Near infrared imaging in colorectal surgery

Ris, Frédéric

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG
Hôpitaux Universitaires de Genève

Clinical Medicine Section

Department of Surgery

Service of Visceral and Transplantation Surgery

" NEAR INFRARED IMAGING IN COLORECTAL SURGERY "

Thesis submitted to the Medical School of

the University of Geneva

for the degree of Privat-Docent

by

Dr. med. Frederic RIS

Geneva

2014

TABLE OF CONTENT

1. Abstract

Introduction: Near infrared imaging technologies are developing quickly. The injection of a dye with the use of a near infrared scope allow to identify structures that are not visible on the regular spectrum. We describe in this work the main applications for colorectal surgery, one for the study of the microvacularisation of the anastomosis and the second on lymphnode mapping for colorectal cancer.

Method

Indocyanine green(IDC) is the dye used for this application, it is very safe. A stimulation of the dye after its injection by a near infrared light allows to see it with the use of the appropriate scope. Three scope are currently used for this application in minimally invasive surgery, the Pinpoint (Novadaq), the Olympus prototype and the D-Light (Storz) .

Results:

The use of this technology allowed to see the microvascularisation of an anastomosis in real time, this could potentially lead to a decrease in leak rate or anastomotic trouble.

The use of the NIR technology is at the early beginning for lymphnode mapping, but seems very promising if we can prove the concept of sentinel lymphnode in laparoscopic colorectal surgery. Early results show the possibility to identify primary lymphnodes in the lymphatic route in real time, shortly after injection.

Conclusion:

The use of IDC and the near infrared technology allows to increase reality in a way that was never possible before. Both indications (microcirculation assessment and lymphnode mapping) are relevant from a clinical point of view and should therefore be further investigated.

2. Introduction :

Near infrared imaging technologies are developing quickly. Injection of indocyanine green associated with a near infrared scope allow to identify structures that are not visible on the regular spectrum, increasing the perception of reality. However application in colorectal surgery has so far been relatively slow. We describe in this work the main applications for colorectal surgery, one for the study of the microvascularisation of the anastomosis and the second on lymphnode mapping for colorectal cancer.

This work is at his beginning and a vast field of development is possible in the near future. The Geneva University hospitals and school of Medicine are one the few main investigators of a multicentric European project with the University Hospitals of Oxford (Prof. N. Mortensen) and Dublin (Prof. R. Cahill), due to the patient recruitment and to a unique expertise in Europe.

Current problems in colorectal surgery:

Colorectal surgery is one of the most common surgeries performed among the world with more than 600'000 procedure each year in the United states, more than a million in the world. Minimally invasive colorectal resection is becoming the standard of care in developed countries.

Anastomotic healing and factors inducing anastomotic leak:

One of the major complications for colorectal surgery is the anastomotic leak. This is a devastating complication of colorectal surgery for the patient, surgeon and healthcare provider. Average leak rate range between 1-3% for ileo-colic anastomosis but can go up to 20% for a low colorectal anastomosis [1].

The process for anastomotic healing is divided into three steps:

a. Inflammation phase (0-6 days)
b. Proliferation phase (3-10 days)
c. Healing phase (6-15 days)

During the initial inflammation process, there is an intense cell proliferation with secretion of a new extracellular matrix. The collagen I to collagen III ratio will change during the healing process, to end up with less than 10% of collagen III at the end of the process. Neovascularisation starts around the 4th post-operative day and will allow a complete healing of the anastomosis. While administration of vascular endothelial growth factors (VEGF) decrease the anastomosis leak rate [2], it is mandatory to have a good perfusion of the anastomosis to allow a proper healing [3]. Animal studies show that a stapled anastomosis will heal the same way as a simple enterotomy if the microvascularisation is well preserved [4].

Various factors have been shown to be responsible for anastomotic leaks, some are due to the patient comorbidities like age, gender (male), smocking habits, diabetes, nutritional status, use of steroids, site and/or size of the disease. While intraoperative technical factors count for other factors involved, like blood loss (or transfusion), type of resection, use of a drain, number of stapler fired, peri-anastomotic hematoma, abscess or anastomotic tension at the time of confection of the anastomosis [5].

However it seems to be a multifactorial event, there is very few factors among which it is possible to act to prevent a leak. The vascularisation assessment during the surgery is one of them.

There are currently a large number of tools developed to try to address this question, but none was converted into a daily clinical practice. The ideal tool should be available in laparoscopic surgery, easy to use, accurate with a minimum of false-negative results and, more importantly, few or no false positives. The ideal technique should be as objective and reproducible as possible and finally cost effective.

The Goligher paradigm of pink vascularised tissue as the only assessment of the perfusion of the tissue cannot be used anymore, we need harder data.

Among the different techniques described in the past, none gather all the necessary qualities needed, as described in table 1.

Table 1: Current techniques to assess the blood supply of an anastomosis

Technique	Laparoscopic surgery	Easy to use	Accurate	Objective	Reproducible	Cost effective
Color of the bowel	+	+	- -	-	+/-	$
Marginal blood vessels	+	+	-	-	+/-	$
On table angiography	+	--	+	+	+	$$$
Pulse oxymetry	-	+	- -	+	+	$
Polarographic Oxygen tension	-	-	+	-	+	$$
Doppler	-	+	+/-	+/-	+/-	$
Intravital microscopy	-	--	+/-	+/-	+/-	$$$ no human use
Spectrophotometry	-	-	+	+	+	$$
Bowel wall contractility	-	-	+/-	+	+/-	$$$
pH measurement	-	--	+/-	+	+	$$
Microdialysis	-	-	+/-	+/-	+/-	$$
Fluorosceine fluorescence	+/-	-	+/-	+	-	$$
Laser Doppler flowmetry	+/-	-	+/-	+/-	+/-	$$
Near infrared	+	+	+	+	+	$

Near infrared technology with the use of indocyanine green seems to gather all those characteristics. It is possible to use in laparoscopic surgery, it is easy to use, reproducible, accurate, objective and once the near infrared laparoscope is bought, the cost of a single procedure is low.

Once we can assess the microvascularisation of an anastomosis in real time, it will be feasible to alter the course of surgery and to prevent the development of a leak.

Hyper-extensive surgery or tailored surgery, the concept of lymphnode mapping:

Currently, the same surgical operation (excision of the primary lesion and all draining lymph nodes) is proposed for all patients with colorectal cancer. With the advent of screening however, more and more patients are being detected with early stage disease (that is a cancer confined to the bowel wall without involvement of any lymph nodes). As there is no treatment benefit for these patients from having such normal lymph nodes taken out, they are currently having a bigger operation than is actually required for cure. This exposes them to additional risks of injury during their operation and necessitates a longer hospital stay than would otherwise be the case. Indeed, a small group of patients (c. 10% of the total) are in fact currently undergoing a full operation when their cancer is in fact potentially removable (and curable) by an endoscopic procedure that would not entail removal of any length of bowel and that could be performed potentially as a day-case procedure.

Recent literature advocate on different philosophy of care between hyper-extensive surgery and limited tailored surgery, in fact the Hohenberger group propose for philosophy of care to perform hyper-extensive dissection to have the maximal number of lymphnodes [6], aiming with that to cure the patient of all potential invaded lymphnodes, especially for right hemicolectomies. Unfortunately, there is scarce evidence for this approach with only a low number of retrospective monocentric studies from the same centres showing a better survival rate, but a much higher complication and mortality rate. Despite very low level of evidence[7], the colorectal community start to be polarized on that question. Detractors argue that 97.5% of all the lymphnodes are found within 5 cm around the tumour [8] and that an hyperextensive

surgery may be useless, especially with an aberrant lymphatic drainage in up to 22% of the cases [9].

In this situation a tailored limited resection could be sufficient if we can correctly identify the invaded lymphnode at the time of resection. This is even worse in rectal surgery because of the risk for the patient to need a stoma bag (either temporarily of permanently) and to functional impairment due to the extent of surgery. New tools are needed for real time lymphnode assessment in colon and rectal surgery.

The concept of post operative / ex vivo lymphnode mapping has also been used to decrease downstaging of the tumors, with an increase in lymphnodes yield and therefore a better staging using those techniques.

Safety of indocyanine green (IDC):

Indocyanine green is a water-soluble, tricarbocyanine compound dye that absorbs NIR light in the region of 800–810 nm (peak spectral absorption = 806 nm) and emits it at 830 nm.

The safety profile of indocyanine green is a very good and it is a relatively old dye used routinely in cardiac surgery, hepatic function assessment and ophthalmology. For its intravenous use it is recognised by the FDA for determining cardiac output, hepatic function and liver blood flow, and for ophthalmic angiography. Median half life is of 5 min and is then excreted by the liver within 15 min through the bile duct. When injected intravenously, the ICG rapidly and extensively binds to plasma proteins and so is confined to the intravascular compartment with minimal leakage into the interstitium under normal conditions. When injected subsersoally or submucosally in the intestine it is taken up by the lymphatic spaces and efferent channels and travels (again bound to protein) to lymph nodes where it deposits in macrophages. This property makes it an ideal agent for the acquisition of high quality images of both the circulatory and lymphatic vasculature.

The primary adverse event/reaction possible with IDC is the risk of anaphylactic reaction (0.003%). A recent report has suggested the efficacy of indocyanine green may be improved by its solubilisation in HSA-, use of this agent will therefore also be associated with a risk of anaphylaxis of 0.099%.

For microvascularisation assessment, IDC is injected intravenously, and for lymphnode mapping it is performed by a peri-tumoral injection at two distinct points. The total amount of injected IDC is much lower than many studies (concentration of 2.5mg/ml, and injection of 3ml for LN mapping and 3.5ml iv for vascularisation assessment (8.75 mg once), while comparing for example with injection for liver function of at least 25mg in a single shot. The maximal non-toxic described dose is of 2.0mg/kg/day, which would be of 140mg for a 70kgs man.

Near infrared (NIR) principles and available laparoscopic devices:

Actually there is 3 main Near infrared devices possible to use, the Pinpoint scope (Novadaq), the Olympus prototype and the D-Light Laparoscope from Carl Storz. The Imaging Systems are installed after biomedical engineering approves the device for installation. The Pinpoint system is being CE labelled after FDA approval, the Storz system and the Olympus system (prototype) are CE labelled. The first article describes the available systems, also we only briefly speak of the Striker which we never used.

The principles of NIR detection is to emit at a defined spectrum (806nm) that will be reemited after IDC injection to a different spectrum (830nm) (Figures 1 and 2). This will be seen in near infrared spectrum and shown on a screen.

Figure 1

Light spectrum of visible and invisible light

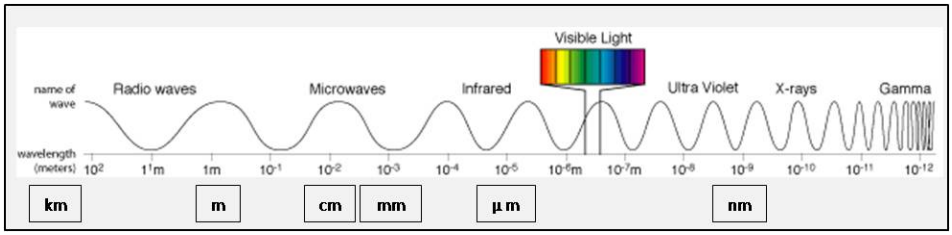
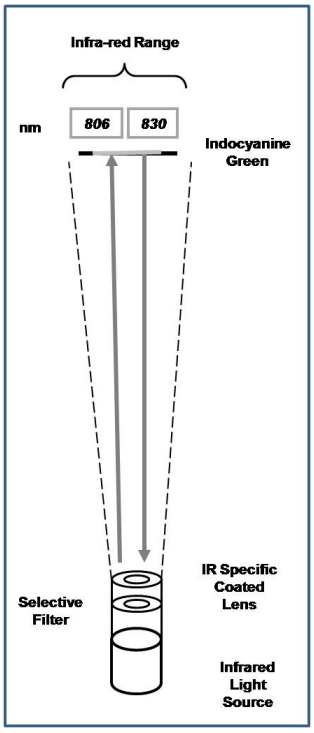


Figure 2

Principles of NIR light re-emission



1.Pinpoint Scope System, Novadaq Corporation.

