OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Reconstructive

Use of Indocyanine Green for Sentinel Lymph Node Biopsy: Case Series and Methods Comparison

Andrew McGregor, MD*
Sabrina N. Pavri, MD*
Cynthia Tsay, MPhil†
Samuel Kim, MD*
Deepak Narayan, MD*

Introduction: Sentinel lymph node biopsy is indicated for patients with biopsy-proven thickness melanoma greater than 1.0 mm. Use of lymphoscintigraphy along with vital blue dyes is the gold standard for identifying sentinel lymph nodes intraoperatively. Indocyanine green (ICG) has recently been used as a method of identifying sentinel lymph nodes. We herein describe a case series of patients who have successfully undergone ICG-assisted sentinel lymph node biopsy for melanoma. We compare 2 imaging systems that are used for ICG-assisted sentinel lymph node biopsy.

Methods: Fourteen patients underwent ICG-assisted sentinel lymph node biopsy for melanoma using the SPY Elite system (Novadaq, Mississigua, Canada) and the Hamamatsu PDE-Neo probe system (Mitaka USA, Park City, Utah). We analyzed costs for 2 systems that utilize ICG for sentinel lymph node biopsies.

Results: Intraoperative use of ICG for sentinel lymph node biopsies was successful in correctly identifying sentinel lymph nodes. There was no difference between the Hamamatsu PDE-Neo probe and SPY Elite systems in the ability to detect sentinel lymph nodes; however, the former was associated with a lower operating cost and ease of use compared with the latter.

Conclusion: ICG-assisted sentinel lymph biopsy using the SPY Elite or the Hamamatsu PDE-Neo probe systems for melanoma are comparable in terms of sentinel node detection. The Neo probe system delivers pertinent clinical data with the advantages of lower cost and ease of operation. *(Plast Reconstr Surg Glob Open 2017;5:e1566; doi: 10.1097/GOX.0000000000001566; Published online 20 November 2017.)*

INTRODUCTION

The Breslow depth is one of the most important prognostic factors with regard to the 5-year survival rate in melanoma. Staging of melanoma requires sentinel lymph node biopsy (SLNB), which is indicated for intermediate thickness melanomas defined as a Breslow depth greater than 1.0 mm.[1] However, this recommendation is in an evolution as studies have demonstrated in high-risk lesions that SLNB should be performed for Breslow depth greater than 0.75 mm, especially those with adverse features such as positive deep margins, ulceration, mitosis, lymphovascular invasion or young age.[2,3] SLNB with completion lymph node dissection for intermediate thickness melanomas has not been demonstrated to improve 10-year disease-specific survival rates compared with observation; however, it has shown to be statistically significant in increasing disease-free survival.[4,5]

The evolution of the SLNB has grown from the use of vital blue dyes such as methylene blue (MB), isosulfan blue (Lymphazurin) and Patent Blue V dye, to lymphoscintigraphy using technetium-99m (Tc-99m) as a marker of the sentinel lymph node. Often, a combined technique using radioisotopes and blue dye are used. Anaphylactic reactions and serotonin syndrome associated with the use of vital blue dyes have been reported in the literature.[6–9] Lymphoscintigraphy remains the gold standard in the identification of sentinel lymph nodes in melanoma. Although this method leads to accurate sentinel lymph node identification, the cost and burden to patients undergoing preoperative lymphoscintigraphy can be a challenge, and SLNB positivity can depend on hospital quality.[10] For patients undergoing lymphoscintigraphy, the patient must undergo a preoperative injection of Tc-99m before the localization procedure. In addition to this prior injection, patients may face long wait times, delays, and additional emotional stress.

*From the *Section of Plastic and Reconstructive Surgery, Department of Surgery, Yale School of Medicine, New Haven, Conn.; and †Yale School of Medicine, New Haven, Conn.*

Received for publication June 3, 2017; accepted September 22, 2017.

DOI: 10.1097/GOX.0000000000001566

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

Fig. 1. Depicted is the SPY Elite System being used for ICG-assisted sentinel lymph node biopsy.

