Am J Nucl Med Mol Imaging 2022;12(4):138-142
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0145887

Editorial

Fluorescent intraoperative navigation: trends and beyond

Lixia Feng[1,2,3], Dawei Jiang[1,2,3]

[1]Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei, China; [2]Hubei Key Laboratory of Molecular Imaging, Wuhan 430022, Hubei, China; [3]Key Laboratory of Biological Targeted Therapy, The Ministry of Education, Wuhan 430022, China

Received August 12, 2022; Accepted August 15, 2022; Epub August 20, 2022; Published August 30, 2022

Surgery, unlike other medical treatments, is highly complex and requires the great skill of the treating physicians within a short period of time. It is crucial to fully understand the area of the body being treated, especially during surgery. Intraoperative image guidance is thus developed in recent years, aiming at establishing an accurate correspondence between the image data of the excised target and the anatomical structure of the patient during the operation, providing necessary information regarding the number, shape, size, edge of the lesions [1]. Opening up a new way for precision medicine, image-guided surgery has played an important role in the treatment of tumors [2-5], neurosurgery [6-8], spinal cord surgery [9-13], oral implantology [14], among others. While almost all researchers believe that intraoperative image guidance may effectively increase surgical accuracy, reduce the operation time, and improve patient safety, complaints from physicians are often heard regarding limited choices of contrast agents and the inability to perform real-time 3D imaging during surgery.

In the second issue of the *American Journal of Nuclear Medicine and Molecular Imaging*, a Delphi consensus survey was performed with feedback from 56 multidisciplinary experts (clinicians: N=30, researchers: N=20, and entrepreneurs: N=6) to investigate the conceptual potential of intraoperative real-time image guidance [15]. Results showed that all experts unanimously agreed that image-guided surgery can minimize positive surgical margins and preserve delicate anatomic structures such as nerves to improve patient outcomes, thus helping promote precision surgery less destructively. However, the survey also reveals disparate expectations over the role of intraoperative imaging.

More and more surgeries are impacted by ever-evolving techniques of image guidance. However, whether intraoperative image guidance should be a part of standard surgical procedures is open to debate. While most clinicians agreed that intraoperative real-time navigation should safeguard the standard surgery to provide optimal treatment, other experts had reservations. This indicates a different perception of unmet clinical needs. First, not all surgeries require intraoperative navigation since adding them to standard surgical procedures results in overtreatment. Regarding the question on “experience and frequency of using image-guided surgery”, 25% of respondents used it in up to 10% of cases, and 18% had not used it in any cases [16]. Second, intraoperative image guidance plays inconsistent roles across surgeries. Intraoperative navigation was superior in rigid targets such as orthopedics [14] and neurosurgery [8], which do not involve the influence of respiratory movements and organ deformation. However, the accuracy of real-time target tracking in flexible organs such as the liver is low, leading to an increased risk of false diagnosis and inadequate treatment [17]. Third, not all medical institutions are able to provide intraoperative image guidance. The results of the questionnaire by Richard *et al*. [16] showed that 86.4% of the respondents had access to image guidance for sinus surgery procedures, and 13.6% did not. And nearly one in five of 331 respondents had never used image guidance in endoscopic sinus surgery.

Table 1. Intraoperative fluorescent navigation probes

Categories	Examples	Applications	Shortcomings	References
NIR-I	ICG	Tumor and sentinel lymph node mapping in human	Limited penetration depth, and insufficient signal-to-noise ratio	[22, 25]
	MB	Thyroid Cancer, identification of breast cancer in human		[26, 27]
NIR-II	CH1055	Evaluate the surgical margin of the tumors in mice	Low affinity for the target	[28]
	NPs	Mice tumor margin identification	Hard to clinical translation	[24, 29]
	IRDye800CW	Specific recognition of murine tumors	Insufficient fluorescence intensity	[30, 31]
Multimodal fluorescence imaging	^{99m}Tc-MAA	Radioguided excisional biopsy and diagnosis of pulmonary embolism in human	Induceing collateral circulation and high uptake of the thoracic spine	[32, 33]
	ICG-^{99m}Tc-nanocolloid	Sentinel lymph node detection in human	Relatively low sensitivity and spatial resolution, radiation exposure	[34, 35]

Thus, experts almost unanimously agreed that image-guided surgical approaches should enhance, rather than replace, conventional surgical imaging when added to existing surgical procedures.

