Original Article

Near-infrared laparoscopy with indocyanine green for axillary sentinel lymph node biopsy in early breast cancer: preliminary experience of a single unit

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Background: A sentinel lymph node biopsy (SLNB) is a routine procedure for axillary staging in cN0 breast cancer (BC) patients. Indocyanine green (ICG) fluorescence can detect sentinel lymph nodes with higher sensitivity than carbon nanoparticle suspension (CNS). The present study investigated the availability and benefits of a near-infrared (NIR) laparoscopy-assisted SLNB using ICG and carbon nanoparticle suspension as tracers.

Methods: Forty patients with invasive BC, who had clinically negative axillary lymph nodes, participated in this observational study. ICG and CNS tracers were injected into the periareolar region simultaneously or sequentially. In the endoscopy-assisted group (n=20), the patients were given NIR laparoscopic SLNB based on ICG fluorescence and CNS staining. In the open-surgery group, the patients were given traditional SLNB using an open incision, and CNS tracers were injected into the same region as that in the endoscopy-assisted group.

Results: In the endoscopy-assisted group, lymphatic vessels and sentinel lymph nodes (SLNs) were successfully identified using ICG fluorescence imaging in most patients (19/20). The average number of SLNs removed was 2.85 (range, 1–4) in the endoscopy-assisted group, and 3.40 (range, 1–7) in the open-surgery group. There was no significant difference between the number of detected nodes (P=0.30). The patients who underwent endoscopy-assisted SLNBs had similar operating times, blood loss and hospital-stay lengths, but lower postoperative drainage volumes and higher satisfaction scores, as they did not have axillary incisions.

Conclusions: The NIR laparoscopy-assisted ICG-guided technique is a feasible and surgeon-friendly method for SLNB with good efficacy and acceptable safety. When combined with CNS, more SLNs can be detected and dissected.

Keywords: Breast cancer (BC); sentinel lymph node biopsy (SLNB); near-infrared fluorescence laparoscopy; indocyanine green (ICG); carbon nanoparticles

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Introduction

Positive axillary lymph nodes (ALNs) predict the development and prognosis of breast cancer (BC). Methods for accurately staging ALNs continue to evolve. Currently, the sentinel lymph node biopsy (SLNB) is the widely accepted, dominant procedure. The SLNB has become a standard procedure for evaluating the axillae in patients with early BC with clinically negative lymph nodes. In the foreseeable future, the status of sentinel lymph nodes (SLNs) will be crucial for treatment selection. A large review confirmed the benefits of the SLNB and axillary sampling as alternatives to ALN dissection (ALND) for the axillary staging of patients with clinically and radiologically uninvolved axillae (1). Additionally, for patients with limited SLN metastases, large, randomized trials have shown that lumpectomy and opposing tangential field radiation combined with ALND or SLNB alone produce equivalent outcomes (2). SLN detection is a minimally invasive, safe, and reliable method for evaluating the status of the ALNs. Compared to the previous method of level I and II ALND, SLNB has a lower morbidity rate, and a lower risk of lymphedema, seroma formation, pain, and functional deficits (3-8).

The identification and evaluation of SLNs is a key factor in the quality of SLNBs. In 1993, Krag *et al.* (9) first applied technetium sulfur colloid to BC patients undergoing SLNBs. In 1994, Giuliano *et al.* (10) first reported that the use of isosulfan blue in the SLN technique accurately predicted axillary nodal status in BC. Due to a higher rate of identification and a lower false-negative rate, a combined technique, which uses both vital blue dye and a radioactive colloid tracer and was introduced by Albertini, has been used by most surgeons, and is recommended by various guidelines for SLNBs (11,12).

The commonly used combined technique has some limitations. Notably, adverse reactions vary from minor to severe anaphylactic reactions (1–3%) requiring vigorous resuscitation. Due to the unavailability of radiocolloid, many units currently use blue dye alone for SLNBs. Methylene blue (MB), a safe and effective, readily available dye, is used in subdermal subareolar injections for SLN localization in the axillary staging of BC, and produces no major adverse reactions (13). Localization techniques that use a combination of blue dye and nonradioactive tracers of comparable accuracy warrant further investigation.