Device generic name: Pinpoint scope System

Device trade name: Pinpoint scope Imaging System

The Pinpoint scope Imaging System is based on a cleared/approved medical device , the SPY scope, which is commercially available in Canada, Japan, Europe and the US and used as an open system. Initially the SPY system was developed for use in coronary artery bypass graft (CABG) procedures. SPY allows cardiac surgeons to visually assess bypass graft quality and patency in real-time while the patient is still in the operating room. Surgeons are able to check the quality of the procedure and revise, re-do or perform additional procedures as necessary as dictated by the ICG angiogram. The SPY system has subsequently been cleared by the FDA for use in cardiovascular procedures (e.g. peripheral bypass, aortic aneurysms etc), plastic and reconstructive microsurgery and organ transplantation.

The SPY Intraoperative Imaging System has been developed for open surgical procedures using ICG. Intraoperative images are acquired during the first pass of a bolus of ICG through the area of interest. The SPY system employed in open surgical procedures makes use of an 806 nm laser, projected through optics to illuminate an area of 7.5 x 7.5 cm, to cause the ICG to fluoresce. The fluorescence images are captured by a CCD (charge coupled device) video camera, sensitive in the NIR and equipped with the appropriate optical filters to block transmission of the laser light while efficiently passing the fluorescence light. These components are housed in an imaging head that is positioned 30 cm (10-12 inches) above the field of view and is attached by means of an articulating arm to a cart containing the electronic peripherals. The SPY system has been the subject of numerous peer reviewed publications demonstrating its safety and efficacy [10, 11]

The SPY system is currently being used in the Oxford University Hospitals by Professor David Taggart, Department of Cardiothoracic Surgery to assess the function of bypass grafts during coronary artery bypass graft surgery.

The laparoscopic Pinpoint is the laparoscopic declination of the open SPY scope, it is a NIR imaging

system that we can use in laparoscopic surgery. It consists of :

a) An endoscopic light source that provides illumination for visible light imaging and NIR fluorescence excitation to the endoscope via a flexible light guide,
b) Rigid endoscopes optimized for illuminating the field of view and transmitting images in the visible and NIR spectrum, and
c) A high definition (HD) endoscopic camera system connected to the endoscope eyepiece and acquiring high resolution visible and NIR fluorescence images.

As with other endoscopic imaging systems, the device is compatible with HD video display, recording and printing devices commonly used in endoscopy and surgical suites.

The operator can select the mode of operation of the device by means of a footswitch control.

In visible light imaging mode (VIS mode), the device operates as a conventional endoscopic imaging system and provides illumination for and image acquisition of a color HD image in the area of interest. The color HD image is displayed on one or more color video monitors and may be recorded or printed on appropriate video output devices.

In visible light-NIR fluorescence mode (VIS-NIR mode), the device operates to excite and image NIR fluorescence of an ICG contrast agent while simultaneously providing illumination and image acquisition of the visible light HD image. The operator has the choice to display the NIR image information on the color video monitor in various ways. In one display mode, the NIR image acquired by the imaging system is displayed as a separate Picture-in-Picture image next to the visible light HD image on the color video monitor. Alternatively, by means of footswitch control, the operator may select to display the NIR fluorescence by combining it with the visible light HD image such that the NIR fluorescence is displayed as a contrasting color within the visible light HD image. Other NIR image display options are also available, but the visible light image is provided in all display modes. All other features and operations of the device are similar to those found in conventional endoscopic light source and video camera systems.Specifically:

a) The brightness of the image adjusts automatically during use in response to light requirements.
b) Colour fidelity is maintained by means of a white balance function.

c) The light source has a standby feature that minimizes the light output and enables convenient decoupling of the endoscope light guide when exchanging endoscopes.

The Pinpoint Scope has recently received clearance from the United States Food and Drug Administration and is now commercially available in the United States.

Endoscopes are reprocessed according to standard reprocessing protocols, and the device has been designed and tested to meet all applicable safety standards, including electro-medical (UL 2601) and EMC safety standards.

Non-clinical Studies

The functionality of the Pinpoint scope and a preliminary prototype of the system has been tested in large animal models (dogs and pigs). In the course of these studies, undertaken at the University of Rochester Medical Center, Strong Memorial Hospital (URMC SMH), Rochester, NY, USA and at the laboratories of the National Research Council of Canada in Winnipeg, Manitoba, Canada the system was shown to be capable of imaging the biliary tree, lymphatics and lymph nodes in addition to the vascular applications previously explored with the open SPY system.

Previous Human Experience

Novadaq.has undertaken several studies aimed at demonstrating the safety and effectiveness of the Pinpoint Intraoperative Imaging System leading to its approval for commercialization and 510(k) clearance in the US. In addition, clinical studies undertaken at the URMC SMH have demonstrated the utility of the pinpoint system in delineating tumor margins during partial nephrectomies. FDA clearance for this latter indication has not been sought yet but rather will be pursued following acquisition of data using the endoscopic version of the imaging system..

To date, it is estimated that over 10,000 patients worldwide have been imaged with the open SPY System in various surgeries.

2. Laparoscopic Near-Infrared Fluorescence Imaging System, Olympus Corporation

Device generic name: Laparoscopic Near-Infrared Fluorescence Imaging System

Device trade name: Laparoscopic Near-Infrared Fluorescence Imaging System

The Laparoscopic Near-Infrared Fluorescence Imaging System is a cleared, CE-approved medical prototype device manufacturer by Olympus Corporation, Tokyo, Japan and supplied for the purposes of the NIR project via Olympus UK. It represents a modification of the standard Olympus Visceral Laparoscopic system that is already widely in use in the UK, Europe, Asia and the US and indeed is already installed in several theatres and endoscopy suites in the Oxford University Hospitals (ORH). In short, the Narrow Band Imaging capability of the standard laparoscopic system has been disabled and replaced by specific facility for Near-Infared Imaging capability. This specific system has been developed for laparoscopic and endoscopic surgical procedures that make use of indocyanine green (ICG).

The system makes use of a near-infrared xenon light source (specifically tuned to correspond to the fluorescent excitation properties of ICG) that is projected through optics to illuminate a specific area of tissue in order to cause the ICG to fluoresce. The fluorescence images are captured by a CCD (charge coupled device) video camera, sensitive in the NIR and equipped with the appropriate optical lenses and filters to block transmission of the laser light while efficiently passing the fluorescence light thereby ensuring optimal light selection. These components are housed in an imaging head that is positioned in the camera head. This laparoscopic system has been the subject of numerous studies and tests demonstrating its safety and efficacy in human subjects.

The laparoscopic/endoscopic scope Olympus IREE imaging system consists therefore of:

a) An endoscopic light source that provides illumination for visible light imaging and NIR fluorescence excitation to the endoscope via a flexible light guide,

b) Rigid endoscopes optimized for illuminating the field of view and transmitting images in the visible and NIR spectrum

c) A standard definition endoscopic camera system connected to the endoscope eyepiece and acquiring high resolution visible and NIR fluorescence images.

As with other endoscopic imaging systems, the device is compatible with video display, recording and printing devices commonly used in endoscopy and surgical suites.

The operator can select the mode of operation of the device by means of a button control on the camera head or an assistant can effect operation on the stack console. In visible light imaging mode (VIS mode), the device operates as a conventional endoscopic imaging system and provides illumination for and image acquisition of a color image in the area of interest. The color HD image is displayed on one or more color video monitors and may be recorded or printed on appropriate video output devices. In NIR fluorescence mode the device operates to excite and image NIR fluorescence of an ICG contrast agent. The operator has the choice to display the NIR image information on the video monitor as an alternate to the conventional optical view.

All other features and operations of the device are similar to those found in conventional endoscopic light source and video camera systems. Specifically:

a) The brightness of the image adjusts automatically during use in response to light requirements.

b) Colour fidelity is maintained by means of a white balance function.

c) The light source has a standby feature that minimizes the light output and enables convenient decoupling of the endoscope light guide when exchanging endoscopes.

Endoscopes are reprocessed according to standard reprocessing protocols, and the device has been

designed and tested to meet all applicable safety standards, including electro-medical (UL 2601) and EMC safety standards. The camera is sterilisable in conventional manners and methods while the light cable sterility is maintained by means of sterile sheathing as is standard for laparoscopic and endoscopic cabling.

Non-Clinical and Clinical Studies

The functionality of the IREE scope and a preliminary prototype of the system has been tested in large animal models. Olympus has undertaken several studies aimed at demonstrating the safety and effectiveness of the IREE Imaging System leading to its approval for certification and commercialization.

3. D-Light Laparoscope from Carl Storz

Device generic name: D-Light Laparoscope Laparoscopic Near-Infrared Fluorescence Imaging System

Device trade name: D-Light Laparoscope

The D-Light Laparoscope is a cleared, CE-approved medical prototype device manufacturer by Storz Corporation, Germany. It represents a modification of the standard Storz Laparoscopic system that is already widely in use in the Switzerland and especially in our unit, Europe, Asia and the US and indeed is already installed in several theatres. In short, the Narrow Band Imaging capability of the standard laparoscopic system has been disabled and replaced by specific facility for Near-Infared Imaging capability. This specific system has been developed for laparoscopic surgical procedures that make use of indocyanine green (ICG).

The system makes use of a near-infrared xenon light source (specifically tuned to correspond to the fluorescent excitation properties of ICG) that is projected through optics to illuminate a specific area of tissue in order to cause the ICG to fluoresce. The fluorescence images are captured by a CCD (charge coupled device) video camera, sensitive in the NIR and equipped with the appropriate optical lenses and filters to block transmission of the laser light while efficiently passing the fluorescence light thereby ensuring optimal light selection. These components are housed in an imaging head that is positioned in the camera head. This laparoscopic system has been the subject of numerous studies and tests demonstrating its safety and efficacy in human subjects.

The D-Light Laparoscope imaging system consists therefore of:

a) An endoscopic light source that provides illumination for visible light imaging and NIR fluorescence excitation to the endoscope via a flexible light guide,

b) Rigid endoscopes optimized for illuminating the field of view and transmitting images in the visible and NIR spectrum

c) A standard definition endoscopic camera system connected to the endoscope eyepiece and acquiring high resolution visible and NIR fluorescence images.

As with other endoscopic imaging systems, the device is compatible with video display, recording and printing devices commonly used in endoscopy and surgical suites.

The operator can select the mode of operation of the device by means of a filter control on the camera head. In visible light imaging mode, the device operates as a conventional endoscopic imaging system and provides illumination for and image acquisition of a color image in the area of interest. In ICG fluorescence mode the device operates to excite and image NIR fluorescence of an ICG contrast agent. The operator has the choice to display the NIR image information on the video monitor as an alternate to the conventional optical view. The picture od the NIR signal come back blue on a dark background.

All other features and operations of the device are similar to those found in conventional endoscopic light source and video camera systems. Specifically:

a) The brightness of the image adjusts automatically during use in response to light requirements.

b) Colour fidelity is maintained by means of a white balance function.

c) The light source has a standby feature that minimizes the light output and enables convenient decoupling of the endoscope light guide when exchanging endoscopes.

