Editorial

Use of indocyanine green (ICG) fluorescence spectroscopy in thoracoscopic surgery: seeing beyond the unseen

Adrian Chi-Heng Fung^, Kenneth Kak-Yuen Wong

Division of Paediatric Surgery, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

Correspondence to: Kenneth Kak-Yuen Wong, PhD. Department of Surgery, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. Email: kkywong@hku.hk.

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In this era of minimally invasive surgery, there has been a paradigm shift towards thoracoscopic surgery in the diagnosis and treatment of pulmonary nodules in many centres worldwide, leading to better postoperative outcomes with less pain and better quality of life as compared to traditional open thoracotomy (1). With the widespread use of computed tomography (CT), many of these nodules can now be detected at an earlier stage and with a smaller size (2).

However, the localisation of pulmonary lesions during minimally invasive surgery can be technically demanding, especially for small deep-seated nodules, and traditional tactile sensation can be hindered by the use of these minimal approaches (3). It is generally recommended that localisation should be performed prior to resection for pulmonary nodules <10 mm in diameter or >5 mm from the pleural surface (4). Given that nodules can sometimes be deeply situated and not visible, and CT information is often insufficient to aid in their detection, various other localisation methods have been implemented, including the use of hookwires, microcoils, methylene blue dye injection, and radiotracer labelling (5,6).

Each of these methods has its limitation and risks, for example local trauma and small-lesion inaccuracy in the use of hookwires and difficulty in identifying deep lesions and diffuse spillage in the use of methylene blue dye. Park *et al.* (5) compare hookwire, microcoil and lipiodol localisation methods in a 2017 systematic review and meta-analysis and report similarly successful targeting rates in all three modalities. However, hookwire localisation was found to have a relatively low successful operative field because of dislodgement or migration. Efforts continue to find a convenient, safe and clear localisation method.

Indocyanine green (ICG) is a fluorescent iodide dye and has recently come to attention as a potential solution for this need. It has been extensively used in both adult and paediatric patients for sentinel lymph node mapping, intraoperative solid tumor identification and organ perfusion assessment (7,8). In thoracic surgery, it is a useful aid not only in sentinel lymph node mapping but also in lung mapping, oesophageal conduit vascular perfusion and lung nodule identification (9). Ujiie *et al.* (10) report their initial experience of CT-guided percutaneous ICG injection and near-infrared (NIR) intraoperative localisation of small lung nodules and found it to be safe and feasible. It was proven to be superior to conventional preoperative hookwire localisation, with a lower complication rate, lower pain score and relatively high success rate (11). Our centre had a similar experience with the safe and accurate ICG localisation of a pulmonary nodule measuring 6 mm at a depth of 1.3 cm in a 4-year-old boy, which was amenable to thoracoscopic wedge resection (12).

There are various routes to ICG administration, including CT-guided percutaneous, endobronchial and intravenous injections, and the effectiveness of each has been evaluated in a recently published systematic review and meta-analysis (13). That review reports success rates of

^ ORCID: 0000-0003-2343-2597.

94.3% (IQR: 91.4–100%) and 98.3% (IQR: 94–100%) in in CT-guided and endobronchial approaches, respectively, while intravenous ICG administration demonstrated sensitivity of 88% (95% CI: 59–0.97%) and specificity of 25% (95% CI: 0.04–0.74%). A complication rate of 15.2% was detected in the CT-guided approach with none reported for the endobronchial or intravenous techniques. Notwithstanding the favourable safety and effectiveness of ICG localisation as reported in this review, the identification of pulmonary nodules less than 5 mm in size and more than 20 mm in depth from the pleural surface was deemed challenging when using a conventional ICG camera and the naked eye (14).

In their recent paper, "A novel system for analyzing indocyanine green (ICG) fluorescence spectra enables deeper lung tumor localization during thoracoscopic surgery", Chiba *et al.* (15) report the successful localisation of deep pulmonary lesions using ICG fluorescence and a new spectroscopy system. We congratulate the authors on their well-designed work and for overcoming the current challenges in intraoperative localisation using conventional NIR cameras. The new spectroscopy system captures ICG fluorescence as a wavelength and enables tumour identification at greater depths. Using an ICG-mixed pseudo-tumour in a sponge and porcine lung model, the authors demonstrate the conventional camera's limitations in detecting lesions covered by tissues thicker than 1 cm. The new spectrophotometer, however, was able to detect tumours at a depth of 2–3 cm.

This study adds to the existing evidence on the effectiveness and limitations of pulmonary nodule localisation using ICG fluorescence. From our own experience, interpreting ICG outcomes with the naked eye can be unreliable, especially in deep and small lesions. Other determining factors include the distance between lesion and camera, the difference in fluorescence signal between the lesions and the background, as well as the timing of ICG injection. Previous data has demonstrated optimal timing for assessment to be 24 h after injection, while there have also been reports of strong ICG signals remaining in the lung for up to 6 days (16). The new spectroscopy system appears to surmount these difficulties by capturing and documenting ICG fluorescence objectively as a wavelength instead of relying on searching through the sometimes indistinct green colour by eye. The authors experimented with intervening materials of various densities and thicknesses, thereby yielding interesting and fruitful findings, and this enhances our understanding of factors affecting NIR detection in biological tissue.

While the study is innovative and presents some interesting findings, there are several noteworthy limitations. The pseudo-tumours were 20 mm in size and may not reflect real-world clinical practice where pulmonary nodules requiring localisation can be as small as several millimetres. There is no doubt that the difficulty of localisation is inversely related to the size of the lesion (4). Although the authors control this confounding factor by using tumours of the same size, the choice of dimensions may hinder its application to real-life practice. It may be worthwhile to consider conducting the same experiment with pseudo-tumours of different sizes to delineate its impact on intraoperative localisation.

Moreover, reporting bias may exist among the three surgeons who were responsible for evaluating the images and the spectral system because of their awareness of the nature of the pseudo-tumour being assessed. It should also be emphasised that any animal model has its limitations and cannot be directly transferred to humans. Here, for example, differences in blood flow and background pulmonary problems may affect ICG uptake and detection. The proposed measurement system is intended for intravenous use but may have additional limitations in reflecting real-life situations where uptake and retention through intravenous injection would be less predictable. We nevertheless acknowledge the need to have carried out this pilot feasibility study before applying the approach with human participants.

As most of the existing evidence in case reports, cohort studies, systematic reviews and meta-analyses focuses on the detection of ICG fluorescence using conventional cameras and the naked eye, this study provides new insights into intraoperative localisation in thoracoscopic surgery. In conclusion, this novel spectroscopy system appears to offer solutions to some of the localisation difficulties in respect of deep and small pulmonary nodules. Further analysis and application of the system in clinical settings would be valuable for improving the quality of thoracoscopic surgery.

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