In the question of "Which kind of image-guided surgery should we use in daily clinical practice?" Of the 56 experts, fluorescence imaging received the highest support (49/56), followed by intraoperative ultrasound (46/56) and radio guidance (45/56). 36 of the experts indicated that augmented reality is appropriate, 28 supported 3D reconstruction, while only 14 felt that 3D printed models needed to be used [15]. Although ultrasound, radiation guidance, and fluorescence imaging are currently used for different types of image-guided surgery, their value has not been consistently emphasized. The effectiveness of intraoperative image guidance depends mainly on the imaging system, tracking system, and displaying system. High-resolution images acquired by varying imaging modalities set the basis for surgical navigation systems, but to achieve complete removal of lesions, imaging alone is not enough. In traditional surgical oncology, surgeons mainly rely on the subjective assessment of tissue structure, color, and touch to distinguish the tumor from the surrounding normal tissue [18], to remove the tumor as completely as possible. However, there is inevitably a possibility of tumor residue or excessive removal of normal tissue in this way. Moreover, the existing medical imaging technologies can not detect tiny tumor lesions of one millimeter or less; and if these tiny lesions are not completely removed, it will lead to tumor recurrence and metastasis, endangering the patient's clinical outcome [19].

Compared with the other two imaging modalities, fluorescence imaging has the advantages of high temporal-spatial resolution and is radiation-free [20], thus being mostly considered for daily clinical practice. But reliable imaging probes are also needed for accurate and sensitive lesion tracking during the surgery (**Table 1**). Near-infrared fluorescence imaging with FDA-approved indocyanine green (ICG) as the tracer is wildly used in clinical settings [21, 22]. Tian *et al*. [20] performed multispectral fluorescence imaging-guided hepatocellular carcinoma surgery with ICG for the first time. The key limiting factors of fluorescence imaging are penetration depth and signal-to-noise ratio. Traditional visible and first near-infrared region (NIR-I, 700-900 nm) fluorescence imaging often requires a craniotomy, skull grinding, and other operations, which will cause damage to brain tissues and cerebral vessels. And the penetration depth was less than 2 mm. A promising second near-infrared region (NIR-II, 1000-1700 nm) imaging technology was later developed by Dai *et al*. [23], enabling noninvasive cerebrovascular imaging through the scalp and skull without craniotomy to a depth of more than 2 mm, greatly reducing photon scattering, absorption, and self-fluorescence of tissues, providing higher signal-to-noise ratio and deeper tissue penetration. A series of NIR-II contrast agents were developed to this end. Song *et al*. [24] constructed NIR-II AIEgen (NIR-920) by molecular engineering. NIR-920 nanoparticles (NPs) with the longest maximum absorption wavelength exhibited bright fluorescence and excellent contrasted images of lymph nodes in the NIR-II/NIR-IIb window. NIR-920 NPs offered several superior advantages over clinically used ICG, including longer retention time, deeper penetration, higher signal-to-noise ratio and

photostability, and can perform quick and accurate navigation of sentinel lymph nodes.

