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Advanced Imaging Digest

Breast cancer risk identification

Breast lymphatic mapping

Indocyanine green (ICG) dye is a fluorescent dye that can be detected using near infrared (NIR) cameras and has been used for more than 50 years with a favorable safety profile. This dye has been studied in mapping in gastrointestinal, melanoma, cervical, vulvar, anal, oropharyngeal, non-small cell lung and breast cancers.

Traditional sentinel lymph node (SLN) mapping in breast cancer uses a radiotracer labeled with technetium-99 (99mTc), visible blue dye (methylene blue or isosulfan blue) or a combination of both. Utilizing 99mTc has several limitations, including nuclear licensing and patient discomfort, as these injections typically occur before surgery. Blue-dye injections can be performed intraoperatively, but there are reported risks such as skin necrosis and anaphylaxis.

The advantages of ICG for SLN detection include the ability to inject intraoperatively, the ability of NIR to visualize the lymphatic anatomy and flow during the injection in real time, lower cost and no special training or certification is required to handle ICG (as with nuclear agents).

A prospective trial comparing ICG and 99mTc demonstrated no difference in the number of removed SLNs. The study suggests that the concentration of ICG injected and the smaller size of the ICG molecule allow it to travel faster than the 99mTc bound to albumin. Patients with a higher body mass index may have failed mapping as the NIR camera penetrates tissue to a maximum depth of two centimeters. This can be circumvented with an axillary image enhancer device that compresses the axillary tissue.

99mTc-labeled radiotracer alone is the more commonly used solo technique of SLN mapping with a detection rate of 97.5% accuracy. When blue dye is the primary mean of detection, it has a lower sensitivity of 91%. Lymph node detection rate using dual mapping with 99mTc and a blue dye is

Magellan Healthcare clinical leaders continually review imaging trends and needs in light of current medical concerns, available literature, and society and Centers for Disease Control and Prevention recommendations and guidelines. This document is a summary of our latest findings. Please consult references for detailed information.

approximately 99%. Due to its high accuracy and low false-negative rates, 99mTc is advocated as the primary technique.

Overall, ICG NIR imaging is an efficient, convenient and equivalent intraoperative method of SLN detection compared with traditional 99mTc regarding the number of SLNs identified, rate of failed mapping and identification of pathologically positive SLNs, and several recent studies support NIR-guided SLN biopsy for standard use. ICG offers the advantages of real-time imaging, ease of handling, low cost and rapid localization to the SLNs.

Magellan Healthcare will continue to monitor the literature, including the use of ICG in different facets of image-guided procedures, such as NIR angiography of blood vessels, skin flap perfusion for mastectomies, identification of the extrahepatic bile ducts and identification of oncologic tumor metastases.

Fluoroestradiol F-18

Fluoroestradiol F-18 (FES) is a new estrogen analog (16 -[18F]-fluoro-17 -estradiol) positron emission tomography (PET) agent, which was approved by the FDA in May 2020. FES may be used in the detection of estrogen receptor positive lesions in patients with recurrent or metastatic breast cancer.

Some retrospective studies show that FES has higher sensitivity for diagnosing metastatic lesions when compared with F-18 fluorodeoxyglucose (FDG) (90.8% to 82.8%, respectively). FES has improved detection at axillary, cervical, mediastinal lymph nodes and bone sites when compared with FDG. Distinguishing inflammatory from malignant lesions can be difficult in FDG exams, causing false-positive results. FES can potentially correct false-positive FDG findings due to its high specificity for estrogen receptor (ER)-positive lesions. In a recent study, FES led to a treatment strategy change in 23.6% of patients. FES may also serve to predict response to endocrine therapy and assess tumor burden and heterogeneity.

A critical shortcoming of FES PET/computed tomography is it cannot be reliably measured to detect liver metastases due to high background activity. Detection of lesions that are in close proximity to the bowel may also be difficult. FES is not specific for breast cancer and may occur in a variety of estrogen receptor positive tumors that are outside the breast, including those of uterine or ovarian origin. A negative scan does not exclude the possibility of ER-positive breast cancer.

To date, only a small number of comparative studies (FDG versus FES) have been performed. These studies document favorable metastatic disease detection rates of ER-positive malignancies; however, large prospective trials are needed.

Additionally, tissue biopsies must still be considered in recurrence of breast cancer and to verify ER status by pathology. FES is not useful for imaging other receptors, such as human epidermal growth factor receptor 2 and progesterone receptor.

