Editorial

Intraoperative molecular imaging in thoracic oncology: pushing the boundaries of precision resection for occult non-small cell lung cancer in the era of minimally invasive surgery

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In the recent paper entitled "A novel system for analyzing indocyanine green (ICG) fluorescence spectra enables deeper lung tumor localization during thoracoscopic surgery", Chiba and colleagues utilize a novel near-infrared (NIR) spectroscopy device that aims to detect nonpalpable and visually occult pulmonary nodules with various well thought-out preclinical and porcine models (1). They describe reliable detection of ICG-labeled tumors as deep as 30 mm from the pleural surface in inflated lungs with their technique, which is an important principle for minimally invasive intraoperative molecular imaging (IMI)-guided cancer resections (2).

The authors' findings are timely and relevant. The rapid adoption and implementation of low-dose CT-based lung cancer screening techniques have led to a substantial increase in the incidence of indeterminate subcentimeter solitary pulmonary nodules (SPNs) and ground glass opacities (3-5). While the majority of these nodules are benign, clinicians must do diligence in evaluating and longitudinal follow-up, as this patient population represents a high-risk group (6,7). Unfortunately, a substantial number of patients with SPNs need tissue sampling in the form of surgical resection for definitive diagnosis and treatment. However, in the era of minimally invasive techniques such as video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), these lesions present a significant challenge to the surgeon, as they tend to be visually occult, which can lead to higher than desired pulmonary resection for potentially benign disease processes (8).

IMI has emerged as a potential technology that addresses these current challenges in thoracic surgery (9-13). IMI involves the systemic infusion of targeted fluorochrome that localizes to the area of the tumor and can be detected using camera systems that are specifically designed for the tracer in question. By leveraging IMI, surgeons can make areas of tracer accumulation (theoretically area containing only the tumor) "glow" and use the tumor fluorescence as a guide for resection.

Chiba *et al.* described a well-studied NIR fluorochrome, ICG, which has long been approved by the Food and Drug Administration (FDA) and is a subject of hundreds of clinical trials (9,14-16). ICG has excitation and emission in the NIR spectrum (>800 nm) and is not visible to the naked eye, therefore requiring an NIR emission camera detection system. This injected nontargeted fluorescent tracer accumulates passively in tumors via the enhanced permeability and retention effect (EPR). This mechanism leverages the increased vascular permeability and decreased lymphatic drainage characteristic of cancerous tissue, which

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causes the tracer to accumulate inside the tumor. Other notable tracers that exploit EPR include methylene blue (long used in preoperative pulmonary nodule localization) and fluorescein (17,18).

Multiple clinical trials have demonstrated the oncologic benefit of various IMIs, particularly for lung cancer resections (9,19). The use of this technology has been associated with superior visually occult primary nodule detection, intraoperative margin assessment, and synchronous occult disease identification, which have been missed by even high-resolution cross-sectional imaging (9). The benefit of the technology goes beyond primary lung nodules, as IMI has been shown to detect occult metastatic pulmonary sarcomas and influence patient survival after IMI-guided metastasectomy (10). Similar observations have been noted for other malignancies, such as melanoma and colorectal and renal cell carcinoma, that metastasize to the lung (13).

Despite the many advantages and benefits of IMI, the technology still remains in its infancy and faces various technical and operational challenges (2,20,21). The majority of the current fluorescence tracers investigated are in the NIR range. The Achilles heel of operating at this wavelength (800–1,000 nm) is that it limits the depth of penetration of the tracer excitation and fluorescence detection (22). Currently, various studies report suboptimal detection of nodules deeper than 10 mm from the pleural surface. Chiba and associates, in this study, attempt to address this significant challenge by implementing a novel ICG fluorescence calibrated spectroscopy device that has tissue penetration deeper than NIR light-source enabled IMI devices. Using calculated and astute preclinical investigative methods, the authors describe ICG fluorescence detection well beyond the current capabilities of *ex vivo* systems (1). This finding has the potential to expand the patient population that can benefit from IMI assistance during minimally invasive resections.

There are several limitations to this study that should be acknowledged, many of which Chiba and associates do carefully consider in their discussion. First, the implementation and validation of the spectroscopic detection of ICG fluorescence is performed entirely in biological silicone and porcine lung modules. While these platforms allow for the spectrophotophysical assessment of NIR tracers and detection devices, they are only crudely representative of findings in humans. Lungs represent a particularly challenging solid organ system for the study of IMI. The organs *in situ* are dynamic due to respiratory variation and are routinely anthracotic due to light absorbing carbon deposition (soot), which produces false fluorescence and has higher normal parenchymal uptake of ICG secondary to rich vasculature (21,23). Any claim without investigation in human clinical trials should be interpreted cautiously in the field of IMI, as countless technological discoveries fail to make clinical impact once introduced into humans. Second, for IMI to be successful and clinically impactful, the technology has to be rapidly scalable and intuitive. While the novel device described by Chiba *et al.* is impressive, it is unclear if the spectroscopic interpretation would be adopted by the wider thoracic surgery community. The technology has to seamlessly integrate into current surgical management, such as VATS and RATS camera systems, and not disturb the clinical momentum of the surgical team (15).

In conclusion, the description and careful experimental curation by Chiba *et al.* serve an important leap in addressing the current challenges in IMI. Future clinical assessment of their novel spectral systems in early phase trials will surely attempt to answer the limitations outlined in their manuscript.

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