NIR-II probes were also used to evaluate the surgical margins of tumors. Wu *et al*. [28] developed two homologous fluorescent agents (CH1055-PEG-PT and CH1055-PEG-Affibody), which can target 143B tumor cells with high affinity for imaging osteosarcoma and its lung metastasis. When imaging small lesions, the performance of CH1055-PEG-PT was superior to CT imaging, and fluorescent agents can delineate malignant tissues at sizes < 1 mm with bright and clear boundaries. Thus, primary and micrometastatic lung lesions of osteosarcoma tissues can be removed completely. However, there was still much room for further development regarding tracer affinity to their target. Zhang's team had made great progress in the study of NIR-II probes [29]. They reported that DNA and peptides modified downconversion nanoparticles (DCNPs) may self-assemble at tumor sites to maintain a high tumor-to-background ratio of ~12.5 at 20-26 h postinjection (p.i), allowing tumors of various shapes and sizes to be visualized with efficient tumor margin identification. The results also showed that the tracer remained stable for 6 h, allowing an adequate time window for image-guided tumor resection. However, this probe proved suboptimal for real-time surgery, highlighting existing challenges of intraoperative imaging and the dire needs of excellent imaging probes. Existing AIE fluorescent dyes mostly exhibit partial solubility in lipid or water environments. Lipid-soluble AIE fluorescent probes will inevitably aggregate in a biological water-based environment, resulting in high background fluorescence and reduced imaging contrast. On the other hand, water-soluble AIE molecules may easily enter the lipid environment (such as lipid droplets in the liver) during transportation in vivo, resulting in off-target aggregation and false positive signals. Many other probes like IRDye800CW [30, 31], CH-4T [36], and quantum dots [37, 38] had been developed with superior performance, but none proved particularly suitable in the clinic, urging further exploration [18].

Radiation-guided intraoperative imaging is also attractive. The radioactive signal is not affected by penetration depth, and many excellent probes had been developed for positron emission tomography (PET) [39] or single-photon emission computed tomography (SPECT) [40]. An injection of ^{99m}Tc-macroaggregated human albumin can guide excisional biopsy, receiving wide clinical recognition [32]. Baranski A-C *et al*. [41] developed a novel PMSA-targeted tracer, ^{68}Ga-IRDye800CW-PSMA-11, for pre-, intra- and postoperative imaging of prostate cancer. PET imaging is good at localization with high penetration depth, and NIR-II fluorescence imaging allows accurate real-time mapping of lesions. Zhang *et al*. [42] combined the two through a biological orthogonal reaction *in vivo*. This strategy greatly improved tumor uptake and tissue contrast of radiolabeled tracer, facilitating tumor diagnosis. The probe (XB1034-cetuximab-TCO) showed clear margins of MDA-MB-231 tumors at 60 h p.i. to enable the detection and resection of in situ and metastatic lesions. In addition, the integration of the two imaging modalities effectively reduced false-positive rates.

Each imaging technology has its own shortcomings, but combining two or more of them may complete each other for clinical needs. Penetration depth and surgical margin differentiation remain major challenges of intraoperative fluorescence imaging guidance in daily practice. Multimodal imaging will help to solve the problems and benefit both physicians and patients. While the usage of ICG-^{99m}Tc-nanocolloid has been clinically recognized [34, 35], the combination of fluorescent imaging and nuclear medicine presents a promising direction for image-guided precision surgery.

Address correspondence to: Dawei Jiang, Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei, China; Hubei Key Laboratory of Molecular Imaging, Wuhan 430022, Hubei, China; Key Laboratory of Biological Targeted Therapy, The Ministry of Education, Wuhan 430022, China. Tel: +86-2787543437; E-mail: daweijiang@hust.edu.cn

References

[1] Guha D, Dmytriw AA, Guest JD and Yang VXD. Chapter 8 - Intraoperative imaging and image guidance. In: Fehlings MG, Kwon BK, Vaccaro AR, Oner FC, editors. Neural repair and regeneration after spinal cord injury and spine trauma. Academic Press; 2022. pp. 125-148.

