Am J Otolaryngol 39 (2018) 485–488

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Sentinel lymph node biopsy in cutaneous melanoma of the head and neck using the indocyanine green SPY *Elite* system

Andrew M. Vahabzadeh-Hagh*, Keith E. Blackwell, Elliot Abemayor, Maie A. St. John

Department of Head and Neck Surgery, UCLA David Geffen School of Medicine, 10833 Le Conte Ave, 62-132, Los Angeles, CA 90095, USA

ARTICLE INFO

Keywords:
Cutaneous melanoma
Sentinel lymph node biopsy
Indocyanine green
SPY Elite
Head and neck
Vital dye

ABSTRACT

Purpose: Lymph node status is the single most important prognostic factor for patients with early-stage cutaneous melanoma. Sentinel lymph node biopsy (SLNB) has become the standard of care for intermediate depth melanomas. Modern SLNB implementation includes technetium-99 lymphoscintigraphy combined with local administration of a vital blue dye. However, sentinel lymph nodes may fail to localize in some cases and false-negative rates range from 0 to 34%. Here we demonstrate the feasibility of a new sentinel lymph node biopsy technique using indocyanine green (ICG) and the SPY *Elite* near-infrared imaging system.

Materials and methods: Cases of primary cutaneous melanoma of the head and neck without locoregional metastasis, underwent SLNB at a single quaternary care institution between May 2016 and June 2017. Intraoperatively, 0.25 mL of ICG was injected intradermal in 4 quadrants around the primary lesion. 10–15 minute circulation time was permitted. SPY *Elite* identified the sentinel lymph node within the nodal basin marked by lymphoscintigraphy. Target first echelon lymph nodes were confirmed with a gamma probe and ICG fluorescence.

Results: 14 patients were included with T1a to T4b cutaneous melanomas. Success rates for sentinel lymph node identification using lymphoscintigraphy and the SPY *Elite* system were both 86%. Zero false negatives occurred. Median length of follow-up was 323 days.

Conclusions: In this pilot study, Indocyanine green near-infrared fluorescence demonstrates a safe, and facile method of sentinel lymph node biopsy for cutaneous melanoma of the head and neck compared with lymphoscintigraphy and vital blue dyes.

1. Introduction

Lymph node status is the most important prognostic factor for patients with early-stage cutaneous melanoma. 15–25% of patients without clinical lymphadenopathy will harbor microscopic nodal metastases [1]. Sentinel lymph node biopsy (SLNB), as established in the 2012 clinical practice guidelines, has become the standard of care for intermediate depth (1–4 mm) melanomas and thin melanomas with high-risk features [2]. The phase 3 clinical trial for SLNB for regional melanoma staging demonstrated prolonged disease-free survival for all patients, with prolonged distant disease-free survival and melanoma-specific survival for patients with nodal disease and intermediate-thickness primary melanomas [3]. Modern SLNB implementation includes technetium-99 lymphoscintigraphy combined with local administration of a blue dye for pre-operative and intra-operative localization respectively. However, sentinel lymph nodes may fail to localize in some cases either as a consequence of erroneous lymphoscintigraphy, its interpretation, or a misguided operation [4]. False-negatives, defined as a regional nodal recurrence in a previously biopsied negative sentinel lymph nodal basin, may occur in 0–34% of cases, 12.5% on average [1,5]. Here we describe our experience with a new sentinel lymph node biopsy technique using the fluorescein dye indocyanine green (ICG) and the SPY *Elite* near-infrared imaging system.

Although sentinel lymph node biopsies are less invasive than selective nodal dissections, they are not without risk. Cigna et al. reviewed 437 cases of lymph node biopsies from nodal basins of the head and neck, groin, axilla and limbs. They found a complication rate of 4.26% with complications ranging from hematoma, seroma, lymphedema, to wound infection [6]. This rivals the reported complication rates for selective and even radical neck dissections. Dedivitis reviewed 708 cases including selective and radical neck dissections and found the most common injuries were neuronal, including the marginal mandibular nerve and spinal accessory nerve which were most often sacrificed secondary to tumor involvement; even this only occurred

* Corresponding author at: 10833 Le Conte Ave, 62-132, Los Angeles, CA 90095, USA.
E-mail addresses: AVahabzadehhagh@mednet.ucla.edu (A.M. Vahabzadeh-Hagh), kblackwell@mednet.ucla.edu (K.E. Blackwell), eabemayor@mednet.ucla.edu (E. Abemayor), mstjohn@mednet.ucla.edu (M.A. St. John).

https://doi.org/10.1016/j.amjoto.2018.05.006
Received 10 May 2018

5.1–5.5% of the time [7]. Goguen et al. reported a frequency of major wound complications following neck dissections in patients who had received chemoradiotherapy at 2.6% [8]. As sentinel lymph node biopsies become more widespread and the standard of care for many disease processes, our efforts must focus on ways to improve the efficacy and safety of these techniques. Tools that can make sentinel lymph node dissections more targeted and precise are welcomed.