The use of indocyanine green (ICG) has emerged as a powerful tool in the assessment of sentinel lymph nodes.[11,12] ICG is a small substance near-infrared fluorophore (774.96 Da), which can be visualized transcutaneously to 1.0 cm. However, it contains sodium iodide, which limits its use in patients with iodine or shellfish allergies. ICG can be used in conjunction with intraoperative imaging modalities such as the SPY Elite system (Novadaq, Mississigua, Canada) and Hamamatsu PDE-Neo probe (Mitaka USA, Park City, Utah). The use of these systems has expanded from their use in flap viability assessment to identification of sentinel lymph nodes.[13–16] We aim to show that the use of these systems is a valuable tool as a clinically safe and effective means of sentinel lymph node identification and compare the clinical efficacy and costs of the 2 systems.

METHODS

This study was exempt from Institutional Review Board review. This case series included 14 patients who underwent SLNB at our institution without the use of preoperative injection of Tc-99m. An intraoperative injection of ICG was performed around the tumor bed. Intraoperative injection of Tc-99m was used to control for the identification of the sentinel lymph nodes by using a standard gamma probe detection device. ICG-assisted SLNB was performed using either the SPY elite system (Novadaq) or the Hamamatsu PDE-Neo probe (Mitaka USA). Then, we performed a financial analysis to compare the costs of each operating system, which were obtained from the manufacturer.

RESULTS

Our case series involved 14 patients who underwent SLNB in conjunction with ICG. The SPY elite system was used for 5 cases, and the Hamamatsu PDE-Neo probe for the remaining 9 patients (Figs. 1–3). All cases correctly identified the sentinel lymph node with no complications of the procedure. This was confirmed by concomitant Tc-99m injection. In certain cases, it was possible to visualize the course of the dye beneath the skin, one involving a digital adenocarcinoma of the thumb and 2 involving cutaneous melanomas of the thigh.

Costs of each operating system used at our institution are shown in Table 1. The cost of the SPY elite system totaled $275,275 with a recurring cost of $275 for the ICG and sterile drape. The cost of the Mitaka Hamamatsu PDE-Neo probe totaled $76,805 with a recurring cost of $105 for the ICG and sterile drape. Owing to the differences in size of the systems involved, the Mitaka Hamamatsu PDE-Neo probe (in the senior author's experience) offered greater ease of use in the operating room.

DISCUSSION

The early use of ICG was centered around calculating liver remnant volume after hepatectomy.[17] As the use of ICG has expanded, it has most notably been used in plas-

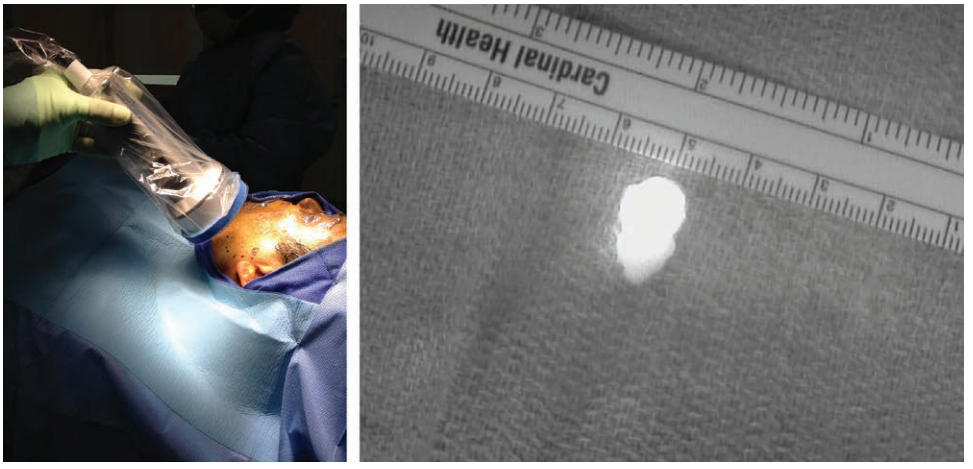

Fig. 2. Hand-held Hamamatsu PDE Neo Probe with ICG in a male patient with cervical melanoma. Positive sentinel lymph node removed and shown on the right.