[2] Nunn A and Barua N. Initial experience with navigated intraoperative ultrasound for brain tumour surgery. Neuro Oncol 2021; 23: iv16-iv17.
[3] Kok END, Eppenga R, Kuhlmann KFD, Groen HC, van Veen R, van Dieren JM, de Wijkerslooth TR, van Leerdam M, Lambregts DMJ, Heerink WJ, Hoetjes NJ, Ivashchenko O, Beets GL, Aalbers AGJ, Nijkamp J and Ruers TJM. Accurate surgical navigation with real-time tumor tracking in cancer surgery. NPJ Precis Oncol 2020; 4: 8.
[4] Pecoraro A, Piramide F, Verri P, Checcucci E, De Cillis S, Piana A, Manfredi M, Fiori C, Porpiglia F and Amparore D. A0345 - Surgical management of complex renal tumors treated with robotic partial nephrectomy: from the planning to the intraoperative navigation via 3D virtual models. Eur Urol 2022; 81: S535.
[5] Passer JZ, Alvarez-Breckenridge C, Rhines L, DeMonte F, Tatsui C and Raza SM. Surgical management of skull base and spine chordomas. Curr Treat Options Oncol 2021; 22: 40.
[6] Sommer B, Roessler K, Rampp S, Hamer HM, Blumcke I, Stefan H and Buchfelder M. Magnetoencephalography-guided surgery in frontal lobe epilepsy using neuronavigation and intraoperative MR imaging. Epilepsy Res 2016; 126: 26-36.
[7] Simfukwe K, Iakimov I, Sufianov R, Borba L, Mastronardi L and Shumadalova A. Application of intraoperative ultrasound navigation in neurosurgery. Front Surg 2022; 9: 900986.
[8] Wilkinson ID, Romanowski CA, Jellinek DA, Morris J and Griffiths PD. Motor functional MRI for pre-operative and intraoperative neurosurgical guidance. Br J Radiol 2003; 76: 98-103.
[9] Shuman WH, Valliani AA, Chapman EK, Martini ML, Neifert SN, Baron RB, Schupper AJ, Steinberger JM and Caridi JM. Intraoperative navigation in spine surgery: effects on complications and reoperations. World Neurosurg 2022; 160: e404-e411.
[10] Carl B, Bopp M, Saß B, Pojskic M, Gjorgjevski M, Voellger B and Nimsky C. Reliable navigation registration in cranial and spine surgery based on intraoperative computed tomography. Neurosurg Focus 2019; 47: E11.
[11] Elmi-Terander A, Burström G, Nachabé R, Fagerlund M, Ståhl F, Charalampidis A, Edström E and Gerdhem P. Augmented reality navigation with intraoperative 3D imaging vs fluoroscopy-assisted free-hand surgery for spine fixation surgery: a matched-control study comparing accuracy. Sci Rep 2020; 10: 707.
[12] Cawley DT, Rajamani V, Cawley M, Selvadurai S, Gibson A and Molloy S. Using lean principles to introduce intraoperative navigation for scoliosis surgery. Bone Joint J 2020; 102-B: 5-10.