Indocyanine green (ICG) is a small substance molecule tricarbocyanine dye with many advantages when compared to the traditional vital dyes (patent blue, isosulfan blue, methylene blue) used for SLNB. ICG is a near-infrared fluorophore approved by the US FDA for human application [9,10]. ICG associates with albumin making it ideal for evaluating both vascular and lymphatic systems. Near-infrared imaging has high penetration into living tissues and ICG can be detected transcutaneous at depths of 0.5 to 1.0 cm. ICG involves no radiation and can be detected for up to 10 h after its administration. ICG also maintains a low risk of anaphylactoid reaction (0.05%) in contrast to the measureable risk of anaphylaxis with other vital dyes such as patent blue (0.3%) and isosulfan blue (1.1%). Furthermore, ICG may provide easier localization and dissection of sentinel nodes as it does not stain or obscure tissue characteristics or risk tattooing unlike vital blue dues.

The SPY *Elite* near-infrared system (LifeCell Corp, Branchburg, NJ) has been used in plastic surgery to assess tissue perfusion following intravascular indocyanine green injection. More recently ICG and the SPY *Elite* system have been adapted for sentinel node localization and biopsy. Korn et al. compared ICG to vital dyes (isosulfan blue or methylene blue) and the radioisotopes (technetium-99) of lymphoscintigraphy. They provided a retrospective review of 90 cases of cutaneous melanoma, the majority of which were on the extremities or trunk. They demonstrated the feasibility of the ICG SPY system for this application and showed improved localization rates and a higher sentinel lymph node yield with ICG [5]. Here we examine the feasibility of the ICG SPY system for SLNB in a cohort of patients with intermediate thickness stage IA to IIC cutaneous melanoma exclusively of the head and neck.

2. Materials and methods

14 cases of primary cutaneous melanoma of the head and neck without locoregional metastasis (N0), underwent SLNB, as per the National Comprehensive Cancer Network criterion, at a single quaternary care institution between May 2016 and June 2017; individual cohort study. Demographic data, tumor stage, location, ulceration, number of mitoses, SLNB status, follow-up and recurrence were documented. Melanoma staging was assigned based on the eighth edition of the American Joint Committee on Cancer staging system [11]. On the morning of surgery, the patients presented for lymphoscintigraphy for sentinel lymph node localization. This was performed using intradermal injections of filtered technetium-99m sulfur colloid totaling 1 mL around the lesion site. 15 min later, a hand-held gamma probe was then used to mark the skin overlying the sentinel lymph node site. Intraoperatively the lesions were all injected with stock ICG solution. This was performed as intradermal injections of 0.25 mL in 4 quadrants around the primary lesion providing a total injectate of 1.0 mL. 36% of cases were also administered a vital blue dye for comparison. Vital blue dye (Isosulfan Blue) was also administered intradermal in aliquots totaling 1.0–5.0 mL. After injection, 10–15 min were allowed to pass, during which time wide local excision of the primary lesion with margins was performed. Incision placement was determined by gamma probe localization. An incision was then made over the sentinel node. The SPY Elite was then used to visualize the sentinel lymph node within this nodal basin. Target first echelon lymph nodes were confirmed with a gamma probe and ICG fluorescence and were subsequently removed. In cases of vital blue dye administration, this was compared to the localization obtained with the radioisotope and/or ICG. Ability to localize the sentinel lymph node, number of sentinel lymph nodes identified, and the sentinel lymph node histopathology were documented. Successful localization was defined as the identification of at least one sentinel lymph node. Localization rates for each method were calculated as the ratio of localization to nonlocalization. False-negative SLNB included regional recurrences within a lymph nodal basin that was previously deemed negative by SLNB. Length of follow-up was defined from the surgical date to the date of last clinical follow-up.

