

Exploring the Use of Indocyanine Green for Delayed Sentinel Lymph Node Biopsy in Breast Cancer: Two Case Reports

Jamila Alazhri^{1*} and Hussain A. Abdulla²

¹Breast and Endocrine Surgery Section, King Fahad Specialist Hospital, Dammam, Saudi Arabia

²Breast Surgery, Salmaniya Medical Complex, Manama, Bahrain

*Corresponding author: Jamila Alazhri, Oncoplastic Breast Surgeon, King Fahad Specialist Hospital, Dammam, Saudi Arabia.

E-mail: drjzhri@hotmail.com

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Abstract

Purpose: In certain patients with breast cancer, the need for Sentinel lymph node biopsy (SLNB) during mastectomy surgery is uncertain. Delayed SLNB has emerged as a potential solution. This study explores the feasibility of delayed SLNB using indocyanine green (ICG).

Materials and Methods: Intradermal ICG was administered to two patients at 1 and 3 weeks prior to breast surgery. On the day of surgery, standard SLNB was performed using blue dye or technetium-99 (Tc-99). SLNs identified as fluorescent (green), blue, or radioactive “hot” were excised.

Results: ICG-stained (green) SLNs were successfully identified in both patients at the time of surgery. ICG demonstrated retention within SLNs for up to 3 weeks, both in the setting of upfront surgery and following neoadjuvant systemic therapy.

Conclusions: ICG can persist within sentinel lymph nodes for up to 3 weeks after injection, supporting its potential role as a safe and cost-effective tracer for delayed SLNB.

Keywords: Breast cancer; Sentinel lymph node biopsy; Ductal carcinoma in-situ; Mastectomy; Indocyanine green, delayed sentinel lymph node biopsy

Introduction

Sentinel lymph node biopsy (SLNB), rather than axillary lymph node dissection (ALND), is the standard of care for axillary staging in clinically node-negative breast cancer [1]. Over the last few decades, the management of the axilla has evolved from routine ALND to SLNB to the omission of axillary surgery altogether in select patients, with varying degrees of acceptance [2]. These cases include ductal carcinoma in situ (DCIS), risk-reducing mastectomy (RRM), and elderly women with early-stage, clinically node-negative, hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative disease, according to Choosing Wisely guidelines [3]. In DCIS, SLNB is indicated if mastectomy is considered due to the technical challenge in performing SLNB after mastectomy if the specimen shows an invasive component [4].

However, our previous work has shown that the rate of upgrade to invasive cancer is approximately 10%, with the incidence of sentinel lymph node positivity around 10% among these upgraded patients [5]. These low rates have also been documented by other investigators, and suggest the safety of omitting or delaying SLNB in DCIS until a definitive diagnosis of invasive cancer is made [6].

SLNB after mastectomy usually fails due to disruption of lymphatic channels [7]. Therefore, a previous mastectomy is generally considered a technical contraindication to performing SLNB [8]. Recently, the SentiNot trial showed that marking the sentinel lymph node with Magtrace in patients with a preoperative diagnosis of DCIS resulted in avoiding upfront SLNB in the majority of the cohort, with delayed SLNB being feasible once invasive disease was found [9]. Despite these promising results, the Magtrace technique has its own limitations, including the need to clear the surgical field of any metal instruments, the frequent need to calibrate the probe before every attempt to search for the node, the cross-interaction between Magseed and Magtrace, the skin discoloration at the injection site, and the considerable cost. Therefore, it is important to find an alternative method that is safe, faster, and more cost-effective.

Since the first reports in the early 1990s, blue dye and radioisotopes, alone or in combination, have been the most commonly used tracers for SLNB [10-12]. Indocyanine green (ICG) has emerged as a safer and cheaper alternative for SLNB [13]. In a recently published meta-analysis, the authors concluded that ICG is clearly and consistently superior to blue dye, non-inferior to technetium-99 (99Tc), and superior to the combination of 99Tc and blue dye [14]. Making it an attractive potential alternative to MagTrace.

We describe two cases where preoperative injection (up to 3 weeks prior to surgery) of ICG succeeded in localizing the sentinel lymph nodes at the time of surgery. This novel technique of pre-marking the sentinel lymph node at the time of mastectomy is promising for safe omission of upfront SLNB in patients who would otherwise be considered for delayed SLNB, if needed, thereby avoiding the unnecessary morbidity of axillary surgery.