Near-infrared (NIR) fluorescence imaging is a newly emerging technique that can enable real-time image-guided surgery. Indocyanine green (ICG) has optical properties that can be detected by NIR fluorescence cameras. The use of ICG for lymphatic mapping techniques offers the ability to use NIR to visualize lymphatic anatomy and flow directly and immediately. NIR fluorescence imaging for SLN mapping has several properties that are advantageous in several types for cancer (14). Studies of BC surgery have also shown that ICG has advantages over blue dye for SLN identification (15). ICG allows real-time transcutaneous lymphography, and provides direct visualization of the lymphatic pathways that can be traced to the axillae to facilitate the SLNB (16,17). There is increasing evidence to support the use of ICG for SLN detection in early BC. Previous studies, either using ICG alone, or more recently in combination with blue dye, have shown that it is safe, and have found identification rates >90%. Wishart *et al.* (18) reported that 201 true sentinel nodes that were blue or radioactive were ICG positive.

In recent years, laparoscopic surgery has become a standard and routine procedure in many types of surgery, but BC surgery has remained largely unchanged. In Asia, many surgeons have started to use endoscopic surgery for BC. The benefits of this surgical method include smaller incisions, an axillary anatomical approach, clear vision, no oncological compromise, and good cosmetic outcomes (19). Endoscopy-assisted ALND is an accurate and harmless alternative to lymphadenectomy performed by a standard axillary incision. The same techniques can be used for SLNB (20).

The fluorescence detection of SLN using NIR laparoscopy has been used in the surgery of various cancers with ICG injection (21). The primary objective of the present observational study was to evaluate the sensitivity and safety of ICG fluorescence imaging in NIR fluorescence laparoscopy-assisted SLN identification in early BC. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-21-223).

Methods

Patients

The study group comprised 20 consecutive patients who underwent a NIR fluorescence laparoscopy-assisted SLNB between April 2019 and January 2020. The control group comprised 20 patients, who underwent a traditional open-SLNB using ICG and carbon nanoparticle suspensions

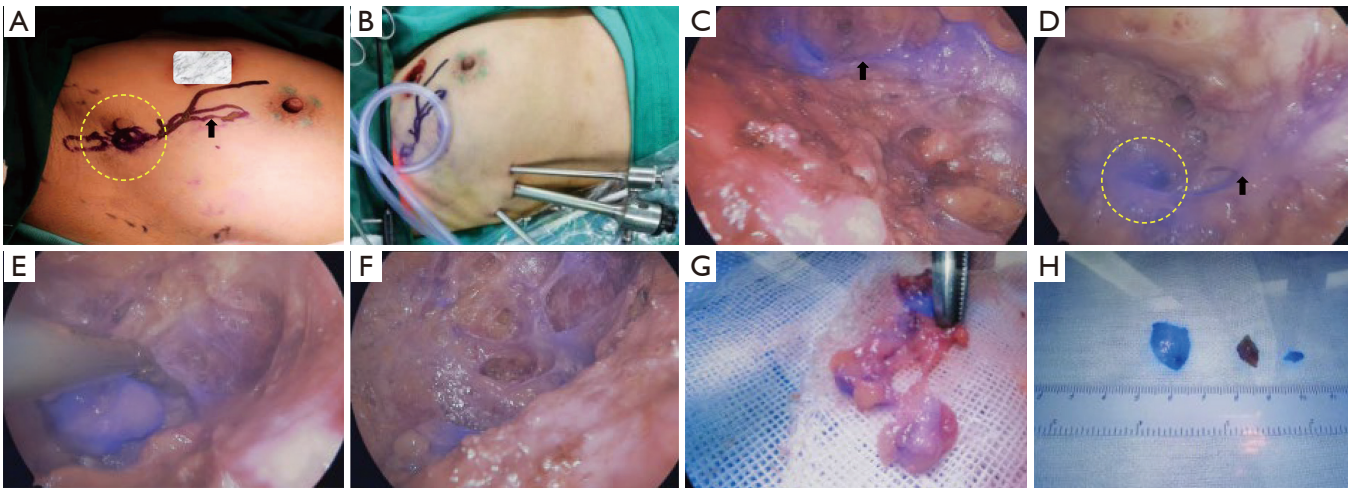

Figure 1 Process of endoscopy-assisted SLNB. (A) Marking the lymphatic vessels guided by ICG fluorescence imaging; (B) constructing the operative space; (C) visualizing the lymphatic vessel; (D) identifying the SLNs; (E) dissecting the SLNs; (F) displaying the surgical field; (G) examining the dissected LNs; (H) showing the SLNs. SLNB, sentinel lymph node biopsy; ICG, indocyanine green; SLNs, sentinel lymph nodes.