While initial results appear promising, FES should be monitored closely as only small clinical trials have been conducted. Magellan Healthcare will continue to monitor the literature for large independent trials supporting use.

About the authors

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Dr. Khalid joined Magellan in 2014. As a board-certified diagnostic radiologist with a career spanning more than twenty years, he has a thorough understanding of the complexities of the U.S. healthcare system and current standards of care. In his current role, Dr. Khalid is involved in training new physicians, auditing, continuing education and policy development.

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References:

Abe H, Mori T, Umeda T, et al. Indocyanine green fluorescence imaging system for sentinel lymph node biopsies in early breast cancer patients.*Surg Today.* 2011;41(2):197-202.

Aoyama K, Kamio T, Ohchi T, Nishizawa M, Kameoka S. Sentinel lymph node biopsy for breast cancer patients using fluorescence navigation with indocyanine green. *World J Surg Oncol.* 2011;9:157.

Ballardini B, Santoro L, Sangalli C, et al. The indocyanine green method is equivalent to the ^{99}mTc-labeled radiotracer method for identifying the sentinel node in breast cancer: A concordance and validation study. *Eur J Surg Oncol.* 2013;39(12):1332-1336.

Efron P, Knudsen E, Hirshorn S, Copeland EM. Anaphylactic reaction to isosulfan blue used for sentinel node biopsy: Case report and literature review. *Breast J.* 2002;8(6):396-399.

Gupta M, Datta A, Choudhury PS, Dsouza M, Batra U, Mishra A. Can 18F-fluoroestradiol positron emission tomography become a new imaging standard in the estrogen receptor-positive breast cancer patient: A prospective comparative study with 18F-fluorodeoxyglucose positron emission tomography? World J Nucl Med. 2017;16(2):133-139.

Hope-Ross M, Yannuzzi LA, Gragoudas ES, et al. Adverse reactions due to indocyanine green. *Ophthalmology.* 1994;101(3):529-533.

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.

Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: Overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol.* 2010;11(10):927-933.

Kurland BF, Wiggins JR, Coche A, et al. Whole-body characterization of estrogen receptor status in metastatic breast cancer with 16 -18f-fluoro-17 -estradiol positron emission tomography: Meta-analysis and recommendations for integration into clinical applications.Oncologist. 2020;25(10):835-844.

Kusano M, Tajima Y, Yamazaki K, Kato M, Watanabe M, Miwa M. Sentinel node mapping guided by indocyanine green fluorescence imaging: A new method for sentinel node navigation surgery in gastrointestinal cancer. *Dig Surg.* 2008;25(2):103-108.

Liu C, Gong C, Liu S, et al. 18F-FES PET/CT influences the staging and management of patients with newly diagnosed estrogen receptor-positive breast cancer: A retrospective comparative study with 18F-FDG PET/CT. *Oncologist.* 2019;24(12):e1277-e1285.

McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: Objective measurements. J Clin Oncol. 2008;26(32):5213-5219. Erratum in: *J Clin Oncol.* 2010 Apr 1;28(10):1808.11.

Schaafsma BE, Mieog JSD, Hutteman M, et al. The clinical use of indocyanine green as a near infrared fluorescent contrast agent for image-guided oncologic surgery.*J Surg Oncol.* 2011;104(3):323-332.

Sugie T, Ikeda T, Kawaguchi A, Shimizu A, Toi M. Sentinel lymph node biopsy using indocyanine green fluorescence in early-stage breast cancer: A meta-analysis. *Int J Clin Oncol.* 2017;22(1):11-17.

Sugie T, Kinoshita T, Masuda N, et al. Evaluation of the clinical utility of the ICG fluorescence method compared with the radioisotope method for sentinel lymph node biopsy in breast cancer.*Ann Surg Oncol.* 2016;23(1):44-50.

Ulaner GA, Jhaveri K, Chandarlapaty S, et al. Head-to-head evaluation of 18F-FES and 18F-FDG PET/CT in metastatic invasive lobular breast cancer. *J Nucl Med.* 2021;62(3):326-331.

Valente SA, Al-Hilli Z, Radford DM, Yanda C, Tu C, Grobmyer SR. Near infrared fluorescent lymph node mapping with indocyanine green in breast cancer patients: A prospective trial. *J Am Coll Surg.* 2019;228(4):672-678.

Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet.* 1997;349(9069):1864-1867.