The camera is sterilisable in conventional manners and methods while the light cable sterility is maintained by means of sterile sheathing as is standard for laparoscopic and endoscopic cabling.

All together the only kit able to gather the 3 mode of vision at the same time is the Pinpoint system. It is clearly superior in term of facility of use to the other 2 systems and allows an excellent enhanced reality assessment of the operative field with the possibility to carry on the intervention while looking at specific task even with the NIR vision, this increases safety compared to the two others.

We actually have the D-Light Laparoscope in Geneva and we received recently the Pinpoint system.

Anastomosis microvascularisation assessment:

The microcirculation of the anastomosis play a capital role in any anastomotic dehiscence, it is emphasized that dividing the vessels lead to a loss of small vessels collaterals which could be crucial for tissues healing. But the only study to date has been performed with iv angiogram in open surgery, which is not amenable to a daily operating practice due to its complexity and lack of laparoscopic applicability [12]. Therefore, microvascularisation of the anastomosis is usually not assessed by lack of an adequate tool to do it, as described in table 1, especially in minimally invasive surgery. The use of near infrared technology has been performed in other fields of surgery, such as plastic surgery to assess flap viability for exemple [13, 14].

Laparoscopic Near-infra red (NIR) could be used to confirm the viability and state of microperfusion of any digestive anastomoses by means of an on table, real-time fluorophoric angiogram. The blood supply assessment is a useful and sensible add-on to the procedure, allowing maybe to prevent joint leak. This procedure can be used in patient at a very low extra cost (63.- Swiss Franc).

This is summarized in the second article of this thesis that has been recently published in Surgical Endoscopy[15] (p.40)

Lymphnode mapping:

The preliminary work described in this thesis, employing the near infrared technology, shows that it is possible to determine whether the first-draining nodes is able to be confidently identified for specific pathological scrutiny. All patients have a conventional resection of the primary tumours with its mesocolic lymphnodes in addition. If a significant positive predictive correlation between the pathology of the sentinel nodes and the pathology of the standard nodal dissection is determined, it could thereafter be proposed that focus on the first draining nodes alone could be sufficient to indicate tailored operative extent.

The first step is to perform successfully a laparoscopic intraoperative imaging of the first draining mesocolic and mesorectal lymph nodes of colon and rectal cancers immediately prior to the performance of therapeutic excision and a correlation of the intraoperative findings to final standard pathology.

The main issue in any consideration of changing surgical extent is to ensure the patient does not suffer any harm during the investigation. This allows to test the principles of lymphatic mapping and sentinel node biopsy against the current 'gold standard approach'.

The addition of lymphatic mapping during the case can be expected to identify first order draining lymph nodes lying outside the field of standard operative resection in approximately 22% of patients, biopsy and analysis of these nodes may provide upstaging of disease extent in a proportion of these thereby improving prognostic and potentially adjuvant therapy prescription. An increasing number of lympnodes can be seen after lymphnode mapping procedures, improving as well TNM staging.

The same technique is used as already part of routine care for patients with breast cancer, melanoma and, more recently, early stage stomach cancer around the world. What is new is the perspective regarding the implications of the results in colorectal cancer and the inclusion of enhanced technology.

The current development aims to confirm the safety of the near infrared intraoperative imaging (including administration of the fluorescent tracer indocyanine green) during laparoscopic and

endoscopic colorectal surgery, with its injection iv and peritumoraly. Then to have a comparison of the accuracy of the first draining nodes as a sentinel node in the reflection of the status of the entire draining lymphatic nodal basin resected by the standard operation now routinely performed.
This will lead to the definition and the determination of the proportion of patients with aberrant nodal drainage (that is the number of patients whose sentinel node lies outside the standard resection field).

The preliminary results are described the in the preliminary study section on p.59
of this manuscript , they have not yet been published.

Impact in colorectal surgery:

Potential impact of this technology has already been reported in some very small studies.

For the microvascularisation, the group of Sherwinter in New York [16], performed a study on 20 patients who had a low anterior resection. He used the endoscopic kit to have a transanal view of the mucosal side of the anastomosis, among the 20 patients, 16 had a normal angiogram while 4 had abnormal view. It resulted in a 50% leak rate for the patient with abnormal angiograms and therefore a strong correlation between leak and vascularisation.

More recently, Jafary et al. published a serie of robotic low anterior resection. The use of the robotic near infrared kit allowed him to reduce the leak rate of 2/3, from 18% in the control group to 6% in the near infrared group. It leads to a change during the surgery according to the vascularisation level and prevented leaks [17].

It appears that this technology could be the tool that will allow a real decrease in leak rate in colorectal anastomosis or any type of digestive anastomosis.

As already discussed, the potential use of this technology will allow to develop new application even for this simple assessment of anastomosis but either for vascular assessment of ureters for example after ureterolysis or kidney transplantations or acute bowel ischemia

3. Near-infrared laparoscopy for real-time intra-operative arterial and lymphatic perfusion imaging

Short summary: This article is a technical description of the different way to perform near infrared imaging in visceral surgery, as well as the different available scopes for a minimally invasive approach.

R. A. Cahill*†, F. Ris#† and N. J. Mortensen†

*Department of Colorectal Surgery, Beaumont Hospital, Dublin, Ireland, #Department of Visceral Surgery, Geneva University Hospital, Geneva, Switzerland and †Department of Colorectal Surgery. Oxford Radcliffe Hospitals, Oxford, UK

Received 25 July 2011; accepted 16 August 2011

Supplementary video content relevant to this manuscript is available at www.fusionsummit.co.uk

Abstract

Multimodal laparoscopic imaging systems possessing the capability for extended spectrum irradiation and visualization within a unified camera system are now available to provide enhanced intracorporeal operative anatomic and dynamic perfusion assessment and potentially augmented patient outcome. While ultraviolet-range energies have limited penetration and hence are probably more useful for endoscopic mucosal interrogation, the near-infrared (NIR) spectrum is of greater potential utility for the purposes of examining inducible fluorescence in abdominopelvic tissue that can be achieved by administration of specific tracer agents, either directly into the circulation (e.g. for anastomotic perfusion assessment at the time of stapling) or into the lymphatic system (e.g. for lymph basin road-mapping and ⁄or focussed target nodal assessment). This technology is also capable of supplementing anatomic recognition of the biliary system while implantable fibres can also be inserted intraoperatively for the purpose of safeguarding vital structures such as the oesphagus and ureters especially in difficult reoperations. It is likely that this technological capability will find a clear and common indication in colorectal specialist and general surgical departments worldwide in the near future.

Keywords Laparoscopic colorectal surgery; near-infrared laparoscopy; on table angiography; anastomotic compli- cations; lymphatic mapping; indocyanine green (ICG)

Introduction

Videoscopic minimally invasive surgery depends on light energy transmitted through an endoscope illuminating the tissue of interest. The resulting reflected light is imaged by the scope camera for display on a video monitor. Near-infrared (NIR) laparoscopic systems pro- vide the capability for extension of the useful electro- magnetic spectrum by switch activation beyond white light up into the NIR range to improve the amount of optical data available to the operator [1]. This property can be best utilized at present by the injection of specific agents ('fluorophores') that have the physical property of 'inducible fluorescence' (that is, the ability to absorb energy at one wavelength and re-emit it at another, usually higher, wavelength). The use of selective, discrete wavelength filters on the camera head allows this energy to then be made visible to the surgeon. NIR differs from ultraviolet appreciation by the absence of natural background fluorescence in this wavelength and by its ability to penetrate deeply into tissues without causing cellular injury.

While there are now several laparoscopic systems coming on stream that possess this technological capabil- ity, the main available fluorphore is indocyanine green (ICG). This compound has distinct properties that make it ideal for the acquisition of high-quality images of the arterial and lymphatic circulations and it has a long clinical safety record. The clinical areas of greatest interest at present are validation of the usefulness of NIR ICG visualization in (i) intestinal perfusion assessment at the time of anastomotic formation and (ii) lymphatic road- mapping, whether by intra-operative laparoscopic NIR angiogram or lymphogram respectively. Bilary duct visualization (NIR cholangiography) and ureteric⁄ oesophageal localization and protection by the means of intraluminal fibreoptic placement are also potential uses of this technology.

Indocyanine green

ICG is a sterile, water-soluble, tricarbocyanine com- pound dye that absorbs NIR light in the region of 800–810 nm (peak spectral absorption = 806 nm) and emits it at 830 nm. When injected intravenously, ICG binds rapidly and extensively to plasma proteins and so is confined to the intravascular

compartment, with minimal leakage into the interstitum under normal conditions. ICG is removed from the blood by the liver with a plasma half life of 3–5 min and is then excreted via the bile without further metabolism within 10– 15 min of administration. When injected subserosally or submucosally in the intestine, ICG is taken up by lymphatic spaces and efferent channels within seconds and travels (again bound to protein) to lymph nodes where it deposits in macrophages, becoming a visible stain within minutes. Such extravascular ICG will ultimately be delivered to the thoracic duct and thus gradually enter the venous return to the heart before being eliminated by the hepato–biliary system. ICG is manufactured by several companies worldwide and has been used for various indications since the late 1950s, including lymphangiography and endoscopic tattooing. The manufacturers recommend a maximum daily dose of 2 mg／kg.

Near-infrared laparoscopes and devices

The common components of currently available NIR systems are shown in Table 1. Two devices (those made by Olympus Corporation, Tokyo, Japan and Karl Storz GmbH, Tuttlingen, Germany) represent modifications of current endoscopic systems that were originally developed for intraluminal videoscopy with narrow wavelength energies. Another system (Novadaq Tech- nologies Inc, Ontario, Canada) is an entirely new device, while the fourth related system (Stryker Corporation, Michigan, USA) is a conventional laparoscope used in conjunction with implantable lighted optical fibre fluorescence.

Laparoscopic NIR Fluorescence Imaging System

The laparoscopic NIR fluorescence imaging system made by Olympus Corp is a cleared, CE (Conformite´ Europe´enne)-approved medical prototype resulting from a modification of the Viscera Laparoscopic system that is already widely in use in the UK, Europe, Asia and the USA. In short, the narrow band-imaging capability of the standard laparoscopic system has been disabled and replaced by NIR imaging capability by means of a xenon light source (specifically tuned to correspond to the fluorescent excitation properties of ICG). The operator can select the mode of operation of the device

by means of a button control on the camera head or an assistant can effect operation on the stack console. In visible light imaging mode (VIS mode), the device operates as a conventional endoscopic imaging system, whereas in NIR fluorescence mode, the device excites and images NIR fluorescence from an ICG contrast agent but loses the white-light image. An intermediate setting is possible where the NIR illumination without filtration allows the surgeon to maintain an image for the purposes of orientation and operating.

D-Light Laparoscope

This CE-clear system is a modification of the Storz Photodynamic Diagnostic D-Light (PDD) device (made by Karl Storz GmbH), which utilizes a xenon light source with an integrated filter wheel to achieve discrete spectral illumination in the ultraviolet region. This short pene- trating energy has been clinically used in gastroentero- endoscopy, cystosocopy and bronchoscopy for either excitation autofluorescence (and hence to look for the disruption of normal patterns as a result of disease infiltration or local inflammatory reaction) or xenofluo- rescence (predominantly caused by the uptake of specific tracer agents) within the mucosa／submucosa [2,3]. Adaption of the device for near-infrared illumination and display is now possible from adaption of the xenon light source and retuning of the D-light endoscopes for ICG detection. Switch activation again allows the surgeon choose the display as either standard white light or NIR viewing modes [4].