[13] Batke JN, Pennington A, Dea N, Nadeau M, Fisher CG, Dvorak MF and Street J. Pedicle screw malposition in revision spine surgery: efficacy of intraoperative CT based navigation. Spine J 2015; 15: S200.
[14] Miller RJ and Bier J. Surgical navigation in oral implantology. Implant Dent 2006; 15: 41-47.
[15] Dell'Oglio P, Mazzone E, Buckle T, Maurer T, Navab N, van Oosterom MN, Schilling C, Witjes MJ, Vahrmeijer AL, Klode J, Vojnovic B, Mottrie A, van der Poel HG, Hamdy F and van Leeuwen FW. Precision surgery: the role of intra-operative real-time image guidance - outcomes from a multidisciplinary European consensus conference. Am J Nucl Med Mol Imaging 2022; 12: 74-80.
[16] Orlandi RR and Petersen E. Image guidance: a survey of attitudes and use. Am J Rhinol 2006; 20: 406-411.
[17] Zachiu C, Ries M, Ramaekers P, Guey JL, Moonen CTW and de Senneville BD. Real-time non-rigid target tracking for ultrasound-guided clinical interventions. Phys Med Biol 2017; 62: 8154-8177.
[18] Yang RQ, Lou KL, Wang PY, Gao YY, Zhang YQ, Chen M, Huang WH and Zhang GJ. Surgical navigation for malignancies guided by near-infrared-II fluorescence imaging. Small Methods 2021; 5: 2001066.
[19] Bertrand TE, Cruz A, Binitie O, Cheong D and Letson GD. Do surgical margins affect local recurrence and survival in extremity, nonmetastatic, high-grade osteosarcoma? Clin Orthop Relat Res 2016; 474: 677-683.
[20] Hu Z, Fang C, Li B, Zhang Z, Cao C, Cai M, Su S, Sun X, Shi X, Li C, Zhou T, Zhang Y, Chi C, He P, Xia X, Chen Y, Gambhir SS, Cheng Z and Tian J. First-in-human liver-tumour surgery guided by multispectral fluorescence imaging in the visible and near-infrared-I/II windows. Nat Biomed Eng 2020; 4: 259-271.
[21] Belia F, Biondi A, Agnes A, Santocchi P, Laurino A, Lorenzon L, Pezzuto R, Tirelli F, Ferri L, D'Ugo D and Persiani R. The use of indocyanine green (ICG) and near-infrared (NIR) fluorescence-guided imaging in gastric cancer surgery: a narrative review. Front Surg 2022; 9: 880773.
[22] Zhang Y, Cheng H, Chen H, Xu P, Ren E, Jiang Y, Li D, Gao X, Zheng Y, He P, Lin H, Chen B, Lin G, Chen A, Chu C, Mao J and Liu G. A pure nanoICG-based homogeneous lipiodol formulation: toward precise surgical navigation of primary liver cancer after long-term transcatheter arterial embolization. Eur J Nucl Med Mol Imaging 2022; 49: 2605-2617.
[23] Hong G, Diao S, Chang J, Antaris AL, Chen C, Zhang B, Zhao S, Atochin DN, Huang PL, Andreasson KI, Kuo CJ and Dai H. Through-skull fluorescence imaging of the brain in a

