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The future of tumour-specific fluorescence-guided surgery for pancreatic cancer

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A crucial issue in the surgical treatment of patients with pancreatic ductal adenocarcinoma is the absence of direct, real-time, intraoperative visualisation of the lesion and its metastases. An unacceptably high number of surgeries with curative intent for localised pancreatic ductal adenocarcinoma result in early locoregional recurrence, suggesting a weakness in our ability to completely remove the tumour at its resection bed and to recognise radiographically occult metastatic disease. There is a need for an agent to enhance the ability of surgeons to assess the tumour and metastases (if present), directly and in real-time. The ideal agent should be safe and cost-effective, with rapid pharmacokinetics and a high sensitivity and specificity to the tumour, lymph nodes, and metastases while sparing non-cancerous tissue.[1,2]

Contrast enhancement using near-infrared fluorescent dyes can provide surgeons with additional information. Indocyanine green is a near-infrared dye used in perfusion assessment, but it has been studied for its ability to preferentially accumulate in tumours due to disorganised tumour neovaculature, impaired lymphatic drainage, and increased permeability. This is called the enhanced permeability and retention effect. Indocyanine green was used for fluorescence-guided surgery for pancreatic ductal adenocarcinoma in an initial cohort of 20 patients.[3] However, indocyanine green is non-specific; moreover, it would be desirable to link the fluorophore to a molecule that binds to the tumour directly. Probes evaluated for tumour-specificity are commonly antibodies, but fragmented antibodies, single-domain antibodies (nanobodies), peptides, and antibody mimetics are also under consideration.[4]

Only two previous clinical trials of tumour-specific fluorescent antibodies for fluorescence-guided surgery for pancreatic cancer exist. The first study assessed cetuximab, a chimeric anti-EGFR antibody linked to IRDye800CW (NCT02736578). The trial was stopped because of adverse infusion reactions. The second study,[5] a phase 1 trial

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of 12 patients undergoing surgery for pancreatic ductal adenocarcinoma, used a chimeric antihuman carcinoembryonic antigen antibody linked to a 700 nm fluorophore (NCT02973672). Carcinoembryonic antigen is overexpressed in 71–98% of pancreatic ductal adenocarcinoma.[6] In this study, the fluorescent anticarcinoembryonic antigen antibody (SGM-101) showed safety and efficacy.

The cell-surface marker EGFR is a rational target for tumour-specific intraoperative fluorescence imaging because it is overexpressed in up to 69% of patients with pancreatic ductal adenocarcinoma.[7] In the study by Lu and colleagues[7] in *The Lancet Gastroenterology & Hepatology*, the authors used a humanised anti-EGFR antibody, panitumumab, linked to an 800 nm fluorophore, IRDye800CW. They report the results of their phase 1 clinical trial of 11 patients who received 25 mg, 50 mg, or 75 mg of panitumumab-IRdye800CW, 2–5 days before surgery. They found that the molecule was safe, with four minor reactions related to the study drug (one grade 2 adverse event and three grade 1 adverse events). The pancreatic tumour was detectable in all dose cohorts. Fluorescence-guided surgery with panitumumab-IRDye800CW was feasible in both an open and laparoscopic setting using existing 800 nm imaging devices for indocyanine green imaging (Novadaq Pinpoint and Spy-PHI [Novadaq, Burnaby, BC, Canada]). Mean fluorescence intensity increased linearly and the tumour-to-background ratio ranged from three to four.

The authors are to be commended for advancing tumour-specific fluorescence-guided surgery using a rational design, with an antibody widely available for therapeutic use, and imaging devices that are already present in operating rooms. However, the study does have some limitations. EGFR expression can be increased in pancreatitis, but Tummers and colleagues[8] showed in their work with cetuximab-IRDye800CW in patients with pancreatic ductal adenocarcinoma that there was a statistically significant difference in fluorescence intensity between tissue with pancreatitis and pancreatic ductal adenocarcinoma.[8] Of note, five of the ten patients in this cohort received neoadjuvant therapy with a fluorescence signal present at the tumour.[8] Lu and colleagues[7] did not comment on whether neoadjuvant therapy affects the fluorescence signal because there is a potential for antigenic shift with pretreatment.[8] More work is needed in this setting.

The work by Lu and colleagues[7] and Hoogstins and colleagues[5] heralds the beginning of a new era of direct, tumour-specific fluorescence-guided surgery. As more agents are tested in clinical trials, more information will be needed to determine the optimal fluorescence signal for navigation. A wide array of factors can affect the overall image at the time of surgery. Comparing pharmacokinetics across a wide combination of probes and fluorophores is difficult. Serum shedding of tumour antigen with serum sequestration of fluorescent probes and differential expression of the antigen in the setting of neoadjuvant therapy can further complicate the issue. The sensitivity of imaging devices can additionally affect detection. Acceptable signal thresholds for molecule and imaging devices need to be established. Current preclinical studies with clinically relevant models—such as patient-derived orthotopic xenografts in nude mouse models, which better recapitulate human patterns of metastases compared with subcutaneous mouse models—suggest a bright future for tumour-targeted fluorescence-guided surgery.[9,10]

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Although tumour-specific fluorescence-guided surgery can never replace clinical judgment, this technology has the potential to greatly enhance intraoperative decision making, increase the likelihood of complete surgical resection, and potentially affect patient outcomes. More information will be forthcoming as evidence accumulates and the field of tumour-specific fluorescence-guided surgery matures.

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