

Coaxial projective imaging for sentinel lymph node mapping in melanoma



Ru Zhang, PhD,^{a,b} Ruijie Yang, BS,^{a,b} Zhongliang Lang, MD,^c Bingxuan Wu, BS,^{a,b} Pengfei Shao, PhD,^{a,b} Peng Liu, PhD,^{a,b} Xiaohong Zhong, MD,^c Carlo M. Contreras, MD,^d and Ronald X. Xu, PhD^{a,e}
Hefei, China and Columbus, Ohio

Key words: augmented reality; coaxial projection imaging system; indocyanine green; melanoma; sentinel lymph node.

INTRODUCTION

Sentinel lymph node biopsy (SLNB) is recommended to identify micrometastasis for stage T1b or greater primary cutaneous melanoma, which impacts prognosis and adjuvant therapy recommendations.¹ SLNB requires preoperative or intraoperative lymphatic mapping. The most common methods are vital blue dyes, gamma probe, ^{99m}Tc, and indocyanine green (ICG) fluorescence imaging. However, vital blue dyes are unsuitable as the sole mapping agent because they are not evident until lymph nodes are surgically exposed.² Gamma probe signaling assists in locating the general region of sentinel lymph nodes (SLN), which is not as accurate as ICG fluorescence imaging.³ Meanwhile, ^{99m}Tc raises the radiation hazard and requires substantial medical infrastructure for material receipt, storage, administration, and disposal, imposing substantial barriers. Recently, ICG fluorescence imaging has emerged as an alternative lymphatic mapping method for SLNB.⁴ It is able to achieve a SLN localization rate of 98%, similar to that of a radioisotope/handheld gamma probe (97.8%) and superior to that of the blue dye method (79.4%).⁵ ICG is the only Food and Drug Administration-approved near-infrared fluorescent agent for human use. After intradermal injection, ICG binds easily to albumin, flows via lymph circulation to lymph nodes, and shows up when illuminated by excitation light.⁶ However, the current technology requires surgeons

Abbreviations used:

AR:	augmented reality
CPI:	coaxial projection imaging
ICG:	indocyanine green
SLN:	sentinel lymph node
SLNB:	sentinel lymph node biopsy
^{99m} Tc:	^{99m} -technetium

to shift their vision from the surgical area to the monitor, which leads to distraction and reduces the accuracy of anatomical identification. To overcome these barriers, we have previously proposed an augmented reality (AR) coaxial projection imaging (CPI) technique, which allows surgeons to directly observe the surgical area with the naked eye.^{7,8} This report evaluates the clinical feasibility of AR-CPI in melanoma SLNB.

MATERIALS AND METHODS

The AR-CPI system

The AR-CPI system (NIRF-2H, Sino-medic) integrates a projector chip (DMD, Hobby) and a camera imaging element (3240N, Thorlabs) into a coaxial optical path in order to realize simultaneous fluorescence imaging and in situ projection (Fig 1, A). Intraoperatively, the camera acquires invisible fluorescence signals from ICG after the 780-nm excitation light was emitted, and the projector projects the near-infrared ICG signal back onto the tissue

From the Department of Precision Machinery and Precision Instrumentation, University of Science and Technology of China (USTC)^a; the Key Laboratory of Precision Scientific Instrumentation of Anhui Higher Education Institutes, Hefei^b; the Department of Plastic Surgery, The First Affiliated Hospital of USTC, Hefei^c; the Department of Surgery, The Ohio State University Wexner Medical Center, Columbus^d; and the Department of Biomedical Engineering, The Ohio State University.^e

Drs Zhang and Yang contributed equally to this article.

Funding sources: None.

IRB approval status: Approved by the Medical Research Ethics Committee of the first affiliated hospital of USTC (Anhui Provincial Hospital).

Correspondence to: Xiaohong Zhong, MD, 17 Lujiang Road, Luyang District, Hefei, Anhui, China. E-mail: successfuldoctor@sina.com; Carlo M. Contreras, MD, 460 W. 10th Avenue, Columbus, OH. E-mail: Carlo.Contreras@osumc.edu; Ronald X. Xu, PhD, 140 W. 19th Avenue, Columbus, OH. E-mail: xu.202@osu.edu.

JAAD Case Reports 2021;15:46-50.