Methods

We administered ICG before surgery at the recommended doses and injection sites for the SLNB procedure: 2 intradermal periareolar injections of 0.1 mL at 12 and 9 o'clock in the right breast, or at 12 and 3 o'clock in the left breast. On the day of surgery, the standard SLNB technique was performed; in one patient, blue dye only was used, and in another, blue dye and 99Tc were used. SLNB was performed by harvesting the blue, hot, or green (ICG-stained) nodes.

Case Presentation

Case 1

A 56-year-old perimenopausal woman presented with a 3-month history of a left breast lump. There was no history of any nipple discharge or skin changes. Family history was significant for a sister with breast cancer at 43 years of age. Physical examination showed a 2 x 2 cm ill-defined mass at the 11 o'clock position of the left breast, with no palpable axillary lymphadenopathy. Ultrasonography showed two irregular heterogeneous masses with spiculated margins at 10 and 11 o'clock of the left breast, measuring 0.7 x 0.7 cm and 1 x 0.6 cm, respectively.

Mammography revealed architectural distortion in the upper inner quadrant of the left breast, approximately 2.4 cm from the nipple, with a small focal asymmetry in the retroareolar region, suggestive of multifocal disease. There were no enlarged lymph nodes seen. Ultrasound-guided core biopsy of the 11 o'clock lesion, followed by clipping of both masses, was performed. The diagnosis was left breast grade 2 invasive ductal carcinoma (IDC), 95% positive for estrogen receptor (ER) and 90% positive for progesterone receptor (PR) but negative (score 1+) for HER2 neu, with a Ki67 index of 25% (cT1N0M0, Luminal B). The case was discussed at the breast multidisciplinary tumor board (MDT) meeting with a recommendation for upfront surgery. The patient was booked for wide local excision using crescent mastopexy and SLNB. One week prior to surgery, the patient received an injection of ICG in the clinic. The ICG (Verdyne™, Diagnostic Green, Ireland) powder was diluted with 5 ml of sterile water to the recommended concentration for SLNB, and 2 injections of 0.1ml of the diluted ICG were administered intradermally at the 12 o'clock and 3 o'clock periareolar positions of the left breast, after applying numbing cream to the skin. On the day of surgery, the standard SLNB technique was performed using methylene blue. After induction of general anesthesia, the blue dye was injected into the retroareolar plexus of Sappey, intradermally at the mastopexy skin planned for excision, and intraparenchymally in the upper outer quadrant, followed by 15 minutes of breast massage to enhance the lymphatic drainage of the blue dye. Intraoperatively, no blue nodes were identified. Nevertheless, 3 green sentinel lymph nodes were identified using a hand-held fluorescent camera (SPY-PHI System, Stryker, USA) (Figure 1). Final histology revealed three negative sentinel lymph nodes, pT1N0M0.