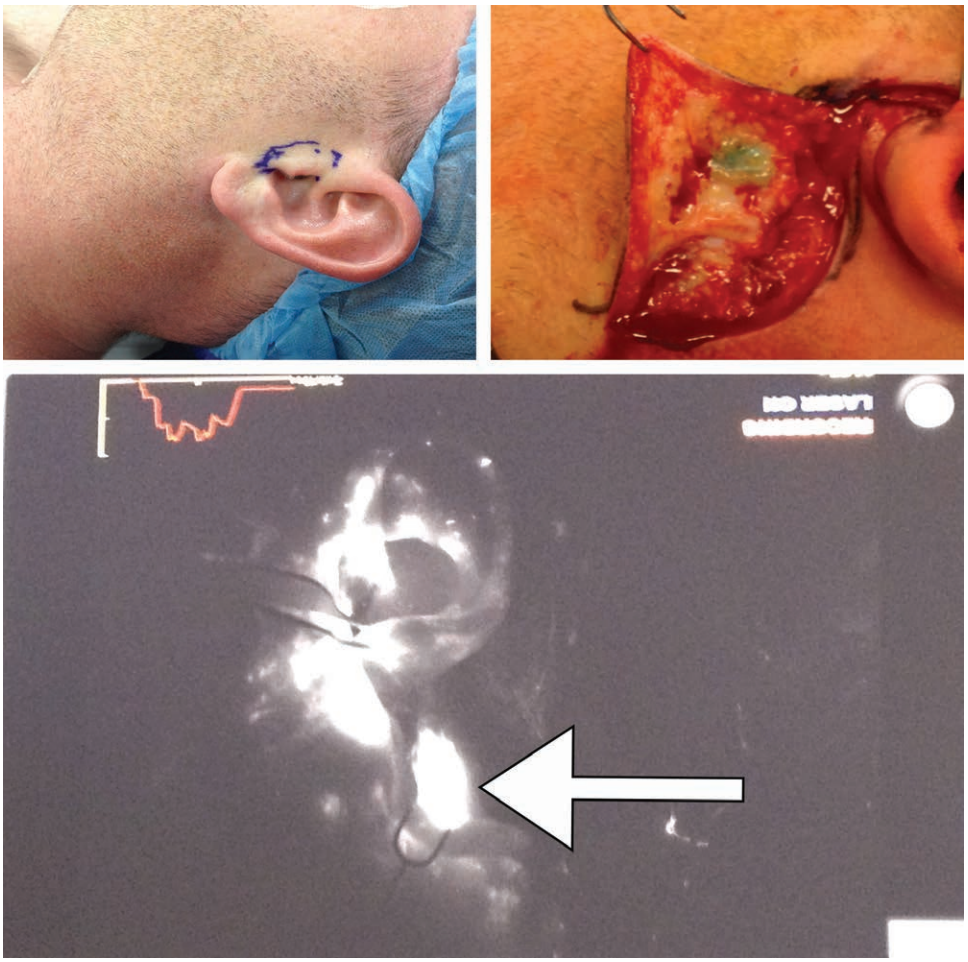

Fig. 3. SLNB for a 37-year old man with a preauricular melanoma. Intraoperative photograph demonstrating ICG staining of the sentinel lymph node and detection of positive node (arrow) using the SPY Elite system.

tic surgery as a tool to assess intraoperative flap perfusion and viability.[18,19] Multiple studies have outlined the positive outcomes associated with using ICG-assisted imaging for SLNB in breast cancer and the better outcomes of decreased surgical-site occurrences.[12,20–22]

The use of ICG for SLNB remains an underexplored but promising area in melanomas.[23] The application of this technique to patients with melanoma was first described in an article by Korn et al.[24] This retrospective review compared a total of 90 cutaneous melanoma patients in 2 cohorts who either received SLNB with the traditional blue dye and radioisotope or received SLNB with a radioisotope and the ICG Spy Elite system. Results demonstrated a statistically significant difference in SLN localization using either the ICG fluorescence or the radioisotope/handheld gamma probe method (98.0% and 97.8%, respectively) compared with the localization rate of 79.4% with the blue dye method. Furthermore, there was a trend toward a reduction in surgery length in the ICG cohort.[24] Other studies have confirmed the utility of ICG for SLNB in cutaneous melanoma and the identification of lymph nodes undetected by traditional radioisotope or blue dye techniques.[14–16]

