Editorial Commentary: Surgery: Other

Intraoperative molecular imaging: a look into the future

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Keywords: Molecular imaging; cancer surgery; future of intraoperative molecular imaging

Received: 08 January 2023; Accepted: 30 June 2023; Published online: 10 August 2023.

doi: 10.21037/amj-23-5

View this article at: https://dx.doi.org/10.21037/amj-23-5

With the increase in detection of early-stage disease, surgical resection has gained increased application in the treatment of solid tumors (1). Achieving an R0 resection has been shown repeatedly to improve oncologic outcomes and is a mainstay of curative-intent cancer surgery (2). Meanwhile, minimally invasive surgery has increasingly been adapted and is found to decrease complications and improve outcomes (3). However, it hinders the advantage of manual palpation of tumors that would have otherwise been an option with open surgery. As such, an *in-vivo* optical scanner was introduced into the surgical field to be able to detect malignancies and aid the oncologist in identifying synchronous lesions, positive margins and tumors invisible to white light (4). The premise of intraoperative molecular imaging (IMI) relies on having a dye injected into patients preoperatively that is excited by a laser and detected by a photon detector. The dye selectively identifies tumor cells and have been under development and modification for years to increase sensitivity and specificity (5).

The use of fluorescence in imaging started in the late 1950s but was not particularly used in detecting malignancy. It was not until the 1990s where these fluorescent dyes were used to detect cancer cells in neurosurgery and the concept of IMI came to be (6). The ability to utilize this technology to identify occult disease, guide surgical resection, and obtain positive margins intraoperatively has prompted the wide research on dye development. Many of these dyes are now FDA-approved or being investigated under clinical trials. In our review, we aim to summarize some currently available dyes with their mechanisms of actions and their applications, describe current imaging modalities, and highlight potential future directions in dye and imaging technology design.

Targeted dyes

There are three major mechanisms of action of fluorescent dyes: passive, targeted, and activatable. Early on in IMI, the dyes were mostly reliant on non-specific passive targeting and relied on the differential of tumor blood supply compared to the juxtaposing parenchyma. This passive method relied on enhanced permeability and retention (EPR) effect whereby the dye concentrated around the tumor and its microenvironment. Indocyanine green (ICG) is a classic example (7). Other dyes were more specific and capitalized on over expression of receptors in malignant cells. An example is pafolacianine (OTL38) that targets folate receptors. It has been widely studied in ovarian and thoracic malignancies with promising results that culminated in its being FDA approved for ovarian cancer in November 2021 and for lung cancer in December 2022 (8). Another targeted dye is SGM-101, an antibody-dye conjugate targeted against carcinoembryonic antigen that is currently being investigated in a phase III clinical trial

for colon cancer after preclinical dose escalation studies (9). In neurosurgery and otolaryngology, panitumumab, an anti-epidermal growth factor receptor antibody is used as a fluorophore (10). Newer dyes are activatable and rely on specific tumor cells characteristics to be activated and eventually fluoresce. Pegsitacianine is an example whereby it is a pH-activatable probe that is activated in the acidic tumor microenvironment with applications in lung cancer and peritoneal metastasis (11). Another dye, VGT-309, is an activity-based probe. This dye has a fluorescent tracer that is quenched until the dye contacts an enzyme that is overexpressed in tumor cells, cathepsin. It cleaves the quencher and the targeted tumor fluoresces. It has already undergone a phase I clinical trial in Australia and is currently being studied in a phase II clinical trial (12,13).

A category of dyes that targets normal tissue has also been developed. These dyes allow the surgeon to visualize normal and commonly injured vital structures during their dissection and avoid iatrogenic injury. For example, a cyanine ureter probe is used to identify the ureter in urologic surgery and prevent inadvertent injury (14). Another dye that is oxazine-derived targets normal neurons with a goal to prevent injury during dissection (15).

The main reason more novel dyes have been under development is essentially to sequentially overcome limitations from previous dyes. Early on, the increased permeability and vasculature of tumors mimicked that of inflammatory non-malignant lesions. This non-selectivity incurred some false positives. There is also a large amount of background that clouds the signal received and does not allow accurate discrimination of malignant cells from their surrounding parenchyma.

