The use of near infra-red fluorescence mapping with indocyanine green in thoracic surgery: an exciting real-world clinical application of an established scientific principle

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The use of near infra-red fluorescence mapping with indocyanine green (ICG) in thoracic surgery for identification of nodules and visualisation of anatomical segmental margins is a contemporary solution to the problem of determining anatomical boundaries in sub-lobar resection. Prior to the publication of the cohort study by Mehta *et al.* (1), the only published evidence of this technique in thoracic surgery was a limited number of case reports (2,3). Whilst these case reports have described and demonstrated how the principle of near infra-red fluorescence mapping with ICG can be applied to pulmonary resections, the study by Mehta *et al.* is the first in the literature aiming to assess the reproducibility and reliability of the technique in routine clinical practice.

ICG is a tricarbocyanine dye which emits light (i.e., fluoresces) when exposed to near-infrared light. Its uses in medicine have been recognised for many years, and indeed ICG has been licensed in the USA for intravenous injection since 1956. Excreted via the liver, whilst the intravascular half-life of ICG is only approximately 3–4 min, its ability to bind readily to proteins means that it remains visible under near infra-red light for up to 60 min when injected into the protein-rich lymphatic system (4). Intra-operative injection (either intravascular or directly into the tissue) of ICG is straightforward and does not significantly extend operative time. ICG is radiation-free and associated with an exceptionally low rate of complications (5). The ever-increasing popularity of minimally-invasive surgery has meant that the quality and availability of endoscopic equipment has continued to improve. Consequently, many cameras used for laparoscopic, thoracoscopic and robotic-assisted surgical procedures are already equipped with infra-red technology as standard, whilst the associated imaging platforms possess the means to display fluorescence imaging in real time, alongside standard images from the camera. These technological advancements mean that ICG fluorescence mapping often does not require any additional specialised equipment beyond that already being used routinely in clinical practice.

A review of the literature demonstrates an exponential increase over the last decade in the number of papers published related to the clinical applications of ICG. Indeed, as recently as 2018 Hackethal *et al.* published a comprehensive review of the use of ICG in clinical practice across a wide number of surgical specialties (4). The use of ICG for sentinel lymph node mapping in breast cancer surgery was first described back in 1999 (6) and multiple studies have since been undertaken investigating its use as an alternative to the more-frequently used Technetium 99 isotope & blue dye combination (7,8). These studies have demonstrated that ICG is safe, reliable and effective with associated benefits in comparison to Technetium including a lack of skin discolouration (associated with injection of blue dye), the absence of radiation protection requirements and reduced overall costs (9). Similar results have been published in cervical and endometrial cancer (10).

A further use of ICG is to assess perfusion of tissue. Anastomotic leak following colorectal resection, which occurs

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in up to 20% of patients, has a high associated rate of morbidity and mortality. Inadequate perfusion of the anastomosed segment is recognised as the key risk factor associated with this potentially catastrophic complication (11). The traditional method to assess perfusion has been that of a subjective visual evaluation, with no robust objective assessment available. The use of ICG fluorescence angiography in this situation has been investigated in a number of studies. These have shown that utilisation of this technique is achievable, and in the majority of studies was associated with a reduction in the incidence of post-operative anastomotic leaks (12,13). However, not all studies demonstrated that benefit (14). Moreover, no formal large-scale multi-centre randomised trials have been undertaken in this area and hence whilst initial results are promising, robust data is lacking.

However, whilst the paper by Hackethal *et al.* purports to be a thorough review of the use of ICG in surgical practice, there is no mention of the use of ICG in thoracic surgery, despite the availability of published work in the literature highlighting a number of potential intra-operative uses of ICG including delineating adjacent pulmonary segments and identifying pulmonary nodules (15). Moreover, additional studies investigating the uses of ICG in thoracic surgery have postulated that the technique could be useful in identifying bullous lesions during minimal-access surgery for pneumothorax, due to the reduced perfusion of bullous tissue in comparison to the surrounding healthy lung tissue (16).