All cases were performed by one of three senior head and neck cancer surgeons. All cases were preceded by lymphoscintigraphy and intraoperative use of radioisotope/handheld gamma probe for localization. All cases used the ICG SPY *Elite* system while 5 cases also utilized vital blue dye for comparison. The ICG fluorescence infrared camera SPY *Elite* System was used for real-time intraoperative fluorescence imaging. Localized sentinel lymph nodes were removed and then re-imaged on the back table to confirm ICG fluorescence.

Table 1
Patient and tumor characteristics. mm, millimeters; No., number; y, years

Characteristic		No.	(%)
Number of patients		14	100
Age, y	< 60	2	14
[55, 86]	60 +	12	86
Sex	Male	13	93
	Female	1	7
Anatomic location	Scalp	5	36
	Forehead	1	7
	Midface	4	29
	Ear	1	7
	Nose	1	7
	Lower face	1	7
	Neck	1	7
Breslow thickness (mm)	< /=1.00	3	21
	1.01–2.00	4	29
	2.01–4.00	3	21
	> 4.00	4	29
Ulceration	Present	5	36
	Absent	9	64
Mitosis/mmˆ2	< 1	3	21
	1 +	11	79
Clinical stage	T1A	1	7
	T1B	2	14
	T2A	3	21
	T2B	1	7
	T3A	2	14
	T3B	1	7
	T4A	1	7
	T4B	3	21

3. Results

14 consecutive patients with newly diagnosed cutaneous melanoma of the head and neck without radiologic evidence of metastasis were included in this study. Table 1 details patient and tumor attributes. The majority of patients were male and over the age of 60 years old. The majority of primary cutaneous melanoma lesions were on the scalp and midface. Breslow thickness was near evenly distributed while the majority of lesions were non-ulcerative and had 1 or more mitosis/mm^2. Clinical T stage was widespread from T1A to T4B disease.

Fig. 1 demonstrates the intraoperative photos and highlights the utility of fluorescence imaging to confirm sentinel lymph nodes especially in this case where the sentinel nodes were merely a couple millimeters in diameter. When performing a sentinel lymph node biopsy, new methods must be able to localize sentinel lymph nodes safely, efficiently, and reliably while maximizing the number of sentinel lymph nodes retrieved for such an operation. Table 2 summarizes the lymph node localization rate for each localizing method. The localization rate for lymphoscintigraphy/gamma probe and the ICG SPY system were both 86% while the localization rate for isosulfan blue was 60%. Table 3 details the mean and median number of sentinel lymph nodes