Pinpoint Endoscopic Fluorescence Imaging System (Novadaq Corp.)

The Pinpoint Endoscopic Fluorescence Imaging System (made by Novadaq Technologies Inc., Canada) is based on a cleared／approved medical device already validated for use in coronary artery bypass procedures (i.e. the SPY Imaging System). This imaging system (currently commercially available in Canada, Japan, Europe and the USA) allows cardiac surgeons to visually assess and react to bypass graft quality and patency in real-time by means of an intra-operative ICG angiogram [5]. In

addition, it is approved for use in peripheral vascular procedures, plastic surgery, reconstructive microsurgery and organ trans- plantation [6]. The Pinpoint System reformats the technology into a laparoscopic system and has recently received clearance from the United States Food and Drug Administration.

The Pinpoint System makes use of an NIR diode laser projected through optics for illumination and ICG fluo- rescence, and the videoscopic device is compatible with a high-definition video display. In colour imaging mode, the light source will generate full visible-spectrum illumi- nation by combining blue／green light from an arc lamp with red light from a light emitting diode (LED) array. In colour／NIR fluorescence imaging mode, the light source will alternate (at a multiple of video field rates) to generate full visible-spectrum illumination (as in colour imaging mode) and a combination of blue／green light from the arc lamp and NIR laser diode excitation light. The synchronized alternating illumination enables the high-definition colour video image and the NIR fluorescence image to be acquired in rapid succession and displayed simultaneously. Uniquely then, while the operator can select the mode of operation of the device by means of a footswitch control and toggle between different displays, the Pinpoint scope can provide superimposed (in which the NIR image signal is assigned a contrasting colour) real-time HD images on the video monitor (see Figure One).

Infravision Laparoscope and Implantable Kits (Stryker Corp.)

Stryker's Infravision KITs are infrared smart tools intended to help surgeons identify and protect critical structures during laparoscopic procedures. Currently two kits are available: an EKIT for the oesophagus and a UKIT for the ureter. Both indications depend on intraluminal passage of a fibreoptic cable (48–60 Fr for the oesophagus and 6 Fr for the ureter) into the organ of interest. The instrument is equipped with special fibres, that, when connected to a specific NIR illuminator outside the patient, will emit NIR and transilluminate (through up to 12 mm of tissue thickness) the organ. This renders it obvious for visualisation by a specific high-definition laparoscope (the InfraVision Imaging System).

Clinical utility of NIR laparoscopy

ICG NIR angiography

While the cause of anastomotic leaks may be multifactorial, undoubtedly arterial insufficiency contributes to a significant degree in some cases. For this reason, surgeons often perform a variety of clinical checks, including palpation of the mesocolon and visualization of the cut end of the intestine, before progressing with anastomotic formation. Both Doppler ultrasound and ICG angiography have been proposed for use in open surgery to give a degree of added security although neither is in routine or widespread use [8]. NIR laparoscopy following ICG venous administration (1.25–3.75 mg, depending on patient weight, given intravenously through a central or a peripheral venous line) provides a means of visualization of the micro- circulation, either immediately before or subsequent to anastomosis formation with the tissues in their anatomic positions. Intra-operative images are acquired during the first pass of a bolus of ICG (see Figure 1). While probably useful in documenting sufficiency (and hence 'technical perfection') at the time of anastomosis formation, it remains at present a linear, graded result that requires subjective interpretation as to the cut-off point between sufficient and insufficient.

ICG NIR lymphangiography

Identification of lymph nodes draining the area of interest by local ICG injection is readily and reliable possible using NIR laparoscopy (see Figures 2 and 3). [9]. To do this, ICG in solution is injected into the interstitum (for the colorectum this can be carried out by laparoscopic／endoscopic tattoo into the submucosa or subse- rosa) and the dye is taken up and deposited into locoregional lymph nodes. Leeching of the dye through the lymph basin occurs over time, and nodes throughout the draining delta can then be readily visualized. While certainly of potential use in road-mapping colorectal cancers in locations with known variable lymphatic drainage (i.e. flexural or transverse colon cancers), the greatest clinical use of this capability would be as a means of rapid (and ideally in situ) determination of the oncological status of the nodes, thus allowing an immediate decision to be made regarding the extent of operative dissection required. A case for minimized resection could be for the unsuspected polyp cancer, especially if the dye could be given at the time of polypectomy (ICG is known to persist

within tissue for at least 8 days) while confirmation of positive tumour metastases in selected locations (e.g. iliac nodal chain) could perhaps be an indication for broadened and even extra-anatomic resection.

ICG cholangiography

Laparoscopic NIR systems after ICG injection are capable of visualizing the biliary anatomy as a result of the hepatic excretion of unmetabolized dye into bile following intravenous injection. The cystic duct, hepatic ducts and common bile duct can be readily visualized, allowing a confirmatory check of the anatomy at the time of cholecystectomy. While the sensitivity may not be suffi- cient to indicate/rule out common bile duct calculi, intra- operative guidance of structures may be particularly useful in difficult cases (perhaps especially acute cholecystitis) or potentially perhaps to augment confidence of safety in single-port cholecystectomy wherein the constrained access and the view along the instrument shafts may reduce the ability to completely and fully appreciate Calot's triangle. Additionally there is a potential role for this technology in determining bile leaks during liver resectional or transplant surgery.

NIR lighted stents for organ transillumination

The concept of transillumination by lighted catheters is intended to augment the surgeon's appreciation and recognition of crucial structures intra-operatively and hence ward away from inadvertent iatrogenic injury (see Figure 4) [10]. This is felt to be particularly advantageous in protection of the ureter in complicated (redo) surgery for advanced malignancy or inflammatory bowel disease [11]. No large-scale prospective studies are likely to be carried out to demonstrate the improved safety profile, and the market is likely to depend on intuitive appreci- ation and on the system technology already being available within a department. Similar in concept is the oesophageal kit; however, here the fluorescent stent doubles as a bougie, which it may replace in hiatal operations such as fundoplication procedures.

Conclusion

The technological capability for augmented reality by an enhanced visualization facility enabled by the harness of a broadened energy spectrum is becoming increasingly available for laparoscopic surgeons and indeed may well become standard issue in new-generation devices in the near future. The potential utility of this technology ranges from straightforward anatomic identification to more complex dynamic, functional demonstrations and, potentially, oncological diagnostic capability. With increasing sophistication of fluorophores, tissue distinc- tion is likely to become considerably more nuanced than mere identification, and the capacity for in situ labelling depending on the pathological process for optical diagnosis becomes likely. Where exactly (and indeed if) this technology breaks into mainstream clinical use is somewhat speculative at present and will need considerable clinical endeavour to specify the exact level of usefulness.

Conflict of interests

The ORH has received near-infrared laparoscopic equip- ment for clinical trialling from Olympus, Novadaq and Stryker. RAC is in receipt of a Career Development Award from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES).

References

1. Cahill RA, Mortensen NJ. Intraoperative augmented reality for laparoscopic colorectal surgery by intraoperative near- infrared fluorescence imaging and optical coherence tomog- raphy. Minerva Chir 2010; 65: 451–62.

2. Zaak D, Karl A, Knuchel R et al. Diagnosis of urothelial carcinoma of the bladder using fluorescence endoscopy. BJU Int 2005; 96: 217–22.

3. Mowatt G, N'Dow J, Vale L et al. Photodynamic diagnosis of bladder cancer compared with white light cystoscopy. Int J Technol Assess Health Care 2011; 27: 3–10.

4. Van der Poel HG, Buckle T, Brouwer OR, Valdes Olmos RA, van Leeuwen FW. Intraoperative laparoscopic fluores- cence guidance to the sentinel lymph node in prostate cancer patients. Eur Urol 2011; 60: 826–33. 5. Balacumaraswami L, Abu-Omar Y, Choudhary B, Pigott D, Taggart DP. A comparison of transit-time flowmetry and intraoperative fluorescence imaging for assessing coronary artery bypass graft patency. J Thorac Cardiovasc Surg 2005; 130: 315–20.

6. Newman MI, Samson MC. The application of laser-assisted indocyanine green fluorescent dye angiography in microsurgi- cal breast reconstruction. J Reconstr Microsurg 2009; 1: 21–6.

7. Boyle NH, Manifold D, Jordan MH, Mason RC. Intraop- erative assessment of colonic perfusion using scanning laser Doppler flowmetry during colonic resection. J Am Coll Surg 2000; 191: 504–10.

8. Kudszus S, Roesel C, Schachtrupp A, Hoer JJ. Intraoperative laser fluorescence in colorectal surgery: a non-invasive analysis to reduce the rate of anastomotic leakage. Langen- becks Arch Surg 2010; 395: 1025–30.

9. Cahill RA, Wang LM, Anderson M, Lindsey I, Cunningham C, Mortensen NJ. Near infrared (NIR) laparoscopy for the intraoperative determination of mesocolic sentinel nodes during definitive surgical resection of early stage colorectal neoplasia. Surg Endosc 2011; Epub ahead of print.

10. Chahin F, Dwivedi AJ, Paramesh A et al. The implications of lighted ureteral stenting in laparoscopic surgery. JSLS 2002; 6: 49–52.

11. Redan JA, McCarus SD. Protect the ureters. JSLS 2009; 13: 139–41.

Tables:

Table I Common components of near-infrared (NIR) laparoscopes.

Specific features of NIR laparoscopes	Other features and operations of the device similar to conventional videoscopic systems
An endoscopic light source that provides illumination to the endoscope via a flexible light guide for both visible light imaging and NIR fluorescence excitation A rigid endoscope (0° lens, 10 mm diameter) optimized for illuminating the field of view and transmitting images in the visible and NIR spectra. The camera head is equipped with a charge coupled device (CCD) for image capture as well as the appropriate optical lenses and filters to block transmission of white light while allowing efficient transmission of fluorescence light, thereby ensuring optimal light selection	The brightness of the image adjusts automatically during use in response to light requirements Colour fidelity is maintained by means of a white balance function The light source has a standby feature that minimizes the light output and enables convenient decoupling of the endoscope light guide when exchanging endoscopes The devices are compatible with video display, recording and printing devices commonly used in endoscopy and surgical suites

Figure 1

Pinpoint Imaging System (Novadaq, Ontario, Canada) in use during an on-table Indocyanine Green (ICG) angiogram after construction of the colorectal anastomosis in a patient undergoing laparoscopic high anterior resection. The sufficiency of perfusion is indicated in the fluorescence alone view in (a) and in the superimposed colour view (ICG denoted by green colouration) (b). Further information re screen layout is given in Figure 3.