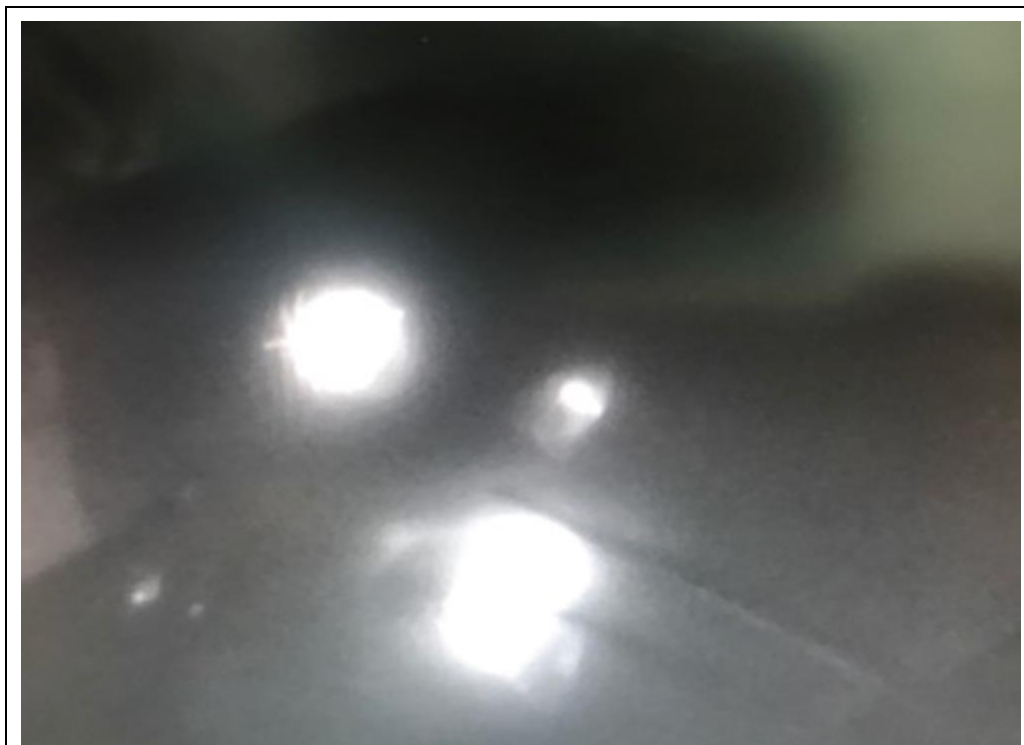


Figure 1: An intraoperative picture of the first case showing the spy mode image of 3 ICG-stained sentinel nodes.

Case 2

A 58-year-old male presented with a 1-year history of progressively enlarging right breast lump. Family history was significant for two sisters with breast cancer, one diagnosed at 37 years and the other at 50 years, and maternal cousins with breast cancer at 40 years of age. His medical history included diabetes mellitus and dyslipidemia. There was a previous surgical history of right breast lumpectomy 8 years prior to presentation at another institution, with unknown pathology. On examination, there was a 3.5 x 5 cm mass in the right retroareolar region, with a palpable, mobile right axillary lymph node. Ultrasonography and mammography showed a 3.6 x 3 cm complex mass with solid and cystic components in the retroareolar region of the right breast, and a right axillary lymph node with cortical thickening suspicious for metastasis. Ultrasound-guided core biopsy was performed for these concerning lesions. The diagnosis was right breast IDC with papillary features and a metastatic right axillary lymph node. Immunohistochemistry was ER-positive (99%), PR-positive (99%), and HER2 neu positive (score 3+), with a Ki67 index of 30%. Staging computed tomography (CT) scan of the chest, abdomen, and pelvis, and bone scan did not reveal distant metastasis (cT2N1M0). The case was discussed at the MDT meeting with a recommendation for neoadjuvant systemic therapy followed by mastectomy and axillary surgery (depending on response to treatment).

The patient underwent neoadjuvant chemotherapy and anti-HER2 therapy and was referred by medical oncology for definitive surgery. Upon reassessment, there was a good treatment response in the right breast tumor and no palpable axillary lymphadenopathy. Repeated ultrasound of the axilla showed normalization of previously abnormal lymph nodes, consistent with a chemotherapy response. The patient was scheduled for mastectomy and SLNB, using dual tracers, within 30 days of his last dose of chemotherapy. Three weeks prior to surgery, he received an intradermal injection of ICG at 12 o'clock and 9 o'clock periareolar positions in the right breast, in the clinic, using the same dose described for the first case. On the day of surgery, the methylene blue dye and Tc99 injection were performed after induction of general anesthesia, followed by 15 minutes of massage. Intraoperatively, 4 sentinel lymph nodes were identified. Two lymph nodes were hot, blue, and green (Figure 2), and the other two only stained blue (Figure 3). Surgical pathology revealed a 4.5 cm residual breast tumor with 1 out of 4 lymph nodes positive for micrometastasis (ypT2N1miM0). The case was re-discussed at the MDT meeting with consensus for axillary dissection. ALND was performed, retrieving 11 lymph nodes, all of which were pathologically negative for metastases.

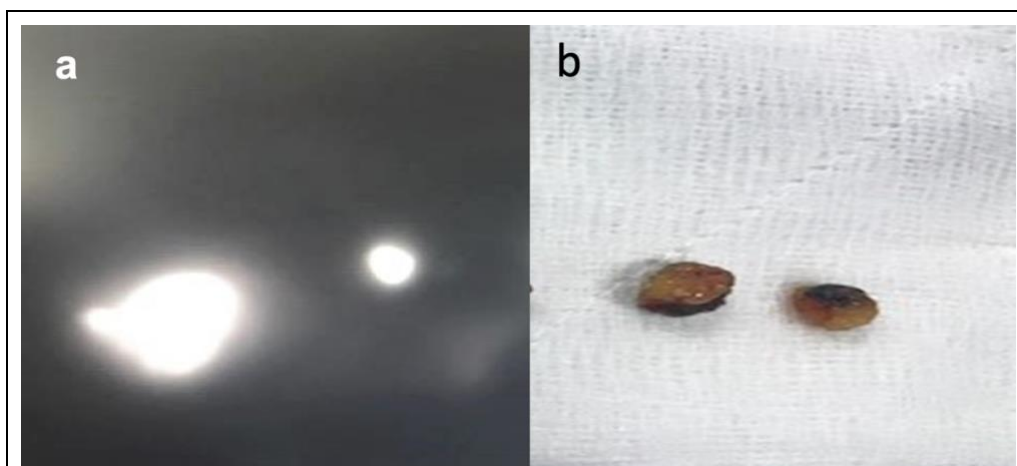


Figure 2: Intraoperative image of the second case showing (a) the 2 hot, blue and ICG-stained sentinel nodes in spy mode, and (b) the other 2 nodes stained in blue only.