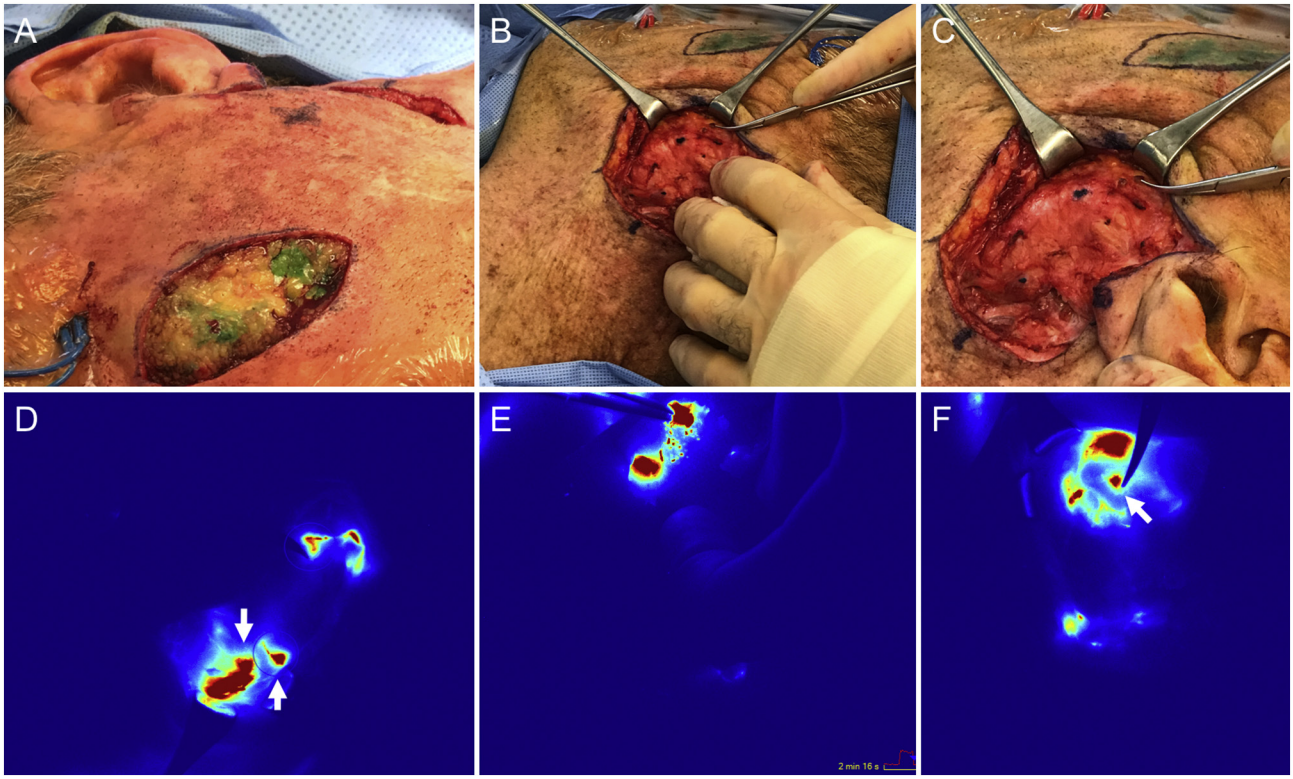

Fig. 1. Intraoperative photographs and fluorescence imaging. A. Left facial melanoma wide local excision defect. B. Modified Blair incision with subcutaneous dissection over sentinel nodes identified by pre-operative lymphoscintigraphy. C. Zoomed image of periparotid sentinel nodes seen in the anterosuperior region of the dissection and pointed out by the tip of the clamp. 2 nodes, each only a couple millimeters in diameter, were seen to be a pale green in color 15 min after intradermal ICG administration. D. SPY *Elite* fluorescence imaging showing the primary lesion (upper right) and the anterosuperior periparotid nodes, denoted by arrows. E. 2 excised ICG positive periparotid nodes. F. Parotid tail ICG positive sentinel node (arrow). ICG, Indocyanine green. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Sentinel lymph node localization rates. ICG, indocyanine green; No., number.

SLNB method	No.	(%)
Lymphoscintigraphy/gamma probe		
No localization	2	14
Localization	12	86
Isosulfan blue		
No localization	2	40
Localization	3	60
ICG SPY Elite		
No localization	2	14
Localization	12	86

Table 3
Mean and median sentinel lymph nodes identified per method. One way ANOVA failed to demonstrate a significant intergroup difference (p 0.34), while post-hoc Least Significant Difference testing showed an insignificant difference between isosulfan blue and ICG methods (p 0.15). ICG, indocyanine green; SD, standard deviation.

Gamma probe		Isosulfan blue		ICG SPY	
Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
0.93 ± 0.47	1 (0–2)	0.60 ± 0.55	1 (0–1)	1.07 ± 0.73	1 (0–3)

retrieved per localization method. One-way ANOVA failed to demonstrate a significant intergroup difference while post hoc Least Significance Difference (LSD) testing showed a trend toward differences in the mean number of sentinel nodes retrieved by isosulfan blue versus ICG (p 0.147). There were no false negatives for either localization method. The average length of follow-up was 281 days with a median follow-up of 323 days from the date of surgery and SLNB. 3 patients developed local recurrence while 1 patient developed lung metastases.

4. Discussion

Here we demonstrate the feasibility of the ICG SPY *Elite* system for the performance of SLNB for intermediate depth cutaneous melanomas of the head and neck. We show that the clarity and confidence that the SPY *Elite* fluorescence imaging system provides intraoperatively is remarkable (Fig. 1) with many advantages over the traditional vital blue dyes. The ICG SPY system achieves a localization rate equal to that of lymphoscintigraphy and the gamma 7probe gold standard (86%) and better than isosulfan blue vital dyes (60%). Additionally, the ICG system identifies an average of 1.07 ± 0.73 sentinel lymph nodes versus 0.60 ± 0.55 sentinel lymph nodes using the vital blue dye. These results are in keeping with other reports on ICG for SLNB in cutaneous melanoma across other subsites. van der Vorst et al. found that ICG was successful in 93% of patients (all comers) and 100% of patients who had successfully identified SLNs via lymphoscintigraphy. Of 30 SLNs identified, 100% had radiotracer, 100% had ICG SPY fluorescence, and only 73% were identified by patent blue dye [12].