2352-5126

© 2021 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2021.06.023>



Fig 1. The augmented reality coaxial projection imaging (AR-CPI) system (NIRF-2H, Sino-med, Jiangsu, China). **A**, The head of AR-CPI system contains a laser element, a camera imaging element and a projector element. Fluorescence emission from indocyanine green (ICG) is stimulated by the laser element, acquired by the camera imaging element, and projected orthotopically to the field of operation by the projector element. An optional monitor is used to adjust system parameters and display the ICG fluorescence images, in comparison with the projected images. **B**, The AR-CPI system provides intraoperative visual guidance for the surgeons to identify and resect lymph nodes in the field of operation. **C**, Without projection imaging, the surgeons have to divert their views to a stand-alone monitor for fluorescence imaging display.

within the operative field so that surgeons can visualize ICG fluorescence directly (Fig 1, B) without diverting their view to a monitor (Fig 1, C). During the operation, the frame rate was set to 1.5 frames per second, the detector acquisition time was 0.66 s, and the fixed focus distance was 50 cm. The spatial resolution decreased, as fluorescence intensity decreased. At the working distance of about 50 cm, the spatial resolution of projection was 0.4 mm when observing exposed lymph nodes, and 0.57 mm when observing lymph nodes under the skin.

CASE DESCRIPTION

A 47-year-old man presented with an enlarging right-heel pigmented skin nodule (Fig 2, A). Physical examination revealed no additional abnormalities. Ultrasound confirmed no pathologic regional lymphadenopathy. On suspicion of melanoma, we recommended wide local excision with 2-cm gross margins, and ICG SLNB, as the treating medical facility does not have nuclear medicine capacity. The operation commenced with excisional biopsy of

the pigmented lesion to confirm the melanoma diagnosis, since a preoperative biopsy was not available. An excisional biopsy with 2-mm gross margins was performed without mobilization of the surrounding skin or subcutaneous tissue. Frozen section confirmed melanoma. We obtained informed consent from the patient before performing SLNB with ICG.

0.5 mg/mL ICG (Yichuang) was injected intradermally in 4 quadrants surrounding the excisional biopsy site for a total of 0.8 mL (Fig 2, B). Hematoxylin-eosin and immunohistochemistry staining (Zhongshan) were performed on formalin-fixed paraffin-embedded tumor tissue sections.

RESULTS

After turning off the shadowless operating lamp, the AR-CPI system was used to identify the SLNs. The AR-CPI images of lymphatic vessels up to 1 cm deep under the skin were observed immediately following ICG injection and tracked from the right-heel injection site to the medial malleolus and calf, and then to

