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ScienceDirect

EJSO the Journal of Cancer Surgery

EJSO xx (2016) 1–7 www.ejso.com

Intraoperative Near-Infrared Fluorescence Imaging using indocyanine green in colorectal carcinomatosis surgery: Proof of concept

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Accepted 4 June 2016
Available online ■ ■ ■

Abstract

Purposes: This study assesses the value of using Intraoperative Near Infrared Fluorescence Imaging and Indocyanine green to detect colorectal carcinomatosis during oncological surgery. In colorectal carcinomatosis cancer, two of the most important prognostic factors are completeness of staging and completeness of cytoreductive surgery. Presently, intraoperative assessment of tumoral margins relies on palpation and visual inspection.

The recent introduction of Near Infrared fluorescence image guidance provides new opportunities for surgical roles, particularly in cancer surgery.

Methods: The study was a non-randomized, monocentric, pilot "*ex vivo*" blinded clinical trial validated by the ethical committee of University Hospital of Saint Etienne.

Ten patients with colorectal carcinomatosis cancer scheduled for cytoreductive surgery were included. Patients received 0.25 mg/kg of Indocyanine green intravenously 24 h before surgery. A Near Infrared camera was used to detect "*ex-vivo*" fluorescent lesions.

Results: There was no surgical mortality. Each analysis was done blindly. In a total of 88 lesions analyzed, 58 were classified by a pathologist as cancerous and 30 as non-cancerous. Among the 58 cancerous lesions, 42 were correctly classified by the Intraoperative Near-Infrared camera (sensitivity of 72.4%). Among the 30 non-cancerous lesions, 18 were correctly classified by the Intraoperative Near-Infrared camera (specificity of 60.0%).

Conclusions: Near Infrared fluorescence imaging is a promising technique for intraoperative tumor identification. It could help the surgeon to determine resection margins and reduce the risk of locoregional recurrence.

Keywords: Colorectal peritoneal carcinomatosis; Indocyanine green; Intraoperative Near-Infrared Imaging Fluorescence System; Surgery

Introduction

Today, peritoneal colorectal carcinomatosis is considered a "regional stage" of metastatic disease. Tumor implantation and growth may lead to invasion of any organ or structure that is covered by peritoneum. This peritoneal dissemination can occur in 30–40% of patients.[1,2] The natural progression of colorectal PC is always fatal, with a median survival rate of 6 months.[3] However, since the early 1990s, several teams have conducted phase I–II studies to assess the combination of intraperitoneal chemotherapy with hyperthermia (HIPEC) and cytoreductive surgery (CRS) for treating this pathology. This combined treatment with pre and postoperative systemic chemotherapy provides a 5-year survival of 30%–48%.[4–8]

The diagnosis of PC in the initial tumor mass is an important prognostic factor of the disease itself. Curability is higher for limited carcinomatosis; it is carefully removed

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http://dx.doi.org/10.1016/j.ejso.2016.06.389

Please cite this article in press as: Barabino G, et al., Intraoperative Near-Infrared Fluorescence Imaging using indocyanine green in colorectal carcinomatosis surgery: Proof of concept, Eur J Surg Oncol (2016), http://dx.doi.org/10.1016/j.ejso.2016.06.389

by the surgeon with wide peri-tumoral tissue. Bulky carcinomatosis requires complex visceral peritoneum resections that leave many microscopic and macroscopic residues. The classical concept of R0 resection (microscopically margin-negative resection)[9] is no longer appropriate in the context of peritoneal surgery and was replaced by CC-0 (macroscopically complete cytoreduction).[10] Moreover, the tumor volume is closely related to the potential for metastatic disease, which determines the progression-free survival rate. The decrease in peritoneal tumor mass is therefore a major goal of the therapeutic strategy for this condition.

The diagnosis of PC of colorectal origin is very difficult and can be done preoperatively or intraoperatively. Preoperatively, Computed Tomography (CT) and Positron Emission Tomography (PET) scans yielded the best results and are useful tools for selecting candidates for peritonectomy and HIPEC.[11] Dromain et al.[12] showed that both examinations systematically underestimate the extent of illness. Thus, intraoperative evaluation of PC is of paramount importance.