Fugisawa et al. reported that the use of ICG for SLNB increased the identification of occult sentinel lymph nodes in 24% of their cases while increasing the number of SLNs detected per cases by 20% [13]. In this prospective cohort study, we found 2 occult sentinel lymph nodes that did not test positive for technetium-99 m activity, but were identified exclusively with the ICG SPY system. Although these sentinel lymph nodes were negative for metastatic disease, the use of ICG SPY

increased our sentinel lymph node yield in these cases. However, when comparing the average number of sentinel lymph nodes identified per method, there was no significant difference between the gamma probe, 0.93 ± 0.47, ICG SPY, 1.07 ± 0.73, or isosulfan blue, 0.60 ± 0.55.

The lymphatics of the head and neck are complex and pre-operative planar lymphoscintigraphy does not provide the finest spatial resolution. Room for improvement is certainly present. While some institutions have adopted the use of single-photon emission computed tomography/computed tomography (SPECT/CT) scans for better pre-operative spatial localization, this technique is more time consuming, increases radiation exposure and is costlier [14,15]. Additionally, a novel radiopharmaceutical compound, known as gamma-Tilmanocept, or Lymphoseek, has been developed for more selective sentinel lymph node mapping thank the traditional technetium-99 m sulfur colloid. Lymphoseek, now FDA approved, is a synthetic nanomolecule containing multiple mannose units which are recognized by myeloid cells within the lymphatics. Phase 2 and 3 trials demonstrated safety and efficacy but its adoption in head and neck surgery has lagged [16–19].

The ICG SPY *Elite* system allows for the ability to more clearly identify lymphatics intraoperatively, which may help streamline surgeries, reduce the extent of dissection and reduce operative times. In Fig. 1 we show a patient with a left cheek melanoma with lymphoscintigraphy localizing to the left parotid region. The ambiguity and small size of the lymphatics in this region and difficulty differentiating it from the adjacent subdermal fat and parotid gland tissue could have significantly prolonged the operative time or might have influenced us to perform a more substantial dissection to include a superficial parotidectomy. With the use of the ICG SPY system, the sentinel nodes were clearly identified expeditiously without disrupting the substance of the parotid. Although we did not specifically evaluate total operative time, reports suggest, and our experience corroborates, that ICG may allow for more rapid identification of lymphatics and sentinel lymph nodes and therefore shorter operative times [5,20].

Lastly, an exciting feature of near-infrared fluorescence imaging of ICG is its ability to be seen transcutaneous. This suggests that one might be able to use the near-infrared camera system to scan the lymphatic basin transcutaneous before incision to better design and target sentinel lymph node approaches and dissection. Namikawa et al. found that ICG could be used to transcutaneously identify the sentinel nodes prior to skin incision in 63.4% of 86 patients who underwent SLNB for cutaneous melanoma. The pre-operative detection rate was as good as 86% for SLNB of the lower extremities and 66.7% in the head and neck [5,21]. With transcutaneous pre-operative identification using ICG and a near-infrared camera, one can envision someday not needing pre-operative lymphoscintigraphy and the exposure to radioisotopes.

5. Conclusion

Indocyanine green near-infrared fluorescence provides a feasible, safe, and perhaps improved method of sentinel lymph node biopsy for cutaneous melanoma of the head and neck compared with the traditional vital blue dyes. Here we demonstrate that the ICG SPY *Elite* system is at least as good as the gold standard lymphoscintigraphy and gamma probe sentinel node localization. In addition to improved localization rates when compared to isosulfan blue, ICG may provide other benefits in the form of pre-operative localization, better anatomic preservation, more focused and shorter dissections and greater sentinel node yields. This study is the first to evaluate ICG for SLNB exclusively for head and neck cutaneous melanomas. Future studies with greater enrollment and randomization are warranted.

Acknowledgments

All authors had full access to all of the data included in this study and take responsibility for the integrity and accuracy of the data.