Another limitation is penetrance of the dyes through the tissue parenchyma. Light within the visible spectrum is absorbed by the surrounding biomolecules increasing local scatter and tissue autofluorescence (16). Near infrared (NIR) light avoids that problem and is preferentially absorbed by the tumor. Also, some characteristics and markers are shared between tumors and other inflammatory conditions. As such, identifying dyes with a differential detection of cancer over inflammation would also be a step in advancing IMI.

Improved cameras

The premise of IMI is having a camera system whereby there is a light source that emits NIR light that excites the fluorophore and a photon detector that detects the emitted wavelength (17). This technology has already been incorporated into laparoscopes and thoracoscopes. Also, an exoscope which follows the same principle is needed to assess the extracted specimen on a back table (18). The major challenges of these modalities is having enough sensitivity to detect the suspicious lesion and enough specificity to decrease background fluorescence in normal tissue (19). As such, more novel robotic imaging technology have modes that detect fluorescent dyes at a higher sensitivity than traditional laparoscopy and can be even used for multi-wavelength fluorescence imaging (20).

Application to lymph node staging

A great challenge for the surgical oncologists, is to identify occult disease in lymph nodes that are structurally intact. Nowadays, novel imaging mechanisms that identify sentinel nodes have saved many patients from a complete nodal basin dissection. Lymphedema with sentinel lymph node biopsy (SLNB) is at 5.6% as opposed to the 19.9% with complete axillary lymph node dissection (21). Although this is a marked improvement, 5.6% of patients still suffer from lymphedema, which is quite debilitating. For instance, in breast imaging, combining methylene blue with a radioactive tracer helps better identify sentinel lymph nodes better than using either alone. Naturally, not all harvested sentinel lymph nodes were positive with as much as 50% being disease free (22). The z0011 trial established that sentinel lymph node dissection was comparable in survival to those who underwent the unnecessarily burdensome complete axillary nodal dissection for those with clinically node negative disease (23). Using IMI can potentially help localize the involved sentinel lymph nodes and more selective surgery thereby decreasing the risk further of lymphedema. Current trials are investigating the role IMI plays in nodal imaging along cancer imaging.

Predictive models and future directions

Over the past few years, there has been increased work on trying to incorporate artificial intelligence in imaging. Being able to utilize patient data combined with imaging may elucidate what tumor a patient most likely has prior to pathologic confirmation (24). Also, when known beforehand, certain histologic subtypes might benefit from one dye over the other. As such, this information can help match patients with a known histologic subtype to a specific dye (8).

Another big question revolves around patient selection

and potential success of IMI. Some patients and tumors do not light up despite using the dyes. This most likely has to do with a combination of patient and dye factors. Current studies are evaluation the ability to identify before hands if the patient has a high likelihood of benefiting from a dye, then we can help optimizing how we allocate our resources.

In summary, IMI has helped in improving precision surgery and focusing oncologic resection. There are multiple dyes in the market with different mechanisms of action: passive, targeted, or activatable. Current research focuses on fine-tuning the dyes used in IMI to overcome some of the challenges we have had with previous dyes (7). Meanwhile, there are several imaging modalities in place to view these dyes. Imaging device development is focused on increasing sensitivity and specificity and expanding fluorescent imaging into other areas such as endoscopic procedures. Finally, there are predictive models being investigated for identifying patients who are candidates for IMI. This can even help personalize patient care by associating each patient and histologic subtype with the most sensitive corresponding dye.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *AME Medical Journal*. The article has undergone external peer review.

Peer Review File: Available at https://amj.amegroups.org/article/view/10.21037/amj-23-5/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.org/article/view/10.21037/amj-23-5/coif). FA serves as an unpaid editorial board member of *AME Medical Journal* from November 2022 to October 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj-23-5
Cite this article as: Bou-Samra P, Zhang K, Chang A, Galandarova A, Ibrahimli A, Karimov Z, Kennedy G, Azari F. Intraoperative molecular imaging: a look into the future. AME Med J 2023;8:21.