(CNSs) as lymph tracers. All patients were diagnosed with invasive BC by a core biopsy and pathological evaluation. Only patients with a clinically negative lymph node (LN) status were involved in our study. The patients were evaluated by clinical examination, imaging (mammography, ultrasound, and/or magnetic resonance imaging), according to the Chinese Society of Clinical Oncology and American Society of Clinical Oncology guidelines. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had tumors >5 cm as evidenced by an ultrasound assessment; (II) had ALN involvement as evidenced by clinical and/or imaging evidence; (III) had a hypersensitivity to iodine or ICG; (IV) had hyperthyroidism; (V) had undergone a previous operation in the breast or axilla; (VI) had undergone neoadjuvant chemotherapy; and/or (VII) refused the procedure.

Patients gave full informed consent for the SLN localization and the SLNB. An immediate axillary clearance was performed if no SLN was identified or the frozen section showed metastasis. This study was approved by the Institutional Review Board of the Air Force Military Medical University (Xi'an, China). All of the procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and national research committee, and the Helsinki Declaration (as revised in 2013). Informed consent for participation in the study was obtained from the legal guardians of all the patients. All patient records were anonymized and de-identified before analysis.

Surgical and SLN excision procedures

CNSs were purchased from the Chongqing Lummy Pharmaceutical Co. (Chongqing, China) in the form of a standard CNS (1 mL: 50 mg). ICG (Yichuang Pharmaceutical Co. Ltd., Dandong, China) was prepared at 5 mg/mL concentration, obtained by dilution of a 25 mg ICG vial with 5 mL sterile water. CNS (0.4 mL) and 2 mL of 0.5% ICG were mixed for 5 min and intradermally injected into the periareolar region at 4 sites (clockwise) before the operation. The tracers were injected [after the injection of CNSs, ICG was also injected (1 mL intradermally, and 1 mL subcutaneously)] at the edge of the areola, at the 2 o'clock position (left breast) or 10 o'clock position (right breast) (see *Figure 1A*). The breast was massaged for 5 min to aid the migration of ICG and CNSs into the lymphatic vessels. The real-time fluorescent subcutaneous lymphatics were visualized using the fluorescence imaging system (MI-2 Type; Micro Intelligence Technology Co. Ltd., Jinan, China) and traced to the axillae where the SLNs could be seen percutaneously (see *Figure 1A*).

The endoscopy-assisted SLNB procedures were performed by 3 surgeons (BG, YP, and PS). General

anesthesia with endotracheal intubation was used, and each patient was placed in the supine position, with the arm at 130° and supported by a bandage roll.

The liposuction fluid comprised 200 mL normal saline, 200 mL distilled water, 20 mL lidocaine, and 2.5 mL adrenaline. Normally, 200 mL of the solution was injected around the visualized SLN (below the hair-bearing region of the axilla). Thereafter, the liposuction canula was introduced through a 10-mm incision in the middle axillary line at the level of the submammary fold. Aspiration was achieved with a vacuum of 800 mbar. An initial 10-mm trocar was then introduced through the existing incision. After insufflation with carbon dioxide at a pressure of 6–8 mmHg, a 10-mm 30° laparoscope (Smart Eye 101; Suzhou Caring Medical Co. Ltd., Suzhou, China) was used. Two additional 5- and 12-mm trocars were placed adjacent to the optic trocar (see *Figure 1B*). The deliberate removal of LNs was guided by conventional criteria (i.e., nodes that were hot and/or blue), or if suspicious nodes were identified at operation (see *Figure 1C,D,E*). The dissected SLNs (ICG positive and/or blue) were removed through the 12-mm trocar using a sample bag, and the surgical field was further detected (see *Figure 1F*). The LNs were separated and sent for pathological examination (see *Figure 1G,H*). The drainage tubes were placed through the trocar holes.

Open-SLNB procedures were performed by the same team. After the location of the SLNs, a 4-cm incision was made, and the SLNs detected with fluorescence imaging system and CNS were excised.

