Intracorporeal lymph node mapping in colon cancer surgery

FLICC II study

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Conflicts of interest

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Introduction

Surgery is the mainstay of treatment for non-metastatic colon cancer [1]–[3], involving the harvest of lymph nodes *en bloc* with the colonic specimen. However, this approach has been associated with local recurrences in 11-23.5% of curative resections (stages II and III respectively) and these were not affected by adjuvant chemotherapy[4]. Hepatic flexure tumours are particularly problematic [5], as these were more commonly associated with local recurrence [6]. The existence of central lymph node metastases occurs in 1-8% of patients and their presence is associated with a significantly lower survival [7]. It is hypothesized that variation in lymphatic drainage patterns is a contributing factor to both these local recurrences and central lymph node metastasis. Interestingly, survival outcomes have not improved in colon cancer at the same rate as rectal cancer [8].

Complete mesocolic excision (CME) with central vascular ligation (CVL) is a technique that includes a more thorough lymph node harvest [9]. CME has been shown to lead to improvements in disease-free survival [10], but the effects on overall survival remain conflicting [11]. CME has also been shown to be associated with a higher frequency of organ damage, including spleen and superior mesenteric artery and vein injury, as well as sepsis requiring vasopressors and respiratory failure [12]. There is no consensus as to the best lymph node harvest technique in the official guidelines of surgical societies [13].

Current strategies of lymphadenectomy are guided by anatomical landmarks. This has resulted in rates of local recurrences that are suboptimal. Lymphatic mapping aims to determine the channels of lymphatic drainage from the tumour in each patient. The use of fluorophores can allow targeted lymphadenectomy as previously demonstrated [14], without contaminating the field of view under white light. Unfortunately, intraoperative lymphatic mapping has not been standardised in terms of technique and outcomes assessed. We aim to describe the technique that allows intracorporeal targeted lymphatic mapping during resection of colonic tumours based on fluorescent signal.

Methods

Setting

Patients with an indication for elective curative resection of colonic tumours after multidisciplinary team discussion were included. The study occurred at a tertiary centre with all procedures undertaken by a single surgeon (MC). Surgeries happened between October and December 2018. Patients allergic to indocyanine green or iodine or pregnant were excluded.

Technique description

Equipment – for this technique all the following items are required (see box 1).

- Coiled connector
- Butterfly needle (19 - 21 gauge)
- Laparoscopic graspers
- Sodium chloride and syringe
- Indocyanine green
- Near infrared camera

Preparation – Ten milligrams of indocyanine green is diluted into 4mLs of saline (concentration 2.5mg/mL) and is injected into the coiled connector. The total volume of the connector is 3.4 ml so a chaser of 3 ml saline is then added to have the system primed with ICG ready for injection near the tip of the needle. The wings of the butterfly device are shortened with scissors to allow a controlled entry into the abdomen, through the laparoscopic port closest to the site of injection.

Injection – after safe port placement and adequate inspection of the abdominal cavity the colonic cancer is identified. Injection is performed after inspection and before specimen mobilisation, as seen in figure 1. The needle and tubing are advanced through the closest port and enough length is ensured to avoid tension in the needle while manoeuvring it intracorporeally. The needle is carefully inserted subserosally in the periphery of the tumour (NOT in the tumour surface). Ideally 1 mL indocyanine green should be injected into each of 4 points around the tumour. Care should be exercised to avoid spillage of ICG in the abdominal cavity. This will contaminate the field and limit visualisation of lymphatic structures. Spillage can happen before subserosal needle positioning by inadvertent injection, and after needle positioning if the tip crosses the subserosal plane again.

Mapping – after injection the surgery continues, and a near infra-red mode camera is used between 30 and 40 minutes after injection to image the area. The mesenteric limits of resection are examined both proximally and distally to assess for the presence of lymph nodes that are highlighted with fluorescence. Both surfaces of the mesentery are assessed if possible.

Ethical considerations

This technique has been used in the context of the Fluorescence Lymph Node Imaging in Colorectal Cancer Study (FLICC II) study, currently ongoing at University College London Hospital. The study was approved by the London Stanmore Research Ethics Committee, reference 18/LO/0789.

Results

The instructional video (see supplementary file 1) demonstrates the technique used in these cases. The characteristics of the patients can be found in table 1. There is a predominance of right-sided tumours and males.

The individual results of the technique are shown in table 2. The detection rate is currently 80% (4/5). No side effects were noted from the administration of indocyanine green either intraoperatively or at 30 day follow up.

Discussion

Based on previous separate descriptions of lymphatic mapping and our group's own experience, we describe a reproducible technique that can be applied successfully to lymphatic mapping in cases of laparoscopic colon cancer surgery. Both right and left sided tumour drainage can be mapped in this fashion. This report demonstrates that lymphatic mapping is safely achievable by means of an intracorporeal subserosal injection. This study can be measured against a framework for investigation of new technologies and configures an IDEAL stage 2a [15].

Oncological treatment, whether medical or surgical, is becoming more precise with a move away from 'blanket' treatments. In surgical terms, colon cancer resection is variable with no standardised technique particularly when it comes to deciding the amount of mesentery to excise. This results in specimens, and consequently nodal counts, of variable size and number. We still wait to better understand the relevance of higher nodal counts and whether this is related to more accurate staging and thus better use of adjuvant chemotherapy, or indeed whether it is related to improved excision of macroscopic disease. Nonetheless there remains an unmet need to standardise colonic surgery.

Fluorescence-guided surgery is an evolving field that is gradually being adopted across several disciplines to augment cancer resection. ICG, which is the fluorophore described in this report, remains non-specific and there is considerable research being undertaken to develop more targeted probes that can specifically track down cancer tissue. These advances will no doubt help in identifying more central nodes in colon cancer to reduce consequent excision morbidity.

A particular strength of this study is the prospective assessment of the potential impact of lymphatic mapping in the surgical decision making. The fact that no changes occurred may be owed to the small number of patients recruited so far. However, the ultimate goal of fluorescence

guided surgery is to direct surgery in a precise manner and provide a roadmap for appropriate oncological excision. With this technique we aim to map lymph nodes outside the planned resection along the proximal and distal mesenteric resection margins. We also aim to map drainage to the central lymph nodes. If these nodes fluoresce then they are resected beyond the previously planned margin. We are actively recruiting patients and aim to achieve an IDEAL stage 2b by the end of the present study.

Limitations of this technique revolve around the fluorophore which is currently non-specific to cancerous tissue and the limited depth of penetration of the imaging system to excite the dye. In cases of a fatty mesentery, it is not always possible to detect fluorescence as the laser is limited to a 5-10 millimetre penetration. To overcome this limitation the mesentery is examined in both surfaces, increasing the region assessed to a depth of up to 20mm. Furthermore, we are not sure on whether the dye is able to pass through the lymphatics in the presence of lymphovascular invasion where the channels may be blocked with cancer cells.

Conclusions

The technical success and safety of intracorporeal lymphatic mapping with indocyanine green fluorescence in colon cancer surgery have been demonstrated in a select group of patients.

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Figure 1 – Timing of indocyanine green injection for intracorporeal lymph node mapping