The "Peritoneal Cancer Index" (PCI) of Sugarbaker is a tool for precise quantitative assessment of carcinomatosis of gastrointestinal tumor origin. It is based on the distribution of tumor nodules and their dimensions.[10,13] The peritoneal cavity is divided into nine regions and four dials for the small intestine, 13 regions in total. The PCI is calculated by assigning a score, ranging from 0 to 3, to each of the 13 regions and summing them, so the PCI can range from 1 to 39. The PCI has proven to have a significant influence on survival.[5]

The best outcomes in surgery are associated with successful debulking surgery (downstaging procedure), which allows a macroscopically complete cytoreduction.[14]

The challenge for surgeons is to carry out the most complete surgical resection, requiring them to find the maximum number of cancerous lesions, some of which are not visible. Current methods for detecting tumor lesions intraoperatively involve palpation and visual inspection. Visual inspection is difficult because of poor tissue contrast and spatial resolution. There is also no way to detect non-palpable lesions. Recently, fluorescence-based image-guided surgery (IGS) has shown great potential to intraoperatively detect tumors. Near infrared (NIR) imaging in combination with NIR fluorescent contrast agents utilizes 700–900 nm wavelengths and is of particular interest because of the minimal autofluorescence from native tissue in this spectrum. This allows a high signal-to-background ratio. Furthermore, excitation at these wavelengths has excellent vascular penetration, providing a means to detect contrast material at depths of several millimeters within a tissue.[15] Several NIR IGS systems are already commercially available or have been examined in clinical settings.[16,17] Clinically, fluorescence-based IGS has been used to map sentinel lymph nodes of tumors arising from the breast, skin, gastrointestinal tract, lung, and other sites.[18–20] Furthermore, this technique has been used for intraoperative imaging of solid tumors using both non-specific agents (e.g., in hepatobiliary tumors and breast cancer)[18] and tumor-specific agents (e.g., in ovarian cancer).[21]

Several studies have utilized the FDA-approved exogenous NIR fluorophore, indocyanine green (ICG), to detect human tumor xenografts in mice and spontaneous tumors in companion canines.[22] These observation led to the characterization of a process of diffusion, the "enhanced permeability and retention" (EPR) effect.[23] This effect illustrates the affinity of ICG towards tumoral and near-tumoral tissue due to tumor neovascularization, which is known to result in a poor architecture with an abnormal basement membrane and fissures between endothelial cells. Because of this, macromolecules are able to permeate through the vessels and into tumor tissue, where they are retained due to impaired lymph drainage.[23] ICG is not a macromolecule but behaves like one after binding to serum proteins. This, combined with the rapid clearance from the circulation, makes ICG a potentially good probe for NIR fluorescence imaging of solid tumors.[24]

ICG has already been used as a marker for colorectal cancer and liver metastases with good sensitivity and specificity.[16,18,19] However its potential use in intraoperative detection of peritoneal carcinomatosis should be further explored.

Thus, we performed a prospective, non-randomized, blind single-center study evaluating the "*ex vivo*" detection of peritoneal carcinomatosis with fluorescence (NIR probe) compared to histological analysis in patients with peritoneal carcinomatosis of colorectal origin after intravenous injection of 0.25 mg/kg ICG, 24 h before surgery.[25,26]

Our secondary objective was a blinded experiment to compare the PCI index obtained with fluorescence with that obtained without fluorescence at the time of surgery.

Materials and methods

Study design

The study was a non-randomized, single center, pilot "*ex vivo*" blinded clinical trial (Number Clinical Trial 01982227) to evaluate the performance of fluorescence (NIR probe) in the detection of malignant cells from surgical specimens of peritoneal colorectal carcinomatosis compared to histological analysis. It was validated by the ethical committee of University Hospital of Saint Etienne (130024A-2012).

Patient eligibility

From April 2013 to September 2014, eligible patients were registered for participation at Saint Etienne University Hospital.

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