Histopathology of SLNs

The SLNs were evaluated postoperatively with routine hematoxylin and eosin (H&E) staining at ~2-mm intervals through the LNs. If the HE staining could not determine whether a SLN was metastatic or not, immunohistochemistry was performed. Metastases were reported as macrometastases (>2 mm), micrometastases (>0.2 and ≤2, or <0.2 mm within LN parenchyma), and isolated tumor cells (≤0.2 mm).

Data collection and statistical analysis

The demographic and clinicopathological variables of each patient were collected, and the details of the procedure, including SLN dissection (SLND) time, visualized lymphatics, the number of ICG-positive LNs, the number of blue LNs, and status of LN metastases were recorded. The mean and range values were calculated using SPSS. Student's t test was used to analyze differences in age, body mass index, the number of SLNs, operating time, duration of axillary drainage, drainage volume, amount of blood loss, and length of hospital stay. Pearson's chi-square test was used to analyze the other characteristics. All statistical analyses were performed using Microsoft Excel (Redmond, WA, USA) and SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Analysis of demographic and clinicopathological variables

The basal demographic and clinicopathological variables are shown in *Table 1*. The mean age of the patients was 56.60±10.59 years in the endoscopy-assisted group, and 48.25±10.43 years in the open-surgery group. Tumor size ranged from 1 to 3 cm, and no significant difference was found between the two groups (P=0.79). Among the 40 BC patients, there were 12 in grade I, 18 in grade II and 10 in grade III. The distribution of molecular subtypes was as follows: 28 cases of positive of estrogen receptor (ER+) and/or progesterone receptor(PR+) (including 3 cases with HER2+), 5 triple negative cases, and 7 Human epidermal growth factor receptor 2(HER2+) only cases.

Analysis of successful SLN identification rate

Transcutaneous fluorescent lymphography was visible in all 40 patients but ALNs were seen percutaneously in only 4 patients. In the endoscopy-assisted group, lymphatic vessels and SLNs were successfully identified using ICG fluorescence imaging in most patients (19/20). As *Table 2* shows, the average number of SLNs removed was 2.85±0.88 in the endoscopy-assisted group, and 3.40±1.47 in the open-surgery group. There was no significant difference in the number of detected LNs (P=0.30). In the open-surgery group, non-SLNs with CNS staining were found in 3 patients. In the open-surgery group, an intraoperative frozen pathological analysis revealed that 1 patient showed metastasis of SLNs, and this patient underwent a complementary ALND. The pathological evaluation of LNs did not reveal further metastasis.

Analysis of surgical safety and reliability

The lymphatic vessels and SLNs were successfully

Table 1 Basic demographic and clinicopathological characteristics of patients in the endoscopy-assisted and open-surgery groups

Variable	Endoscopy-assisted group (n=20)	Open-surgery group (n=20)	t/χ^2	P
Age (mean ± SD), years	56.60±10.59	48.25±10.43	2.51	0.79
BMI (mean ± SD), kg/m^2	23.50±0.48	24.18±0.66	0.84	0.44
Menstrual status			3.60	0.06
Premenopause	7	13		
Postmenopause	13	7		
Tumor size (cm)			0.40	0.53
≤2	10	8		
2–5	10	12		
Histology			5.16	0.08
I	8	4		
II	10	8		
III	2	8		
TNM stage			1.65	0.44
I	9	6		
II	10	11		
III	1	3		
Pathological type			0.11	0.74
Ductal	12	13		
Non-ductal	8	7		
Ki-67			0.44	0.51
High[a]	6	8		
Low	14	12		
ER			2.13	0.14
1–10%	3	7		
>10%	17	13		
PR			1.03	0.31
1–20%	5	8		
>20%	15	12		
Her-2			0.78	0.38
Positive[b]	2	4		
Negative	18	16		

[a], Ki-67 >30%; [b], IHC 3+ or ISH positive. P<0.05 indicates statistical significance. BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.

Table 2 Successful SLN identification rate in the endoscopy-assisted and open-surgery groups

Variable	Endoscopy-assisted group	Open-surgery group	χ^2	P	OR (95% CI)
Mean positive detection number of SLNs	2.65	2.65	0.88	0.35	0.50 (0.23–1.11)
Mean negative detection number of SLNs	0.20	0.75			
Total	2.85	3.40			

P<0.05 indicates statistical significance. SLNs, sentinel lymph nodes.