Results

In the first case, ICG was injected one week prior to upfront surgery and was retained in the sentinel lymph node until the time of surgery. Three Green nodes were successfully identified.

In the second case, ICG was injected 3 weeks prior to surgery in a male patient who received NACT, and the dye was retained in the sentinel lymph nodes until the time of surgery. Two green nodes were successfully identified, which were also blue and reactive to Tc99 (hot).

No immediate or delayed complications have resulted from the preoperative ICG injection

Discussion

These two cases demonstrate that ICG persists within the sentinel nodes for at least 3 weeks after injection, enabling reliable localization at the time of surgery. This finding provides proof of concept that ICG could be used to pre-mark sentinel nodes in patients in whom upfront SLNB is not required and the SLNB procedure can be delayed until final pathology confirmation, when deemed necessary. To the best of our knowledge, this is the first study that demonstrates the feasibility of using ICG in delayed SLNB.

The National Comprehensive Cancer Network (NCCN) guidelines state that SLNB should be performed in patients with DCIS undergoing mastectomy or in a patient for whom the location of BCS may compromise future SLNB (for example, upper outer quadrant lesions) [2]. In this setting, ICG-guided delayed SLNB may be an alternative solution. ICG can be injected during the index surgery (before mastectomy or lumpectomy) without harvesting the stained sentinel lymph nodes. Excision of the sentinel node could be safely deferred for up to 3 weeks, until invasive cancer is confirmed on final pathology, allowing most DCIS patients to avoid upfront SLNB. Another potential advantage is in DCIS patients who undergo a therapeutic reduction mammoplasty, which involves rearrangement of glandular tissue and mobilization of the nipple-areola complex, thereby risking damage to lymphatic drainage, which may compromise future SLNB.

The current evidence does not support routine use of SLNB during RRM [3]. Nevertheless, the detection of occult invasive cancer mandates ALND for staging, thereby prompting some surgeons to consider SLNB at the time of bilateral or contralateral RRM [15], especially in the presence of MRI-detected suspicious findings that are inaccessible to image-guided biopsy. In this setting, ICG-guided delayed SLNB can be performed instead of SLNB to avoid excising any nodes unless final mastectomy pathology confirms occult invasive cancer. The Choosing Wisely guidelines discourage the routine performance of SLNB in elderly patients (above 70 years) with early-stage, cN0, hormone receptor-positive and HER2-negative tumors, if adjuvant therapy decisions will not be influenced by nodal status [16]. The recently published SOUND and INSEMA trials have also provided similar recommendations, which have been adopted in the NCCN guidelines [17,18]. However, in patients in whom axillary staging will affect the decision on adjuvant treatment, this technique can be selectively used to perform SLNB in a delayed setting. Moreover, since ICG-guided delayed SLNB allows for the omission of axillary surgery at the time of the first operation, it also allows performing SLNB in the event of ipsilateral breast tumor recurrence because the axilla would still be intact [19], and further reduces the need for axillary dissection and risk of upper limb lymphedema.

In both cases, we used the standard-of-care technique at our institution on the day of surgery: blue dye in the first patient and a combination of blue dye and a radioisotope in the second patient to overcome potential ICG washout from the SLN during surgery. ICG is visualized intraoperatively using near-infrared fluorescence, providing real-time visual navigation with greater tissue penetration than blue dye, as demonstrated in a previously published study [20]. This was demonstrated in the first case we presented, where there was no blue dye uptake, whereas ICG was taken up by 3 nodes, despite ICG having been injected 1 week prior to surgery.

Conclusion

Our preliminary findings indicate that ICG can remain in the axillary SLNs for a sufficient duration to enable performing a delayed SLNB. To our knowledge, this is the first study to explore the feasibility of using ICG in delayed SLNB. While our experience is preliminary and limited to two cases, it opens the door for larger studies exploring the potential of ICG as a safe, MRI-compatible, affordable, and more practical tracer for delayed SLNB in breast surgery.

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