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Review

Can intra-operative fluorescence play a significant role in hepatobiliary surgery?

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Abstract

Liver resection remains the cornerstone of curative treatment for hepatocellular carcinoma and colorectal cancer liver metastases. Its success is dependent upon the extent of resection achieved. To this end, intra-operative imaging techniques have been experimented with to aid the surgeon. Fluorescence guided surgery (FGS) utilises the properties of near infrared light emitting molecules to identify malignant tissue, enabling the surgeon to maximise resection of diseased tissue and minimise collateral damage. Data from early trials showed increased superficial lesion detection when using fluorescence to guide liver resection. However, with far greater tissue penetration, intra-operative ultrasound (IOUS) remains the gold-standard intra-operative imaging modality. Subsequent trials have shown that the concomitant use of both FGS and IOUS may increase tumour detection rates intra-operatively. This review provides a comprehensive analysis of the most compelling evidence regarding fluorescence in hepatobiliary surgery and addresses the challenges faced introducing it into common practice.
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Keywords: Fluorescence guided surgery; Liver resection; Hepatocellular carcinoma; Liver metastases

Principles of live fluorescence in oncological surgery

Surgical resection remains the cornerstone of curative treatment for solid tumours. Its success is dependent upon the extent of resection achieved. The level of invasion by malignant tissue is assessed pre-operatively using imaging techniques such as computed tomography (CT) and magnetic resonant imaging (MRI). This allows staging of the disease and provides the surgeon with a blueprint of the local anatomy. Yet the pre-operative assessment often does not tell the whole story. Intra-operatively, the surgeon uses vision and palpation to assess the extent of tumour invasion and resects tissue accordingly. A trade-off occurs between removing malignant tissue and preserving vital structures, the relationship between the two often only becomes apparent during the procedure. Over the last decade, intra-operative imaging techniques have been experimented with to aid the surgeon maximise resection of diseased tissue and minimise collateral damage.

Fluorescence describes the phenomenon by which a molecule absorbs light of a particular wave-length (excitation) and emits it at a longer wave-length (emission).[1] Light within the visible spectrum resides between wave-lengths of 350–740 nm and cannot penetrate tissue. However, near infra-red light (NIR) has wave-lengths between 750 and 1000 nm and is able to penetrate tissue up to 10 mm in depth.[1] To apply this in oncological surgery, a fluorescent marker taken up by malignant tissue is required. Non-specific markers, such as indocyanine-green (ICG) are the workhorses of fluorescence guided surgery (FGS) but specific fluorescent markers, guided by molecular targets are being developed. When malignant tissue (having taken up the fluorescent marker) is exposed to NIR light, it re-emits it. This is detected by a NIR camera system and images are merged with the white light images of the surgical field.[2] The resulting images display the tumour in bright

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lights compared with the surrounding healthy tissue. Not only are structures on the surface highlighted, but those up to 10 mm in depth are also revealed. Theoretically, the advantages of this aiding resection of diseased tissue, whilst preserving healthy structures is evident, the question is whether it translates to improved patient outcomes.

Value of the R0 resection in hepatobiliary malignancy

Hepatocellular Carcinoma (HCC) is a leading cause of cancer related death worldwide. Although only the 6th most common malignancy, it has the second highest mortality, resulting in over 700,000 deaths annually.[3] The highest incidence rates are in China, Japan and throughout Africa, with incidence in Europe relatively low at 6 per 100,000.[4] Liver resection is the first line treatment for patients with localised, resectable tumours in the non-cirrhotic liver, or in selected patients with Child-Pugh A liver cirrhosis.[5] It should be noted that with large tumours, or in the presence of cirrhosis, liver transplantation is often the preferred option. Outcomes of transplant in this setting are favourable, with 5- and 10-year survival rates reaching 62% and 51% respectively.[6]