Table 3 Surgical safety and reliability in the endoscopy-assisted and open-surgery groups

Variable	Endoscopy-assisted group	Open-surgery group	P
Number of SLNs (mean ± SD)	2.85±0.88	3.40±1.47	0.30
Operating time (mean ± SD, min)	131.85±43.89	121.00±43.94	0.44
Drainage volume (mean ± SD, mL)	122.00±50.69	158.15±91.04	0.13
Blood loss (mean ± SD, mL)	53.00±42.69	56.50±29.43	0.74
Hospital stay (mean ± SD, d)	3.90±0.23	4.65±0.44	0.07
Patient satisfaction score (mean ± SD)	1.50±0.51	1.30±0.13	0.72

P<0.05 indicates statistical significance. SLNs, sentinel lymph nodes.

identified under NIR laparoscopy using ICG fluorescence imaging, which was suitable for the accurate removal of true SLNs (see *Figure 1C*). The operating time of SLNB was 131.85±43.89 min in the endoscopy-assisted group, and 121.0±43.94 min in the open-surgery group; no significant difference was found between the two groups (P=0.44) (see *Table 3*). The axillary drainage volumes, blood loss, and hospital-stay lengths were similar between the two groups from postoperative days 1 to 3. Patients were asked to rank their level of satisfaction on a scale on which 0 represented unsatisfactory, 1, less than satisfactory and 2, satisfactory. Due to the absence of axillary incisions, the patients given endoscopy-assisted SLNB showed levels of higher satisfaction. Specifically, patients in in the endoscopy-assisted-group gave an average score of 1.50±0.51 and those in the open-surgery group gave an average score of 1.30±0.13 (P=0.72).

Discussion

The SLNB has become a standard procedure for axillary staging in patients with BC with clinically negative LNs; however, the standardization and modification of the methodology represent a significant area of research. The combined technique of radioisotope (RI) and blue dye are widely used to detect SLNs in BC (22,23). However, both the single procedure and the combined techniques still have some limitations. RI has a high detection rate, but requires special protection against radiation and specific apparatus, which is not available in many units. A randomized trial comparing blue dye alone with blue dye and isotope reported equivalent identification rates (18); however, blue dye has a lower detection rate, and may be particularly difficult to detect, especially in overweight patients (24-26). Further, both RI detected by an acoustic signal and blue dye cannot show visualized transcutaneous lymphatic mapping or "true" SLN localization.

ICG is a popular reagent that is usually injected intravenously, and is currently approved for clinical usage. It absorbs light in the NIR range (maximally at a wavelength of approximately 800 nm) (27). The ICG fluorescence navigation technique has been widely used for precise dissection in various types of cancers (28-30). As the ICG fluorescence system appears to be safe, have low toxicity, and produce few adverse effects and allergic reactions (31), it has been proposed as an alternative technique for SLNB (32,33). The procedure can offer ICG fluorescence images in the surgical field for real-time navigation during SLNB; the identification rates for ICG alone are in excess of 90% (18,34,35). A small study of 30 women undergoing a SLNB with ALND showed a false-negative rate of 8% for ICG compared with 23% for RI (36). Guo *et al.* (37) reported

that the detection rate of SLNB was higher when ICG fluorescence was used than blue dye (on average, 3.6 SLNs were detected in the ICG fluorescence group compared to only 2.1 in the blue dye group).

Recent practice has favored a combination of ICG with either blue dye or RI, which allows for both conventional and fluorescent visualizations of the lymphatic vessels and nodes. Results have shown that such combinations have high levels of nodal recognition by fluorescence, and very few nodes (<5%) are classified as blue and/or hot but not fluorescent (38). The identification rates vary among the blue dye (68–86%), RI (86–99%), combined technique (89–97%), and ICG (73.8–99%) (39). ICG could potentially replace radioactive colloid, and is more widely accepted by breast surgeons (31). As our study showed, the technique enables a visualized and real-time navigation of subcutaneous lymphatic vessels, which assists surgical localizations and can be used to confirm sentinel status once a node has been identified. Thus, it has the potential to guide the surgical procedure and improve overall sensitivity.