Conflict of interest

None. The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] Valsecchi ME, Silbermins D, de Rosa N, Wong SL, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: a meta-analysis. J Clin Oncol Off J Am Soc Clin Oncol 2011;29(11):1479–87.
[2] Wong SL, Balch CM, Hurley P, Agarwala SS, Akhurst TJ, Cochran A, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. J Clin Oncol Off J Am Soc Clin Oncol 2012;30(23):2912–8.
[3] Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370(7):599–609.
[4] Karim RZ, Scolyer RA, Li W, Yee VS, McKinnon JG, Li LX, et al. False negative sentinel lymph node biopsies in melanoma may result from deficiencies in nuclear medicine, surgery, or pathology. Ann Surg 2008;247(6):1003–10.
[5] Korn JM, Tellez-Diaz A, Bartz-Kurycki M, Gastman B. Indocyanine green SPY elite-assisted sentinel lymph node biopsy in cutaneous melanoma. Plast Reconstr Surg 2014;133(4):914–22.
[6] Cigna E, Gradilone A, Ribuffo D, Gazzaniga P, Fino P, Sorvillo V, et al. Morbidity of selective lymph node biopsy for melanoma: meta-analysis of complications. Tumori 2012;98(1):94–8.
[7] Dedivitis RA, Guimaraes AV, Pfuetzenreiter Jr EG, Castro MA. Neck dissection complications. Braz J Otorhinolaryngol 2011;77(1):65–9.
[8] Goguen LA, Chapuy CI, Li Y, Zhao SD, Annino DJ. Neck dissection after chemoradiotherapy: timing and complications. Arch Otolaryngol Head Neck Surg 2010;136(11):1071–7.
[9] Gilmore DM, Khullar OV, Gioux S, Stockdale A, Frangioni JV, Colson YL, et al. Effective low-dose escalation of indocyanine green for near-infrared fluorescent sentinel lymph node mapping in melanoma. Ann Surg Oncol 2013;20(7):2357–63.
[10] Gioux S, Choi HS, Frangioni JV. Image-guided surgery using invisible near-infrared light: fundamentals of clinical translation. Mol Imaging 2010;9(5):237–55.
[11] Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(6):472–92.
[12] van der Vorst JR, Schaafsma BE, Verbeek FP, Swijnenburg RJ, Hutteman M, Liefers GJ, et al. Dose optimization for near-infrared fluorescence sentinel lymph node mapping in patients with melanoma. Br J Dermatol 2013;168(1):93–8.
[13] Fujisawa Y, Nakamura Y, Kawachi Y, Otsuka F. 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(1):41–5.
[14] Martinez Castillo R, Fernandez Lopez R, Acevedo Banez I, Alvarez Perez RM, Garcia Solis D, Vazquez Albertino R, et al. Utility of single photon emission computed tomography-computed tomography in selective sentinel lymph node biopsy in patients with melanoma. Revista espanola de medicina nuclear e imagen molecular 2014;33(3):129–35.
[15] Trinh BB, Chapman BC, Gleisner A, Kwak JJ, Morgan R, McCarter MD, et al. SPECT/CT adds distinct lymph node basins and influences radiologic findings and surgical approach for sentinel lymph node biopsy in head and neck melanoma. Ann Surg Oncol 2018;25(6):1716–22.
[16] Azad AK, Rajaram MV, Metz WL, Cope FO, Blue MS, Vera DR, et al. Gamma-tilmanocept, a new radiopharmaceutical tracer for cancer sentinel lymph nodes, binds to the mannose receptor (CD206). J Immunol 2015;195(5):2019–29.
[17] Leong SP, Kim J, Ross M, Faries M, Scoggins CR, Metz WL, et al. A phase 2 study of (99m)Tc-tilmanocept in the detection of sentinel lymph nodes in melanoma and breast cancer. Ann Surg Oncol 2011;18(4):961–9.
[18] Sondak VK, King DW, Zager JS, Schneebaum S, Kim J, Leong SP, et al. Combined analysis of phase III trials evaluating [(9)(9)mTc]tilmanocept and vital blue dye for identification of sentinel lymph nodes in clinically node-negative cutaneous melanoma. Ann Surg Oncol 2013;20(2):680–8.
[19] Wallace AM, Hoh CK, Ellner SJ, Darrah DD, Schulteis G, Vera DR. Lymphoseek: a molecular imaging agent for melanoma sentinel lymph node mapping. Ann Surg Oncol 2007;14(2):913–21.
[20] Fujiwara M, Mizukami T, Suzuki A, Fukamizu H. Sentinel lymph node detection in skin cancer patients using real-time fluorescence navigation with indocyanine green: preliminary experience. J Plast Reconstr Aesthet Surg 2009;62(10):e373–8.
[21] Namikawa K, Tsutsumida A, Tanaka R, Kato J, Yamazaki N. Limitation of indocyanine green fluorescence in identifying sentinel lymph node prior to skin incision in cutaneous melanoma. Int J Clin Oncol 2014;19(1):198–203.