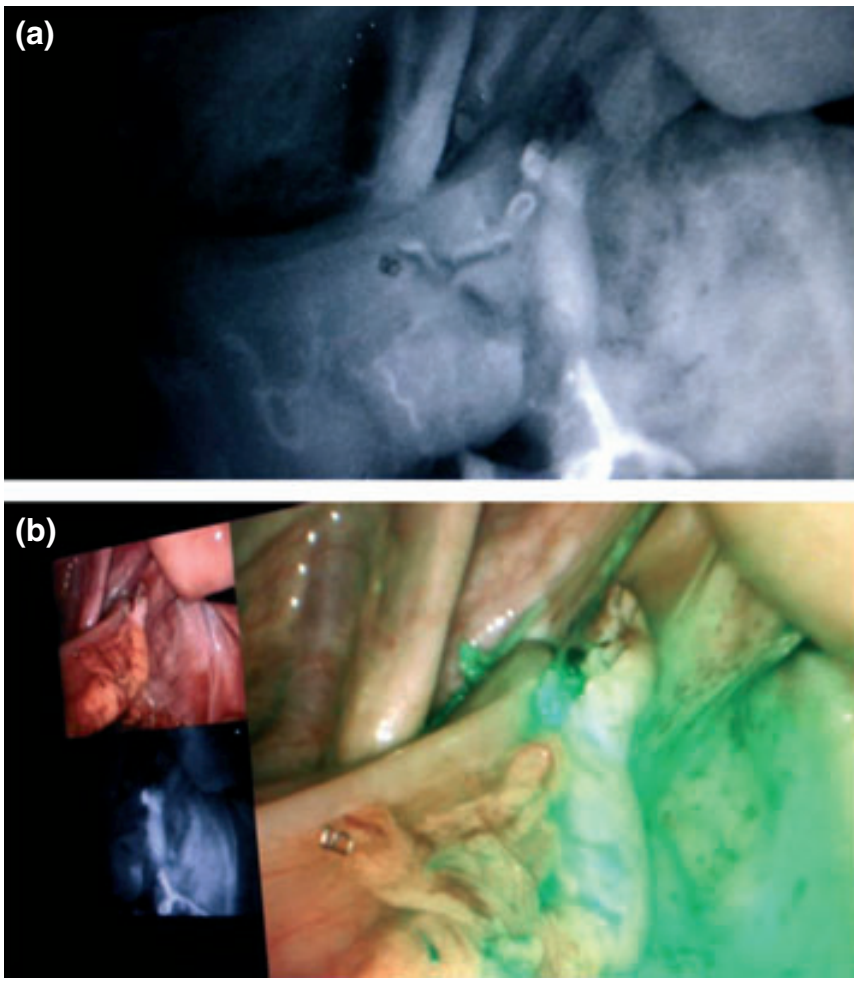


Figure 2

(a–c) Intra-operative lymphogram obtained using an Olympus Near-infrared Laparoscope in a patient with a distal sigmoid cancer endoscopically labelled by submucosal injection of indocyanine green (ICG) minutes before these photographs were taken. (a) Standard white-light view showing mesentery of the left colon near the origin of the inferior mesenteric artery. (b) Near-infrared (NIR) illumination shows 'blue' appearances with a dark area (maximum absorption of illuminating light) consistent with the white light view. (c) Filtered view of (b) showing the fluorescent lymph node as a bright spot against a dark background. (d) A different patient with caecal cancer who underwent an ICG tattoo 24 h before laparoscopic right hemicolectomy. The filtered view of NIR illumination here shows several bright areas within the right colonic mesentery, all of which are lymph nodes within the tumour's lymphatic delta.

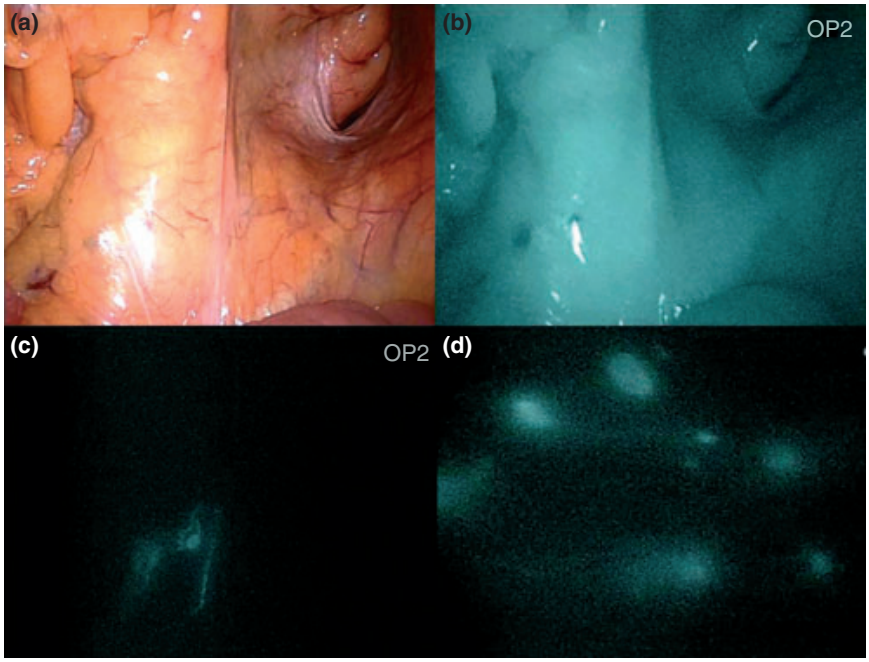


Figure 3

Intra-operative lymphogram images taken using the Pinpoint System (Novadaq Corporation) in a patient with a mid-sigmoid cancer who had undergone intra-operative sigmoidoscopy with submucosal injection of indocyanine green (ICG). With this endoscopic system, the near-infrared (NIR) image information may be displayed in various ways depending on operator preference. In the main screens here, the NIR fluorescence image is combined with the visible-light High Definition image such that the NIR fluorescence is displayed as a contrasting colour-overlay (green). The smaller pictures to the side show the corresponding white-light (above left) and NIR (below left) images. (a) Fluorescence associated with the peritumoral endoscopic injection site. (b) A lymph node with feeding vessels within the mesocolon. (c) Another lymph node near the origin of the inferior mesenteric artery at the base of the mesocolon.

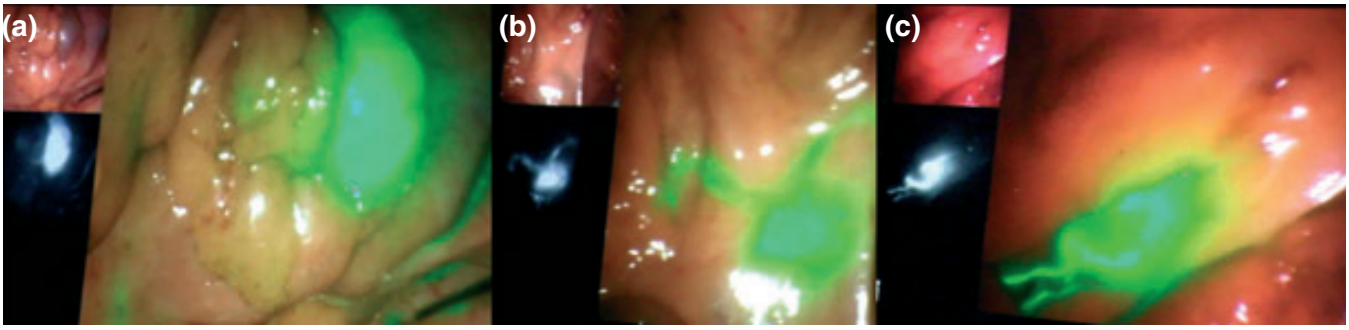
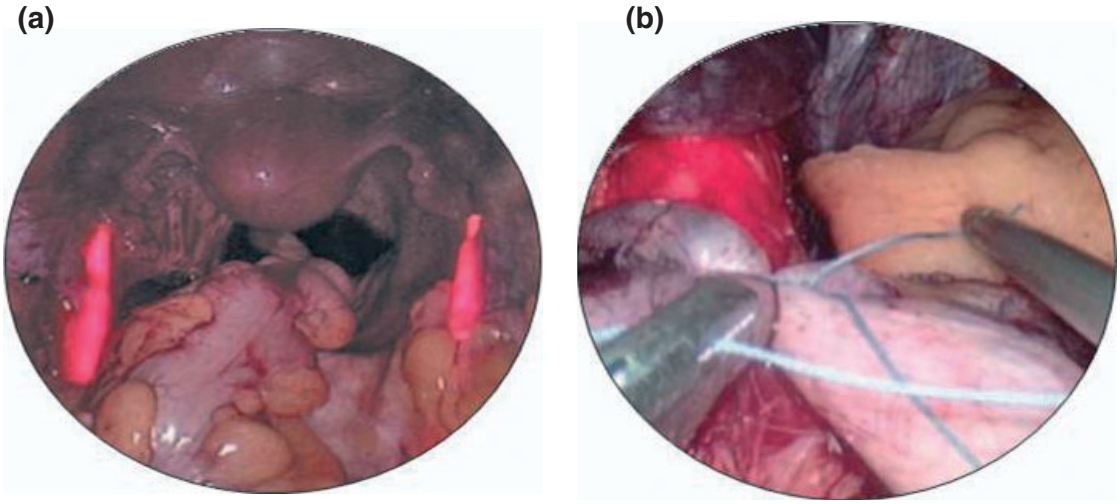


Figure 4

Intra-operative images obtained with placement of the near-infrared emitting optical fibres into (a) the ureters bilaterally and (b) the oesophagus. The fluorescence emits as a blinking light and can be turned on and off independently of the intra-abdominal laparoscope as it inc- orporates a separate illumination source (images courtesy of Stryker Corp [www. stryker.com]).



4. Near Infra-red (NIR) perfusion angiography in minimally invasive colorectal surgery

Short summary: This article is one of the first description of a minimally invasive colorectal anastomosis assessment of the microvascularisation.

Short-title: Assessing colorectal anastomotic perfusion by laparoscopic NIR.

Frederic Ris, MD[1,2], Roel Hompes, MD[1], Chris Cunningham, MD[1], Ian Lindsey, MD[1], Richard Guy, MD[1], Oliver Jones, MD[1], Bruce George, MD[1] , Ronan A Cahill, MD[1,3] , Neil J Mortensen, MD[1]

[1]Departments of Colorectal Surgery, Oxford University Hospitals, Oxford, United Kingdom

[2] Geneva University Hospital, Geneva, Switzerland and [3]Beaumont Hospital, Dublin, Ireland.

Abstract Word Count: 237.

Manuscript Word Count: 1976.

Published in Surgical Endoscopy , 2014 Feb 25

ABSTRACT

Introduction: Anastomotic leakage is a devastating complication of colorectal surgery. There is however no technology indicative of in situ perfusion of a laparoscopic colorectal anastomosis.

Methods: Here, we detail the use of near-infra red (NIR) laparoscopy (PinPoint-System, NOVADAQ, Canada) in association with fluorphore (Indocyanine Green, ICG, 2.5 mg/ml) injection in 30 consecutive patients undergoing elective minimally invasive colorectal resection using the simultaneous appearance of the caecum or distal ileum as positive control.

Results: The median (range) age of the patients was 64 (40-81) years with a median (range) BMI of 26.7kg/m^2 (20-35.5). Twenty-four patients had left sided resections (including six low anterior resections) while six had right sided resections. Of the total, 25 operations were cancer resections while five were for benign disease [either diverticular strictures (n=3) or Crohn's disease (n=2)]. A high quality intraoperative ICG-angiogram was achieved in 29/30 patients. After ICG injection, median (range) time to perfusion fluorescence was 35(15-45) seconds. Median (range) added time for the technique was 5 (3-9) minutes. Anastomotic perfusion was documented satisfactory in every succesfull case and encouraged avoidance of defunctioning stomas in three patients with low anastomoses. There were no postoperative anastomotic leaks.

Conclusion: Perfusion angiography of colorectal anastomosis at the time of their laparoscopic construction is feasible and readily achievable with minimal added intraoperative time. Further work is required to determine optimum sensitivity and threshold levels for assessment of perfusion sufficiency, in particular with regard to anastomotic viability.

Key-words: Laparoscopy, colorectal resection; anastomotic leak; Near Infrared (NIR) Laparoscopy; Indocyanine Green (ICG); perfusion.

