy for sentinel node biopsy in breast cancer: echoes from the past and the periareolar blue method. Ann Surg 2000; 232:81–89.

22 Zhang L, Huang Y, Yang C, Zhu T, Lin Y, Gao H, *et al.* Application of a carbon nanoparticle suspension for sentinel lymph node mapping in patients with early breast cancer: a retrospective cohort study. World J Surg Oncol 2018; 16:1–6.

23 Yang SX, Wei WS, Jiang QH, Zhou YF, Qu W, Tu JH, *et al.* Analysis of 246 Sentinel Lymph Node Biopsies of Patients With Clinical Primary Breast Cancer by Application of Carbon Nanoparticle Suspension. J Obstet Gynaecol Res 2018; 44:1150–1157.

24 Xie P, Yang ST, Huang Y, Zeng C, Xin Q, Zeng G, *et al.* Carbon NanoparticlesFe(II) complex for efficient tumor inhibition with low toxicity by amplifying oxidative stress. ACS Appl Mater Interf 2020; 12:29094–29102.

25 Fattahi AS, Tavassoli A, Rohbakhshfar O, Sadeghi R, Abdollahi A, Forghani MN. Can methylene blue dye be used as an alternative to patent blue dye to find the sentinel lymph node in breast cancer surgery? J Res Med Sci 2014; 19:918–922.

26 Olivier F, Courtois A, Jossa V, Bruck G, Aouachria S, Coibion M, Jerusalem G. Sentinel lymph node mapping with patent blue dye in patients with breast cancer: A retrospective single institution study. Gland Surg 2021; 10:2600.

27 Govaert GA, Oostenbroek RJ, Plaisier PW. Prolonged skin staining after intradermal use of patent blue in sentinel lymph node biopsy for breast cancer. Eur J Surg Oncol 2005; 31:373–375.

28 Joshi M, Hart M, Ahmed F, McPherson S. Adverse reaction; patent blue turning patient blue. BMJ Case Rep 2012; 2012:bcr2012007339.