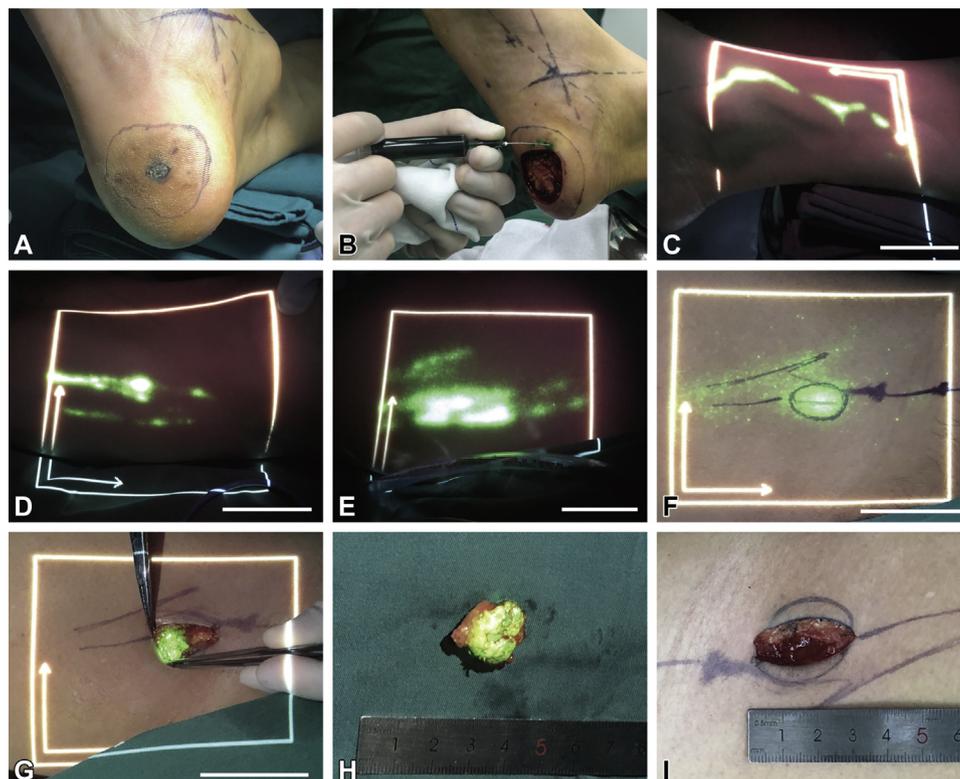


Fig 2. Sentinel lymph node (SLN) detection and resection surgery utilizing indocyanine green (ICG)-based lymphatic mapping. **A**, The pigmented lesion prior to incision. **B**, ICG was injected intradermally in 4 quadrants of the skin around the tumor after excisional biopsy with 2-mm circumferential margins. **C-E**, 1 min after ICG injection, the augmented reality coaxial projection imaging (AR-CPI) system projected a fluorescence images of the lymph drainage pathways from the right medial malleolus (**C**) to the right medial calf (**D**), and then to the right medial thigh (**E**). **F**, Eventually, the AR-CPI system projected a fluorescence image of the SLN onto the skin surface of the patient's right inguinal basin, which allowed the surgeon to mark the location of the SLN and lymphatic channel on the patient's skin surface. Two lines on the left marked the boundary of the afferent lymphatic channel; the circle in the middle marked the presumed location of the SLN; the line with triangles on the right marked the blood vessel detected with the handheld intraoperative Doppler probe. **G**, The AR-CPI system projected a fluorescence image of the exposed in situ SLN. **H**, The AR-CPI system projected a fluorescence image of the ex-vivo SLN with a diameter of 20 mm. **I**, The right inguinal SLN incision length was 30 mm. Scale bars in **C-G** represent 5 cm.

the right medial thigh (Fig 2, C-E). Five minutes after ICG injection, the projected images showed abrupt termination of lymphatic drainage in the inguinal basin, noted by focal subcutaneous fluorescence (Fig 2, F and Video 1, available on www.jaad.org). The AR-CPI projection on the inguinal skin showed the fluorescing afferent lymphatic channel and the SLN, which were marked with ink. A vein adjacent to SLN was detected by Doppler ultrasound, and marked prior to incision (Fig 2, F). Based on the real-time AR-CPI imagery, the skin incision location was determined, and the detected SLN was resected (Fig 2, G). After resection, ICG fluorescence emission of the ex-vivo SLN was further verified (Fig 2, H). The AR-CPI

system provided precise SLN localization by facilitating a small skin incision (incision 30 mm; SLN 20 mm) (Fig 2, I). A frozen section of the SLN confirmed nodal tissue without melanoma micrometastasis (Fig 3). Subsequently, we completed the 2-cm wide local excision of the primary melanoma site and repaired it with a full-thickness skin graft.

Final histologic evaluation of the primary tumor resection specimens demonstrated invasive melanoma with a maximal depth of 2 mm, Clark II level, mild histologic ulceration, and 30% mitotic index. In the superficial dermis and the tumor cell interstitium, there was a large amount of lymphocyte infiltration with no lymphovascular or perineural invasion.

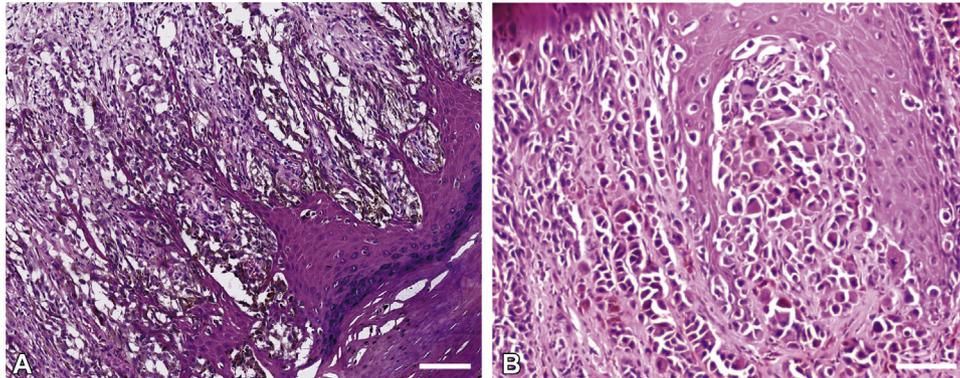


Fig 3. Resected tissue and SLN sample staining. **A**, Resected tissue sample stained with soluble protein-100 immunohistochemistry confirms the occurrence of melanoma. **B**, No metastasis is observed in the SLN sample (stained with hematoxylin-eosin). Scale bars in **A** and **B** represent 300 μm .