Introduction:

Colorectal resection is a common operation with more than 600,000 procedures being performed each year in the United States alone. Anastomotic leakage remains its most concerning complication with often devastating clinical result for the patient and considerable economic consequence for the healthcare provider.[1] While relatively uncommon in any single surgeon's practice, average leak rates of 1-3% for ileo-colic anastomoses and up to 10-20% for low colorectal anastomoses impact adversely on postoperative outcomes worldwide. [2,3] These incidences have persisted despite widespread and increasing uptake of laparoscopic approaches which have made a significant and positive impact on postoperative complication rates.[4]

Various patient and procedure related variables have been implicated as risk factors for anastomotic breakdown although absolute prediction of its occurrence in any one individual remains difficult.[5] Although a common determining factor of viability is adequate arterial perfusion to ensure sufficient local tissue oxygenation[6], there is currently no accepted method to assess the viability of a colorectal anastomosis in situ after its laparoscopic construction. Common practice nowadays is simply to use crude visual assessment of the transected proximal bowel at the time of specimen extraction and thereafter inspection of the whole anastomosis after stapling. A more sophisticated capability to view the actual vascular and microvascular perfusion at the time of re-anastomosis may increase confidence of technical perfection or alternatively indicate perfusion deficiency and so prompt reconstruction or even abandonment of anastomosis. Here, we report the use of near-infra red (NIR) laparoscopic technology to confirm and document viability and perfusion of digestive anastomoses by means of an on table, real-time fluorophoric (Indocyanine Green, ICG) angiogram in a series of consecutive patients undergoing laparoscopic colorectal resection with primary anastomosis. This builds on the early experience in very recent publications examining similar technology employed endoluminally[7-8] and within the Da Vinci robot platform and indeed for non-gastrointestinal indications.[10-11]

Methods:

Patient selection and ethical approval: Full ethical approval for this study was granted after application to an Independent Research Ethics Committee (North London REC-2, Ethical committee approval number: 10/H0724/13) and institutional, departmental and external peer approval of the entire protocol was obtained. Thirty consecutive patients undergoing elective colonic or rectal resection for either colorectal cancer or benign pathology were consented in full before their agreed recruitment; with all being informed that inclusion in the study was voluntary and simply additive to routine care.

ICG: ICG is supplied as sterile water-soluble lyophilized powder (25 mg, ICG Pulsion®, Pulsion Medical Systems, Munich, Germany) with the formula of $C_{43}H_{47}N_2O_6S_2Na$.[12] It is an anhydro-3,3,3',3'-tetramethyl-1,1'-di-(4-sulphobutyl)-4,5,4',5',-dibenzoindotricarbocyanine hydroxide sodium salt with molecular weight of 775 Daltons. A fluorophore in response to NIR irradation, it absorbs light between 790 to 805 nm and re-emits it with an excitation wavelength of 835 nm.[13] ICG half-life is 3-5 minutes and it is eliminated by the liver in 15-20 minutes. These properties in conjunction with the absence of any native biological fluorescence within these wavelengths make ICG an ideal agent for the acquisition of high quality images of both the circulatory and lymphatic systems.[14] While generally very safe for intravenous use, vasovagal or allergic reactions can occur while the incidence of fatality due to its use is estimated as 1 per 333000.

Laparoscopic Near-Infrared Fluorescence Imaging System: A prototype NIR laparoscopic system (PinPoint Endoscopic Fluorescence Imaging System, NOVADAQ, Canada) was used to provide high definition white light, NIR irradiation and back-filtration specifically tuned for ICG. This system also provides a superimposition of both modalities using false colouring technology allowing an enhanced real-time appreciation of dynamic perfusion without loss of the standard white light view. As not yet CE-marked, the system was used with approval after specific MHRA and Ethics clearance. ICG injection

was performed immediately after anastomosis construction with a segment of unoperated right colon or ileum used as positive comparator in each case.

Operative procedure: Colorectal resection was performed in a standardized fashion by multiport laparoscopy for every case, utilizing a fully laparoscopic technique for left sided resections (classified as either high or low anterior resection depending on whether the double stapled colorectal anastomosis was above or below the peritoneal reflection) and laparoscopic-assisted approach (stapled extracorporeal anastomosis with subsequent relaparoscopy) for right sided resections. A medial to lateral dissection technique was used and the splenic flexure was mobilized routinely for left sided resections.

Data collection: Patient characteristics, intraoperative parameters as well as postoperative outcomes were collected prospectively. Perfusion images were recorded and qualitatively judged in real-time. Specific NIR criteria relating to the timing and quantity of injection as well as anastomotic fluorescence intensity and persistence were measured and any change in operative protocol prompted by the ICG angiogram noted. Intraoperative adverse reactions were recorded in real-time and postoperative complications were classified according to the Dindo- Clavien classification.

Statistical analysis: Results were expressed as median (range). Continuous variables were compared with the Student *t*-test and categorical variables with the Chi-square test. All tests were conducted using the standard alpha level of 0.05 to indicate statistical significance.

Results:

30 consecutive patients were recruited for the study over a five month period. Patient and disease characteristics are shown in Table One with operation parameters shown in Table Two. An intraoperative ICG perfusion angiogram of the anastomosis and supporting colorectal mesentery was achieved in every patient except one (patient number 2) when the system failed to detect any visible fluorescence. The time of visible ICG fluorescence at the anastomosis was less than one minute in each successful case, the median time being 35 seconds (see Table 3 and video1). Fluorescence persisted at the site of interest for more than three minutes with a remaining residual weak signal being visible up to 30 minutes after the initial injection (video2). Once fading, a second ICG injection could re-fluoresce the target tissue after five minutes from the first injection. With the normal near-adjacent caecum or terminal ileum, in case of right hemicolectomy, being used as a comparative positive control, the perfusion appearances of the colorectal anastomosis were judged satisfactory in every patient and did not prompt revision or other technical adjustment of any anastomosis. A defunctioning stoma however (normally our preference for anastomoses within 8 cm of the anal verge) was avoided in three out of six patients in part because of the confidence imparted by the perfusion angiogram. There was no need to redo the anastomosis in any patient based on the angiogram findings. The median added procedure time by employment of this technological modality was 4.5 minutes (3-9 min) with the shorter times occurring with experience. There was no long term or short term morbidity related to ICG injection. None of the patients developed a problem related to the anastomosis (no leaks in this series) and the only postoperative morbidity (see Table 4) related to carbonarcosis due to analgesic drugs.

Discussion:

Although improved minimal access techniques and optimized perioperative care protocols[16] have greatly impacted on short and intermediate postoperative outcomes, anastomotic complications (especially early postoperative anastomotic leaks) remain unpredictable and are often devastating. While a proximal defunctioning stoma may mitigate the consequences of anastomotic dehiscence, diversion can also impact negatively on the patient in terms of psychological and physical functioning as well as with regard to actual complications in their formation and closure. Furthermore, aside from acute dehiscence or breakdown, impaired perfusion can also contribute to intermediate or late stricture formation. Any means of minimizing or indeed avoiding anastomotic complications would justify considerable investment in time, effort and direct investment. Current means of assessing anastomosis viability however relate only to simple inspection and checking mechanical integrity (i.e. donut assessment and air leak testing). Assessment of the collateral flow is at present only possible on the extracted proximal bowel and of course may not represent actual flow when the anastomosis is constructed within the abdominopelvic cavity. The perfusion angiogram clearly shows perfusion along the antimesocolic border of the colon proximal to the anastomosis for left sided operations and distal to the anastomosis for right sided resections. This is demonstrative of direct vascularisation from the marginal artery which lies along the mesocolic aspect of the colon and flow on this aspect is likely as sufficient. Equally, a mechanical intact anastomosis may still breakdown some days after its formation due likely, at least in a proportion, to vascular insuffiency.

Realtime NIR fluorescence angiography using ICG during laparoscopic colorectal operation proved here feasible and reproducible with a minimum of added complexity. While a large prospective study is required to investigate its relatability to postoperative anastomotic leak rates, the images appear compelling and seem at least to document technical sufficiency with regard to in situ vascularisation of the proximal conduit at the time of anastomotic construction. Whether additional useful information could be gleaned by intraoperative assessment of the rectal stump prior to anastomosis or indeed the intraluminal aspect of the anastomosis after construction by transanal use via a sigmoidoscopy both

during the operation and perhaps even on a daily basis after (in order to detect the failing anastomosis to allow corrective intervention prior to overt clinical deterioration) also requires further focused study. Finally, analytic measures to objectively quantify signal intensity are already evolving and require investment for their development and correlation with clinically important outcomes.[18]

Acknowledgements:

We acknowledge the support of the Oxford Colon Cancer Trust (OCCTOPUS).

The laparoscopic NIR (Pinpoint) system was provided under an unrestricted use agreement from Novadaq. No right of review of the data or manuscript was requested or provided.

The authors also wish the endeavor and contributions of Ms Lian Lee RN, and her scrubnurse team as well as the fellows and registrars of the Colorectal Department at Oxford Radcliffe Hospitals.

Figure Legends:

Figure 1: NIR perfusion assessment in laparoscopic right hemicolectomy:

(a: normal light, b: near infrared fluorescence, c: superposition of NIR and normal light in green)

A: Intraoperative pictures showing a clear demarcation line after vessel division

B: ileo-transverse anastomosis before IDC injection, showing no fluorescence

C: Perfusion assessment of the ileo-transverse anastomosis.

Figure 2: NIR perfusion assessment in laparoscopic low anterior resection:

(a: normal light, b: near infrared fluorescence, c: superposition of NIR and normal light in green)

A: Colo-rectal end to end anastomosis before IDC injection, showing no fluorescence

B: Perfusion assessment of the Colo-rectal anastomosis.

Figure 3: Positive control

(a: normal light, b: near infrared fluorescence, c: superposition of NIR and normal light in green)

A: Image of the normal ceacum after IDC injection

Table 1: Patient characteristics

Characteristics	
N	30
Gender (M/F)	19/11
Median age (years)	64 (40-79)
Median BMI (kg/m^2)	26.7 (20-35.6)
Anaesthetic risk	
- ASA I	3(10%)
- ASA II	25 (83%)
- ASA III	2 (7%)
- ASA IV	0 (0%)
Indication for surgery	
Colorectal cancer	25 (83%)
Diverticular disease	3(10%)
Crohn's disease	2(7%)

BMI, body mass index; ASA, American Society of Anesthesiologist

Data are expressed as median (range) or number (%)

Table 2: Peroperative datas

Peroperative data	
Laparoscopic high anterior resection	18 (60%)
Laparoscopic low anterior resection	6 (20%)
Laparoscopic right hemicolectomy	6 (20%)
Conversion	3(10%)
Early	2(7%)
Late	1(3.5%)
Splenic flexure mobilisation (high and low anterior resection, n=25)	24(96%)
Protective ileostomy (low anterior resection)	3/6(50%)
Median length of procedure (min)	
Right hemicolectomy	146(146-147)
High anterior resection	195(95-296)
Low anterior resection	250(188-270)

Data are expressed as median (range) or number (%)

Table 3: Perfusion assessment

Peroperative data	
Median lenght of the procedure (min)	4.5 (3-9)
Median time to reach the anastomosis (sec)	35 (15-45)
Quality of the perfusion	
Good	29 (96%)
Average	0
Bad	0
Technical failure	1(4%)
Change in anastomosis	0
Change in strategy (no diverting stoma in low anterior resection)	3 (50%)

Data are expressed as median (range) or number (%)

Table 4: Postoperative data, Hospital stay, short and long term complications according to Clavien-Dindo classification,

Postoperative data	*n*(%)
Hospital stay (days)	5(2-8)
No complication	24
Complication (Clavien-Dindo) / in patient (n)	7/6
Grade I	3 (10%)
Grade II	3 (10%)
Grade IIIa	1 (3.5 %)
Grade IIIb	0
Grade IV	0
Reoperation	0
Anastomotic related complication	0
Long term complication	0