Tumour free resection margins is vital for good outcomes, with R1 resection having been shown to be the only prognostic indicator precluding >10 years survival.[7] A randomised trial compared survival outcomes of patients with narrow (1 cm) and wide (2 cm) resection margins; the 1-, 2-, 3-, and 5-year overall survival rates for the narrow and the wide margin groups were 92.9%, 83.3%, 70.9%, and 49.1% and 96.5%, 91.8%, 86.9%, and 74.9%, respectively.[8] Resection margin was a significant prognostic indicator for recurrence (OR 0.598), with all 13 recurrences at the transaction margin occurring within the narrow resection group. With careful selection of patients, 3-year and 5-year survival rates for complete, tumour free resection (R0) is 54% and 39% respectively, compared with 23% and 0% for R1-2 resections.[9]

Surgical resection of the liver is also vitally important for the management of colorectal cancer. Colorectal cancer rates have steadily increased in the UK since the late 1970s. In 2013, over 40,000 patients were diagnosed with it, an incidence of over 70 per 100,000.[10] The liver is often the first site of metastasis, with around 20–25% of patients with liver metastases at diagnosis and half of all patients going on to develop them in their lifetime.[11] Unfortunately, survival without treatment is poor and it has become increasingly recognised that surgical resection is the only chance for long-term survival. This has been reflected in the increasing number of resections being performed in the UK, which rose from 1.7% in 1998, to 3.8% in 2004.[12] It is anticipated that 10–20% of patients with liver metastases have surgically resectable disease.[13] This rise in resections is a direct result of the changing beliefs of what is considered resectable. Currently, surgically resectable disease is defined as the ability to perform R0 resection, sparing at least two liver segments with independent inflow, outflow and biliary drainage. The amount of the liver remnant after resection should not be less than 20% and 30% of the total liver volume in normal and cirrhotic patients, respectively.[14] Once surgical management has been decided upon, obtaining R0 resection, whilst preserving healthy tissue is key, with significantly worse outcomes if tumour extends past the resection margin.[15] In both of these scenarios, identification of malignant versus healthy tissue is vital to achieve good outcomes. It was the advances in the use of FGS during assessment of coronary artery bypass grafts and identification of lymph node metastases[16–18] that led surgeons to experiment with fluorescence in liver malignancy.

Fluorescence guided liver resections

Ishizawa et al.[19] published the first report detailing the use of ICG fluorescence to identify liver malignancy during resection. Their investigation commenced as they noted that HCCs fluoresced when performing fluorescence guided intra-operative cholangiography during a previous study.[20] The following prospective study involved 49 patients undergoing resection for liver malignancy (37 HCC and 12 colorectal cancer liver metastases (CRLM)). All of the pathologically confirmed HCCs and CRLMs exhibited fluorescence when examined after resection. Intra-operatively, fluorescence imaging identified 21 of the 41 (51%) of the HCCs examined and all of the CRLM present. No tumours at a depth greater than 8 mm were identified. This is perhaps the most significant finding and is predictable as near-infrared (NIR) light penetrates human tissue to depths of 5–10 mm.[21] In one patient with HCC, fluorescence imaging of the specimen identified a large volume of residual malignancy, not identified by examination which required further resection. ICG is excreted by hepatocytes into the bile canaliculi. It was surmised that liver malignancy, by disturbing biliary drainage, caused stasis and impaired excretion of ICG. As such, the malignancy fluoresced, whereas healthy tissue, having excreted ICG prior to the operation, does not.

These results were echoed by other studies published at the time. Gotoh et al.[22] reported the results of a similar study involving 10 patients with HCCs. Their case series contained 4 malignant lesions first identified by fluorescence. Ishizawa et al. continued their work investigating the prospects of ICG FGS, publishing works regarding delineating the biliary tree and liver segments using ICG. In 2014 the Tokyo based team revealed the first use of FGS during laparoscopic hepatectomy.[23] NIR fluorescence identified 75% of HCCs and 69% of liver metastases in 17 patients.

In the same year, Inoue et al.,[24] published their use of 5-Aminolevulinic acid (5-ALA); a new fluorescent agent in Hepatobiliary surgery. Their aim was to establish whether 5-ALA fluorescence was advantageous as an adjunct to

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