The affinity of ICG for protein-rich lymph means that this technique has also been employed in the identification and management of chylothorax following iatrogenic damage to the thoracic duct. The advantage of ICG over traditional lymphangiography and lymphoscintigraphy is its ability to provide real-time intra-operative imaging, which can facilitate successful thoracic duct ligation (17). A further use for ICG is the identification of pulmonary nodules, particularly those too small to be visualised during minimal-access thoracic surgery, an environment where palpation of nodules is often not possible. A number of different techniques for identification of nodules have previously been trialled, including staining with methylene blue, with variable results. More recently, a number of studies have demonstrated that identification of pulmonary nodules (including sub-centimetre nodules) using ICG is feasible, and not associated with complications such as bleeding and pneumothorax, which are more frequently encountered when employing alternative techniques (18). Indeed, the trial performed by Okusanya *et al.* highlighted that after ICG injection, near infra-red cameras were able to identify a number of nodules which were neither detected intra-operatively by palpation during open surgery nor pre-operatively on CT scanning (18).

Due to the increasing number of sub-centimetre nodules being detected, as a result of the combination of the development of more sophisticated imaging techniques and the introduction of lung cancer screening programmes, there is an increased demand for parenchymal-sparing pulmonary resections over formal lobectomy. The anatomical segmentectomy has found favour in recent times, with evidence suggesting that the oncological outcomes are broadly similar to pulmonary lobectomy for early-stage lung cancer (19) (i.e., tumour less than 2 cm), however results from definitive clinical trials are still pending. An exponential increase in the number of video-assisted thoracoscopic surgery (VATS) procedures being performed has more recently been accompanied by a sharp rise in the number of robotic procedures being undertaken (20,21). As this trend has developed, so has the quality of cameras issued for thoracoscopic surgery, meaning that increasingly complex surgery can now be carried out via a video-assisted or robotic approach, with minimal concerns as to the clarity of the images displayed on-screen.

The delineation of intersegmental planes during a segmentectomy remains a challenge. Too judicious a resection risks losing the parenchymal-sparing benefits of undertaking sub-lobar resection, whilst an anatomically inaccurate resection where not all of the segmental parenchyma is removed carries a significantly increased risk of disease recurrence as a result of incomplete oncological clearance (22,23). Current assessment of the intersegmental plane is limited to subjective visual evaluation, either with or without accompanying inflation of the lung after division of the segmental bronchus. The use of ICG has been proposed as an objective method of improving this assessment.

The study by Mehta *et al.* investigating the feasibility of ICG in the context of minimally-invasive anatomical segmentectomy is currently the only published trial undertaken in this area. Despite the fact that almost 40% of patients recruited did not undergo ICG injection (due to an alternative procedure being performed) their initial results are encouraging, demonstrating that implementation of the technique is safe and reliable. Importantly, they report no technical failures when utilising the ICG, and also no side effects or complications directly attributable to utilisation of ICG. Whilst they demonstrate an increase in resection margins when using ICG, this was not found to be

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statistically significant. Long-term oncological data will also be useful in this group of patients when attempting to assess the long-term implications of this technique.

The use of near infra-red fluorescence mapping with ICG is a well-established technique supported by a large quantity of data published by a number of different surgical specialties over many years. More recently, the potential of utilising this technique in thoracic surgery has been recognised and several possible applications have been postulated, including the delineation of anatomical segmental margins during pulmonary resection. The recent research undertaken in this area by Mehta *et al.* is a welcome addition to the literature, demonstrating for the first time that utilisation of ICG in thoracic surgery is achievable and reproducible. However, whilst their initial results are promising, this cohort study was comprised of a small number of patients and was unable to demonstrate statistical significance when analysing their results. It is apparent that further large-scale randomised trials with a focus on long-term oncological outcomes are required, in order to robustly assess the impact of ICG in this context.

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