Data are expressed as median (range) or number (%)

Figure 1

Figure 1

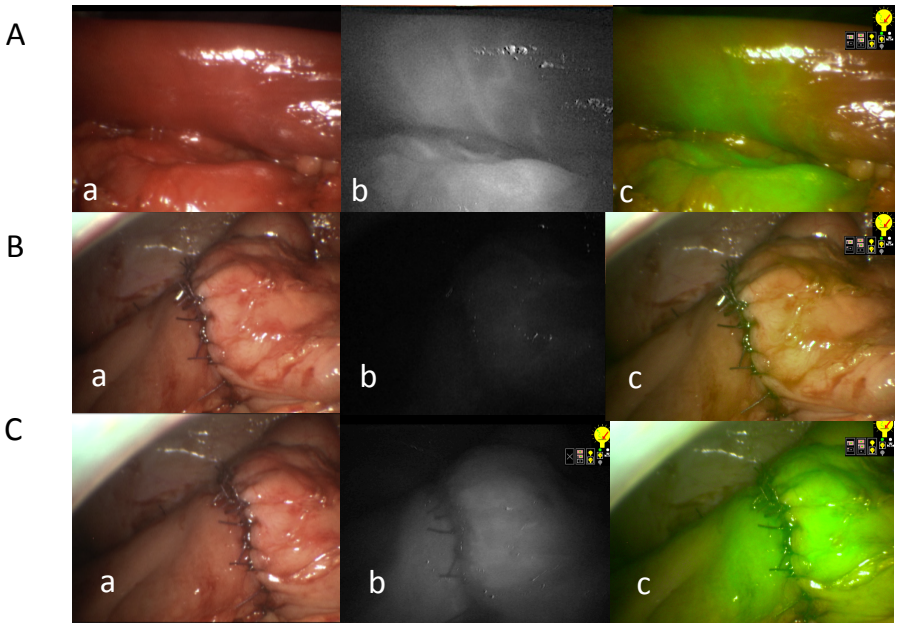


Figure 2

Figure 2

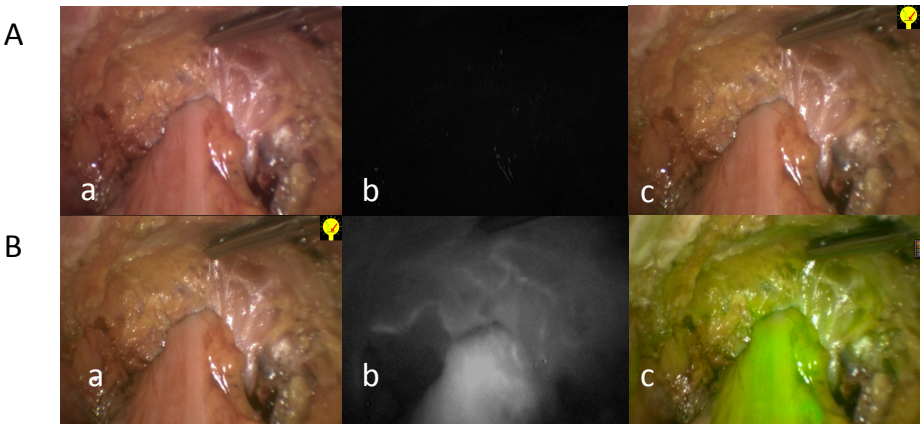
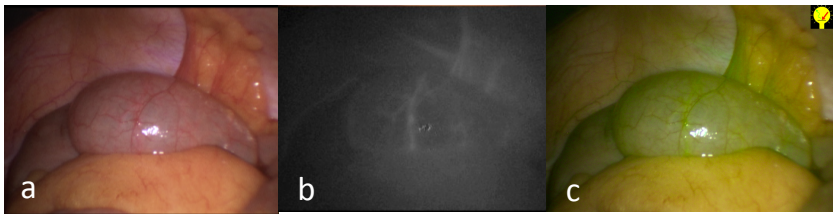


Figure 3

Figure 3

A



Disclosures:

Drs. Frederic Ris, Roel Hompes, Chris Cunningham, Ian Lindsey, Richard Guy, Oliver Jones, Bruce George, Ronan A Cahill, Neil J Mortensen have no conflicts of interest or financial ties to disclose

References:

[1] Ashraf SQ, Burns EM, Jani A, Altman S, Young JD, Cunningham C, Faiz O, Mortensen NJ. The economic impact of anastomotic leakage after anterior resections in English NHS hospitals: are we adequately remunerating them? Colorectal Dis. 2013;15(4):e190-8.

[2] Vignali A, Gianotti L, Braga M, Radaelli G, Malvezzi L, Di Carlo V. Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. Dis Colon Rectum. 2000;43(1):76-82.

[3] Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, Strong SA, Oakley JR. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg. 1997;185(2):105-13.

[4] Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochranesystematic review of randomised controlled trials. Cancer Treat Rev. 2008;34(6):498-504.

[5] Shogan BD, Carlisle EM, Alverdy JC, Umanskiy K. Do We Really Know Why Colorectal Anastomoses Leak? J Gastrointest Surg. 2013 May 21. [Epub ahead of print]

[6] Allison AS, Bloor C, Faux W, Arumugam P, Widdison A, Lloyd-Davies E, Maskell G. The angiographic anatomy of the small arteries and their collaterals in colorectal resections: some insights into anastomotic perfusion. Ann Surg. 2010;251(6):1092-7.

[7] Sherwinter DA. Transanal near-infrared imaging of colorectal anastomotic perfusion. Surg Laparosc Endosc Percutan Tech. 2012;22(5):433-6.

[8] Sherwinter DA, Gallagher J, Donkar T. Intra-operative transanal near infrared imaging of colorectal anastomotic perfusion: a feasibility study. Colorectal Dis. 2013;15(1):91-6.

[9] Jafari MD, Lee KH, Halabi WJ, Mills SD, Carmichael JC, Stamos MJ, Pigazzi A. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. Surg Endosc. 2013 Feb 13. [Epub ahead of print]

[10] Liu DZ, Mathes DW, Zenn MR, Neligan PC. The application of indocyanine green fluorescence angiography in plastic surgery. J Reconstr Microsurg 2011;27(6):355-64.

[11] Onoda S, Azumi S, Hasegawa K, Kimata Y. Preoperative identification of perforator vessels by combining MDCT, doppler flowmetry, and ICG fluorescent angiography. Microsurgery 2013;33(4):265-9.

[12] Paumgartner G. The handling of indocyanine green by the liver (1975) Schweiz Med Wochenschr 105:1.

[13] Cahill RA, Ris F, Mortensen NJ. Near-infrared laparoscopy for real-time intra-operative arterial and lymphatic perfusion imaging. Colorectal Dis 2011;13 Suppl 7:12-7.

[14] Cahill RA, Anderson M, Wang LM, Lindsey I, Cunningham C, Mortensen NJ. Near-infrared (NIR) laparoscopy for intraoperative lymphatic road-mapping and sentinel node identification during definitive surgical resection of early-stage colorectal neoplasia. Surg Endosc 2012;26(1):197-204.

[15] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205-13.

[16] Zhuang CL, Ye XZ, Zhang XD, Chen BC, Yu Z. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum 2013;56:667-78.

[17] Sharma A, Deeb AP, Rickles AS, Iannuzzi JC, Monson JR, Fleming FJ. Closure of defunctioning loop ileostomy is associated with considerable morbidity. Colorectal Dis 2013;15(4):458-62.

[18] Diana M, Noll E, Diemunsch P, Dallemagne B, Benahmed MA, Agnus V, Soler L, Barry B, Namer IJ, Demartines N, Charles AL, Geny B, Marescaux J. Enhanced-Reality Video Fluorescence: A Real-Time Assessment of Intestinal Viability. Ann Surg. 2013 Mar 25. [Epub ahead of print]

5. Preliminary results on lymphnode mapping in colorectal surgery:

We performed some preliminary experiment to prove the feasibility of lymphnode mapping (Figures 1-4), but a larger number of cases needs to be done to allow a correct mapping of the lymphnodes and a reliable correlation between the first draining lymphnode (sentinel node) seen and the results of the histopathologic examination.

The initial work-up allowed us to establish a reliable method of endoscopic submucosal injection and NIR (Near Infrared) Lymphnode mapping, either in vivo or ex vivo.

The NIR node identification is possible after an intraluminal injection of indocyanine green (ICG, concentration of 2.5mg/ml or 1.25 mg/ml) at the site of the lesion (Figure1), the near infrared imaging acquisition of the lymphatics and nodes as seen in Figure 2. IDC was injected at the time of surgery, except in one case where it was very difficult to see the nodes because of a very strong background and diffusion of IDC. The nodes are identified with the indocyanine green label (as hyperfluorescent in a dark background), they were marked (putative sentinel nodes with a clip or a stich as well as further labelled nodes) (Figure 3). Aberrant nodal drainage when seen is documented trough the cases. An aberrant drainage was reported to be seen in about 10% of the cases, however we could not reproduce this because of a large number of NIR on the ex vivo specimen.

For ex-vivo mapping, the specimen has been labelled with the same principles as in vivo, as shown in figure 4, but it has been performed after the initial resection. No aberrant drainage can be seen with this approach

Altogether, we performed 14 in vivo and ex-vivo imaging.

A conventional resection (laparoscopic high anterior resection) was carried out in every cases and the specimen re-imaged on the bench and any anomalies noted.

It was possible to identify LN in every cases except in one, median number of LN retrieved of 5 (0-6).

There was only one N1 patient where the LN was identified, all other 13 patients were N0. Histopathology confirmed the presence of lymphnodes were we labelled them.

Figure 1:

Endoscopic intraluminal injection of Indocyanine green, on two differents areas, after injecting some saline solution first (NaCl 0.9%), then 1.5 ml of the IDC solution at 2.5mg/ml.

A. before injection

B. after the injection

C. laparoscopic view of the dye in normal light at the site of the lesion.

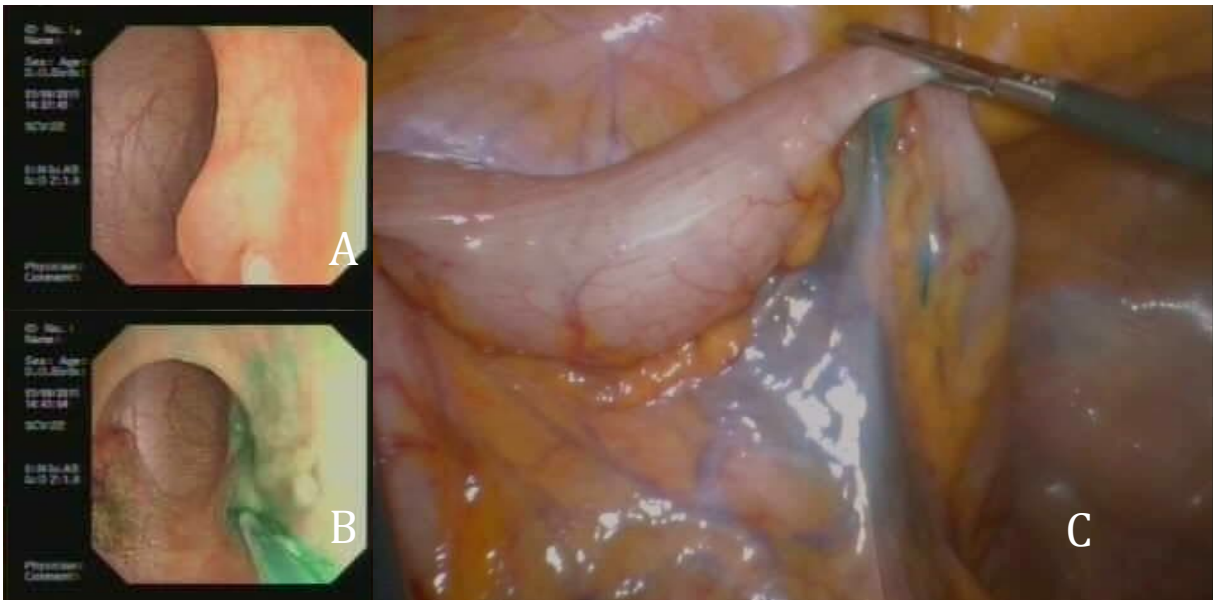


Figure 2:

Near infrared imaging of the lymphnodes, on normal light on the left (the arrow shows where the lymphode is located, which is invisible on white light), then with the near infrared imaging on the right.