new near-infrared window. Nat Photonics 2014; 8: 723-730.
[24] Song S, Wang Y, Zhao Y, Huang W, Zhang F, Zhu S, Wu Q, Fu S, Tang BZ and Wang D. Molecular engineering of AIE luminogens for NIR-II/IIb bioimaging and surgical navigation of lymph nodes. Matter 2022.
[25] Troyan S, Gibbs-Strauss S, Gioux S, Oketokoun R, Azar F, Khamene A, Kianzad V, Rosenberg M, Clough BL and Frangioni JV. Image-guided near-infrared fluorescent sentinel lymph node mapping in human breast cancer. J Clin Oncol 2009; 27: e11591-e11591.
[26] Zhang C, Mao Y, Wang K and Tian J. The identification of breast cancer by Near-Infrared fluorescence imaging with methylene blue. J Clin Oncol 2018; 36: e12591-e12591.
[27] Jermain PR, Fischer AH, Joseph L, Muzikansky A and Yaroslavsky AN. Fluorescence polarization imaging of methylene blue facilitates quantitative detection of thyroid cancer in single cells. Cancers 2022; 14: 1339.
[28] Zhou H, Yi W, Li A, Wang B, Ding Q, Xue L, Zeng X, Feng Y, Li Q, Wang T, Li Y, Cheng X, Tang L, Deng Z, Wu M, Xiao Y and Hong X. Specific small-molecule nir-ii fluorescence imaging of osteosarcoma and lung metastasis. Adv Healthc Mater 2020; 9: e1901224.
[29] Wang P, Fan Y, Lu L, Liu L, Fan L, Zhao M, Xie Y, Xu C and Zhang F. NIR-II nanoprobes in-vivo assembly to improve image-guided surgery for metastatic ovarian cancer. Nat Commun 2018; 9: 2898.
[30] Polikarpov DM, Campbell DH, McRobb LS, Wu J, Lund ME, Lu Y, Deyev SM, Davidson AS, Walsh BJ, Zvyagin AV and Gillatt DA. Near-infrared molecular imaging of glioblastoma by miltuximab®-IRDye800CW as a potential tool for fluorescence-guided surgery. Cancers 2020; 12: 984.
[31] Zhang Y, Hong H, Engle JW, Yang Y, Barnhart TE and Cai W. Positron emission tomography and near-infrared fluorescence imaging of vascular endothelial growth factor with dual-labeled bevacizumab. Am J Nucl Med Mol Imaging 2012; 2: 1-13.
[32] Manca G, Mazzarri S, Rubello D, Tardelli E, Delgado-Bolton RC, Giammarile F, Roncella M, Volterrani D and Colletti PM. Radioguided occult lesion localization: technical procedures and clinical applications. Clin Nucl Med 2017; 42: e498-e503.
[33] Kersting D, Guberina N, Umutlu L, Stuschke M and Hautzel H. Superior vena cava syndrome induced collateral circulation on 99mtc-macroaggregated albumin lung perfusion scintigraphy. Clin Nucl Med 2020; 45: e435-e438.
[34] Paredes P, Vidal-Sicart S, Campos F, Tapias A, Sánchez N, Martínez S, Carballo L, Pahisa J, Torné A, Ordi J, Carmona F and Lomeña F. Role of ICG-^{99m}Tc-nanocolloid for sentinel lymph node detection in cervical cancer: a pilot study. Eur J Nucl Med Mol Imaging 2017; 44: 1853-1861.
[35] KleinJan GH, van den Berg NS, van Oosterom MN, Wendler T, Miwa M, Bex A, Hendricksen K, Horenblas S and van Leeuwen FWB. Toward (hybrid) navigation of a fluorescence camera in an open surgery setting. J Nucl Med 2016; 57: 1650-1653.
[36] Antaris AL, Chen H, Diao S, Ma Z, Zhang Z, Zhu S, Wang J, Lozano AX, Fan Q, Chew L, Zhu M, Cheng K, Hong X, Dai H and Cheng Z. A high quantum yield molecule-protein complex fluorophore for near-infrared II imaging. Nat Commun 2017; 8: 15269.
[37] Michalska M, Florczak A, Dams-Kozlowska H, Gapinski J, Jurga S and Schneider R. Peptide-functionalized ZCIS QDs as fluorescent nanoprobe for targeted HER2-positive breast cancer cells imaging. Acta Biomater 2016; 35: 293-304.
[38] Wen Q, Zhang Y, Li C, Ling S, Yang X, Chen G, Yang Y and Wang Q. NIR-II fluorescent self-assembled peptide nanochain for ultrasensitive detection of peritoneal metastasis. Angew Chem Int Ed Engl 2019; 58: 11001-11006.
[39] Ding Y, Zhang D, Wang M, Zhang L, Liu Y, Deng Y, Jiang D, Liu Y and Cao W. Glomerular filtration rate calculation based on ^{68}Ga-EDTA dynamic renal PET. Am J Nucl Med Mol Imaging 2022; 12: 54-62.
[40] Chakravarty R, Siamof CM, Dash A and Cai W. Targeted α-therapy of prostate cancer using radiolabeled PSMA inhibitors: a game changer in nuclear medicine. Am J Nucl Med Mol Imaging 2018; 8: 247-267.
[41] Baranski AC, Schäfer M, Bauder-Wüst U, Roscher M, Schmidt J, Stenau E, Simpfendörfer T, Teber D, Maier-Hein L, Hadaschik B, Haberkorn U, Eder M and Kopka K. PSMA-11-derived dual-labeled PSMA inhibitors for preoperative PET imaging and precise fluorescence-guided surgery of prostate cancer. J Nucl Med 2018; 59: 639-645.
[42] Zhang X, Ding B, Qu C, Li H, Sun Y, Gai Y, Chen H, Fang H, Qian K, Zhang Y, Cheng Z and Lan X. A thiopyrylium salt for PET/NIR-II tumor imaging and image-guided surgery. Mol Oncol 2020; 14: 1089-1100.