However, there is no standard consensus and thus considerable variability continues to exist among surgeons (40). Several studies have reported that there are no significant effects on the identification rate or the number of SLNs excised with different LN mapping methods, including the use of delayed or immediate imaging, periareolar or peritumor injection. At our center, the tracers were mainly injected periareolarly, and the clinical results were reliable. Some studies have suggested that the detection rate of the ICG + blue dye method is close to 100%, and the number of SLNs detected is around 4 (41,42). Others have contended that while the addition of blue dye to ICG might not improve the identification rate significantly, it does have a definite benefit in improving the false-negative rate (43). Additionally, in 5% of patients, upper extremity lymphatic drainage into the SLN led to the risk of developing lymphedema in this group (44). Axillary reverse mapping can preserve the upper extremity lymphatic pathways during ALN surgery. ICG fluorescence imaging can also be used to preserve the upper extremity lymphatic pathways during ALN surgery to decrease the risk of lymphedema (44).

In China, CNSs have been widely used for the intraoperative identification of SLNs in various cancers, and have been found to have high detection rates and accuracy (45-47). CNSs can be used successfully for SLN identification in patients with early BC (39), and have been shown to have a higher SLNB success rate than nanocarbon staining (99.59%, with 97.06% accuracy and 93.22% sensitivity), and a lower false-negative rate (6.78%) (48). The detection rate of the CNS-alone method was lower than that of the ICG + MB method (98.3% vs. 100%); however, the difference was not significant (49). In our unit, CNSs have been used for LN tracing during cancer surgery for 10 years, and for LN imaging in ALND and SLND in BC patients.

Surgical techniques for BC have undergone a dramatic change recently with breast-conserving surgery and SLNB. Endoscopy-assisted breast surgery is an acceptable alternative technique for breast-conserving surgery in early BC as well as skin- or nipple-sparing mastectomy to facilitate breast reconstruction. Endoscopy-assisted breast surgery has comparable oncological, surgical, and aesthetic outcomes to conventional techniques (50). Endoscopy-assisted breast surgery has lowered the morbidity of ALND (51), and shows good functional and cosmetic outcomes (52). Further, endoscopic SLND in BC patients has some benefits, including that it results in less pain and paresthesia and better-quality shoulder mobility (20). Endoscopy-assisted SLNB has also been used in the treatment of many cancers, including in the detection of SLNs using ICG fluorescence (53).

In the present study, ICG and CNS mapping techniques were used for fluorescent laparoscopic SLND. It has been suggested that separate lymphatic tracts pass toward the axillae rather than converging in one lymphatic duct; thus, 2 tracer agents may act in a complementary manner to maximize the chance of detecting those nodes with a high probability of harboring metastases. Conversely, percutaneous lymphatic vessel visualization could help surgeons to determine the precise location of true SLNs, which is conducive in SLND.

In the present study, we dissected ICG-positive and blue LNs. In most cases, SLNs were successfully removed using an endoscopy-assisted technique or traditional open procedure using double tracers. The intraoperative identification rate of SLNs in the endoscopy-assisted group was 95% compared to that of 90% in the open-surgery group; however, this difference was not significant. Black staining of non-sentinel LNs was observed in 3 patients in the open-surgery group. This suggested that the combined application of CNSs might increase the number of LNs removed. During LN dissection, removal must be performed meticulously to avoid ICG leakage into the axillary tissues, producing nonspecific staining. Adjacent non-sentinel LNs can become fluorescent and increase the

nodal yield.

In the endoscopy-assisted group, lymphatic vessels and SLNs were successfully identified using ICG fluorescence imaging. The results of the present study suggest that endoscopy-assisted techniques are appropriate for the accurate removal of true SLNs. Compared with the open-surgery group, fewer SLNs were dissected in the endoscopy-assisted group. However, the average nodal count was not significantly different between the two groups. The patients who underwent endoscopy-assisted SLNB had similar operating times, postoperative drainage volumes, and hospital-stay lengths as those in the open-surgery group. However, due to the absence of axillary incisions, the endoscopy-assisted group had higher satisfaction scores than the open-surgery group.

Conclusions

NIR laparoscopy can be used to detect SLNs in early BC patients. The specific surgical technique enables the lymphatic vessels to be visualized, and true SLNs to be precisely dissected with less surgical disturbance. The technique requires further research, including randomized controlled studies.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-21-223). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of the Air Force Military Medical University (Xi`an, China). All of the procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and national research committee, and the Helsinki Declaration (as revised in 2013). Informed consent for participation in the study was obtained from the legal guardians of all the patients. All patient records were anonymized and de-identified before analysis.

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