Table 1. Comparison of Costs Obtained from Manufacturers for the 2 Systems Used in Conjunction with ICG for SLNB

Operating System	SPY Elite System	Mitaka Hamamatsu PDE Probe + Monitor
Cost of operating unit	$275,000	$76,700
Cost of ICG/drape	$275	$105
Total cost	$275,275	$76,805
Recurring cost	$275	$105

The cost of the operating unit refers to the initial investment required to purchase the device. The recurring costs include the cost of the ICG and the disposable drape, which are incurred with each case. The Mitaka Hamamatsu PDE Probe requires a smaller drape, given its smaller, hand-held probe, compared with the Spy Elite system, which accounts for the lower recurring cost per case.

Our study demonstrated the comparable effectiveness of using the SPY Elite or the Mitaka Hamamatsu PDE-Neo probe system with ICG in correctly identifying all sentinel lymph nodes in our cohort of patients. The lower cost and mobility offered by the Hamamatsu probe makes it the more advantageous system in SLNB. Despite the success of the ICG for SLNB, the limited data make it difficult to recommend its use in lieu of traditional, radioisotope-based lymphoscintigraphy; however, it does offer clinical benefits as an adjuvant technique to identify otherwise missed lymph nodes.

The SPY Elite system and the Hamamatsu PDE Neo probe are systems that can utilize ICG in the identification of sentinel lymph nodes. The SPY Elite system allows surgeons to control the camera and screen intraoperatively. Images can be saved and reviewed during the case; however, limitations to this technology include its large size as well as the need to purchase the ICG/Drape exclusively from Novadaq. Conversely, the Hamamatsu PDE is a small hand-held device with an additional CPU unit, which makes it freely moveable with handheld adjustments for color versus black/white options. Additions to the device can be bought independently. Therefore, given the comparable success rates between the 2 systems in identifying sentinel lymph nodes, the mobility and cost-effectiveness offered by the Hamamatsu PDE probe make it the more advantageous system.

There are inherent limitations with our study, given the small study size and the single surgeon experience. Further studies are necessary to more clearly delineate the role of ICG in SLNB for melanoma. We cannot recommend the use of ICG alone in SLNB, but believe that it can serve as a useful adjunct to existing methods such as vital blue dyes and radiotracers. The clinical utility of ICG stems from its usefulness as an intraoperative tool in the open identification of sentinel lymph nodes. Given the visibility of the fluorescent dye in 3 cases without the use of infrared light, the degree of skin thickness in individual cases can allow for additional uses of ICG. Furthermore, Tc-99m uptake in sentinel lymph nodes was observed to occur more rapidly than uptake of ICG, suggesting that the 2 modalities used in conjunction may increase the sensitivity of localizing sentinel lymph nodes in cutaneous melanoma.

CONCLUSIONS

ICG-assisted SLNB using the SPY Elite or the Hamamatsu PDE-Neo probe systems are safe and effective methods for the identification of sentinel lymph nodes. In our experience, the Hamamatsu PDE-Neo probe system is a more user friendly and cost-effective method compared with the SPY Elite system.

Deepak Narayan, MD, FRCS, MBBS
Section of Plastic and Reconstructive Surgery
Department of Surgery
Yale School of Medicine
330 Cedar Street Boardman Building
New Haven, CT 06520
E-mail: deepak.narayan@yale.edu