Immunohistochemical staining of the primary tumor confirmed primary melanoma. Permanent sections revealed that the peripheral and deep margins of the heel specimen were uninvolved with tumor. Gross evaluation of the SLN specimen revealed 4 adjacent lymph nodes. Hematoxylin-eosin and immunohistochemistry revealed no melanoma SLN metastasis.

DISCUSSION

ICG fluorescence imaging induces no radiation hazard and is a promising alternative to $^{99\text{m}}\text{Tc}$ mapping in medical centers lacking access to radiopharmaceuticals, especially when that resource is geographically remote. The ability of the AR-CPI system to project real-time fluorescence images directly onto the surgical area enhances the advantages of ICG-based SLNB. The AR-CPI system allows the surgeon to visualize the ICG fluorescence without diverting his/her gaze away from the operative field toward a stand-alone monitor. This report represents the first effort of using AR-CPI for fluorescence imaging-guided SLNB in melanoma. The AR-CPI system clearly demonstrated the subcutaneous lymphatic trajectory projected onto the skin surface, which facilitated rapid and precise identification of SLNs. In comparison with the previously reported lymph node localization rate of 44% by ICG fluorescence imaging prior to skin incision,⁵ we successfully identified the lymph nodes in 6 out of 7 melanoma cases in the extremities prior to skin incision, representing a higher localization rate of 85%. The improved preoperative localization rate might be attributed to the enhanced ICG visibility, the improved coregistration, and the interactive user interface provided by direct image projection on skin surface. Our pilot study indicates that the AR-CPI

system can locate the SLNs in about 80% of patients prior to skin incision. After the superficial fascia is incised, the anticipated SLN localization rate for the AR-CPI system is about 98%, similar to that of $^{99\text{m}}\text{Tc}$. For further validation of clinical utility, a randomized controlled trial comparing the use of the AR-CPI system and $^{99\text{m}}\text{Tc}$ for SLNB would be a logical progression following this pilot study. It is our expectation that the proposed AR-CPI system can assist surgeons in locating superficial SLNs prior to skin incision and provide another option for medical institutions that do not have the conditions to use $^{99\text{m}}\text{Tc}$.

Conflicts of interest

None disclosed.

REFERENCES

- Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019;17(4):367-402.
- Rosso KJ. Techniques that accurately identify the sentinel lymph node in cancer. *World J Surg Proced*. 2015;5(1):14-26.
- Knackstedt R, Couto RA, Ko J, Cakmakoglu C, Wu D, Gastman B. Indocyanine green fluorescence imaging with lymphoscintigraphy for sentinel node biopsy in melanoma: increasing the sentinel lymph node-positive rate. *Ann Surg Oncol*. 2019;26(11):3550-3560.
- Pameijer CR, Leung A, Neves RI, Zhu J. Indocyanine green and fluorescence lymphangiography for sentinel node identification in patients with melanoma. *Am J Surg*. 2018;216(3):558-561.
- 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):914-922.
- Marshall MV, Rasmussen JC, Tan IC, et al. Near-infrared fluorescence imaging in humans with indocyanine green: a review and update. *Open Surg Oncol J*. 2010;2(2):12-25.
- Liu P, Shao P, Ma J, Xu M, Li C. A co-axial projection surgical navigation system for breast cancer sentinel lymph node mapping: system design and clinical trial. Paper presented at:

Advanced Biomedical and Clinical Diagnostic and Surgical Guidance Systems XVII, 108680N; 2-7 February, 2019; San Francisco, California, United States.

8. Zhang F, Zhu X, Gao J, et al. Coaxial projective imaging system for surgical navigation and telementoring. *J Biomed Opt.* 2019; 24(10):1-9.