REFERENCES

1. Wong SL, Balch CM, Hurley P, et al.; American Society of Clinical Oncology; Society of Surgical Oncology. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. *J Clin Oncol.* 2012;30:2912–2918.
2. Han D, Yu D, Zhao X, et al. Sentinel node biopsy is indicated for thin melanomas ≥0.76 mm. *Ann Surg Oncol.* 2012;19:3335–3342.
3. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. *J Clin Oncol.* 2013;31:4387–4393.
4. Morton DL, Thompson JF, Cochran AJ, et al.; MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370:599–609.
5. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg.* 1992;127:392–399.
6. Gil-Moreno A, Perez-Benavente A. Images in clinical medicine. Anaphylaxis associated with blue dye. *N Engl J Med.* 2012;367:2026.
7. Iqbal FM, Basit A, Salem F, et al. Feeling blue, going green and finding other attractive alternatives: a case of biphasic anaphylaxis to patent blue and a literature review of alternative sentinel node localisation methods. *BMJ Case Rep.* 2015;2015.
8. Shah-Khan MG, Lovely J, Degnim AC. Safety of methylene blue dye for lymphatic mapping in patients taking selective serotonin reuptake inhibitors. *Am J Surg.* 2012;204:798–799.
9. Bézu C, Coutant C, Salengro A, et al. Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surg Oncol.* 2011;20:e55–e59.
10. Kinnier CV, Paruch JL, Dahlke AR, et al. Adjusted hospital sentinel lymph node positivity rates in melanoma: a novel potential measure of quality. *Ann Surg.* 2016;263:392–398.
11. Polom K, Murawa D, Rho YS, et al. Current trends and emerging future of indocyanine green usage in surgery and oncology: a literature review. *Cancer.* 2011;117:4812–4822.
12. Benson J. Indocyanine green fluorescence for sentinel lymph node detection in early breast cancer. *Ann Surg Oncol.* 2016;23:6–8.
13. Liu DZ, Mathes DW, Zenn MR, et al. The application of indocyanine green fluorescence angiography in plastic surgery. *J Reconstr Microsurg.* 2011;27:355–364.
14. Cloyd JM, Wapnir IL, Read BM, et al. Indocyanine green and fluorescence lymphangiography for sentinel lymph node identification in cutaneous melanoma. *J Surg Oncol.* 2014;110:888–892.
15. Fujisawa Y, Nakamura Y, Kawachi Y, et al. A custom-made, low-cost intraoperative fluorescence navigation system with indocyanine green for sentinel lymph node biopsy in skin cancer. *Dermatology.* 2011;222:261–268.
16. Fujisawa Y, Nakamura Y, Kawachi Y, et al. Indocyanine green fluorescence-navigated sentinel node biopsy showed higher sensitivity than the radioisotope or blue dye method, which may help to reduce false-negative cases in skin cancer. *J Surg Oncol.* 2012;106:41–45.
17. Okamoto E, Kyo A, Yamanaka N, et al. Prediction of the safe limits of hepatectomy by combined volumetric and functional measurements in patients with impaired hepatic function. *Surgery.* 1984;95:586–592.
18. Wormer BA, Huntington CR, Ross SW, et al. A prospective randomized double-blinded controlled trial evaluating indocyanine green fluorescence angiography on reducing wound complications in complex abdominal wall reconstruction. *J Surg Res.* 2016;202:461–472.
19. Bauermeister A ZA, Newman MI. Laser-assisted indocyanine green fluorescent dye angiography in breast reconstruction. *Breast Reconstruction.* Basel, Switzerland: Springer International Publishing; 2016:1175–1184.
20. Park DJ, Kim HH, Park YS, et al. Simultaneous indocyanine green and (99m)Tc-antimony sulfur colloid-guided laparoscopic sentinel basin dissection for gastric cancer. *Ann Surg Oncol.* 2011;18:160–165.
21. Oh Y, Lee YS, Quan YH, et al. Thoracoscopic color and fluorescence imaging system for sentinel lymph node mapping in porcine lung using indocyanine green-neomannosyl human serum albumin: intraoperative image-guided sentinel nodes navigation. *Ann Surg Oncol.* 2014;21:1182–1188.
22. Nagata J, Fukunaga Y, Akiyoshi T, et al. Colonic marking with near-infrared, light-emitting, diode-activated indocyanine green for laparoscopic colorectal surgery. *Dis Colon Rectum.* 2016;59:e14–e18.
23. Niebling MG, Pleijhuis RG, Bastiaannet E, et al. A systematic review and meta-analyses of sentinel lymph node identification in breast cancer and melanoma, a plea for tracer mapping. *Eur J Surg Oncol.* 2016;42:466–473.
24. Korn JM, Tellez-Diaz A, Bartz-Kurycki M, et al. Indocyanine green SPY elite-assisted sentinel lymph node biopsy in cutaneous melanoma. *Plast Reconstr Surg.* 2014;133:914–922.