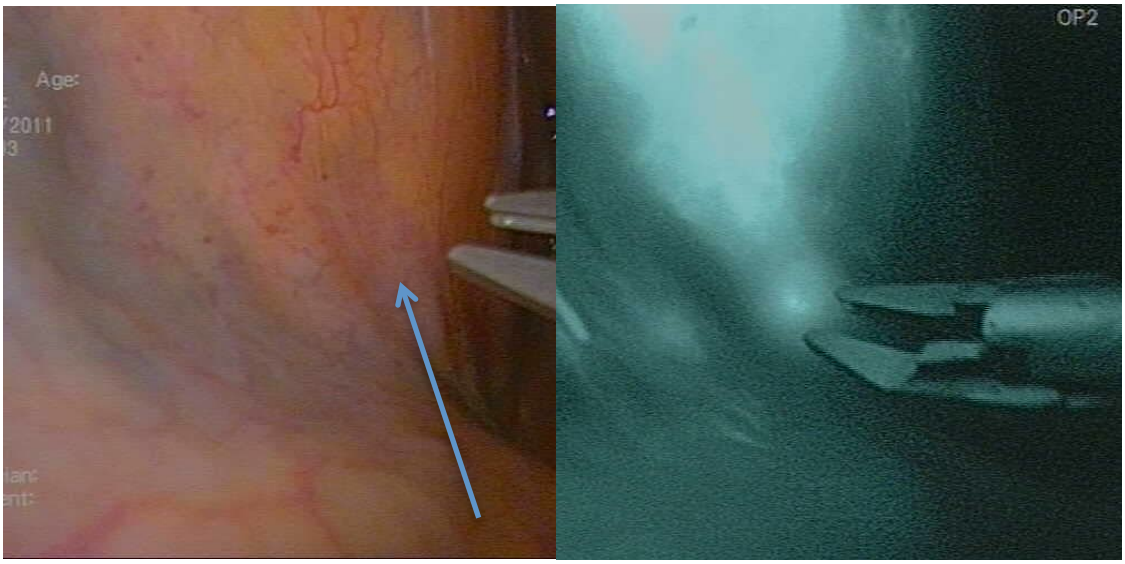


Figure 3:

Lympnode labelling in vivo: it is possible to follow the labelling of the lymphnodes with near infrared light.

It allows as well to tag them with a clip or a tie.

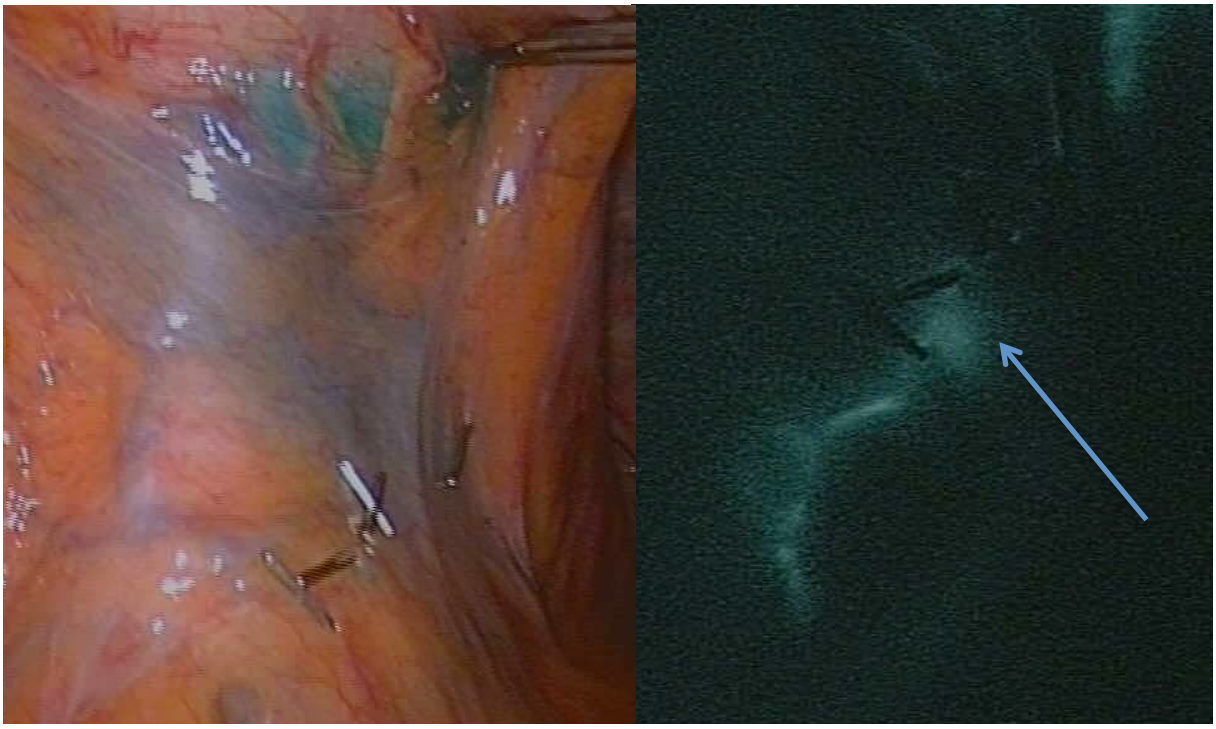
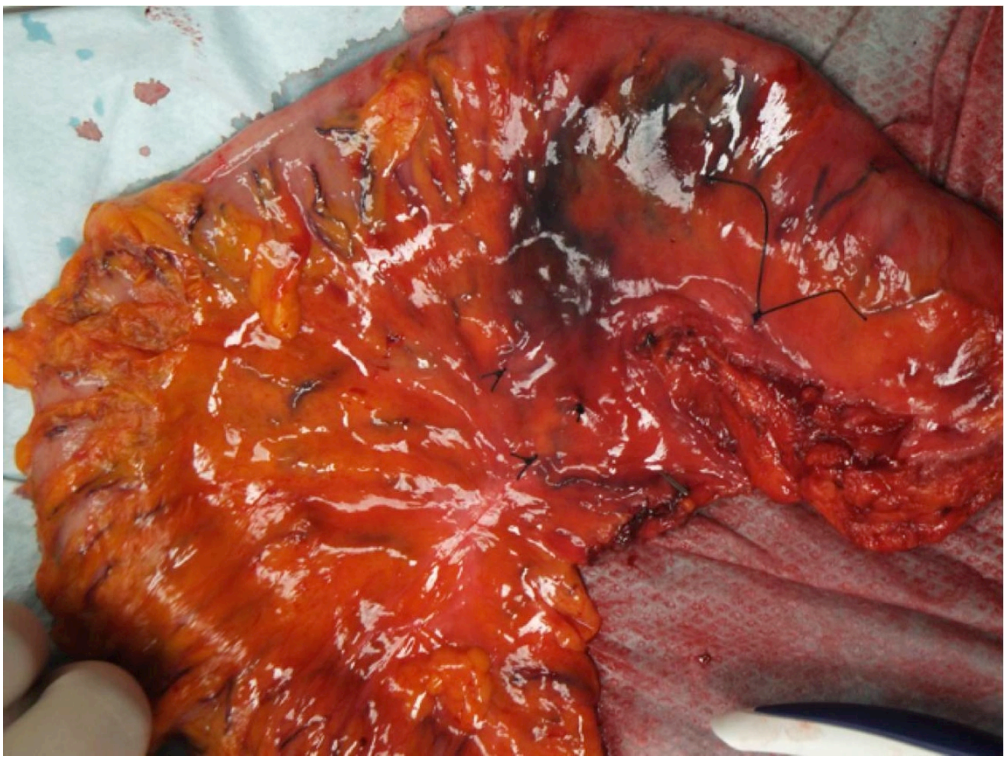


Figure 4:

Ex-vivo lymphnode mapping, the sentinel node is tagged with a long stich, while the other are the following identified lymphnodes, they are not visible on normal light.



6. Perspectives

Indocyanine green is one of the most interesting and promising tool to increase surrounding reality at this time. It is a tool to assess blood supply as well as to follow lymphatic spread in colorectal surgery. Those two aspects are part of my research focus.

NIR anastomosis angiogram:

According to the published results, we know that the NIR evaluation of an anastomosis is highly feasible and seems reproducible in all kind of surgeries (cancer, Crohn's disease, right hemicolectomies, high and low anterior resections). NIR microvascularisation assessment is not prolonging the length of surgery (median time to do the procedure less than 5 min). Furthermore, in low anterior resection it allowed us not to perform a stoma in 3 out of 6 of the cases. The tolerance is excellent after an iv infusion and their was no side effects to report. There was no anastomotic leak, even in the ASA III patient, despite a respiratory distress and the need of an ITU stay.

One of the limitation of the published studies is the small number of patients and according to our power calculations, a decrease of 50% of anastomotic leak would need a prospective study in more than 800 patients, with 400 patients in each arm, to be able to see a difference between the 2 arms.

We need a prospective trial among fluorescence oriented centers which could answer the question of the clinical relevance of this new technology. A decrease in leak rate even by 1or 2% would considerably decrease the cost related to a leak in quality of life or financial terms.

Quantitative assessment of the quality if the perfusion also needs to be addressed to be able to give a clear cut off value among which an anastomotic insufficiency would be predictable.

This technique is very promising due to the possibility to assess an anastomosis even in case of minimally invasive surgeries in a very short amount of time.

The future will lead to the development of algorithms to allow a better real time quantification of the signal at the time of injection, as well as the time to reach the anastomosis.

Other application of the technology from the vascularisation point of view is the use in an acute setting for example for an ischemic bowel or after reperfusion, as well as in other field of surgery, like for example in upper Gastrointestinal surgery anastomosis (oesophageal resection/ gastric resection or gastric bypass) or in plastic surgery in case of complex flap procedures to assess the viability during the procedure or the follow up.

In conclusion this on time evaluation of the microvascularisation is highly valuable especially in minimally invasive surgery, there is many development possible just in this area with a wide range of application in the future. At this time there is no valid alternative available.

Lymphnode mapping:

A facility to confidently identify the first order draining or 'sentinel' nodes (i.e. those nodes first to harbour metastatic cells in the case of lymphatic dissemination occurring) independent of the performance of the radical resection could allow determination of nodal status of the patient without radical resection and hence, in the future, allow those without lymph node involvement be considered for localised resection of their primary cancer alone as their definitive surgical therapy.

We believe, according to our preliminary work, that it is possible to map the first draining node. If we can first prove that the sentinel lymphnode mapping is a reliable tool to assess lymphnode invasion compared to routine histopathology, we will be able to move forward and to plan a real time lymphnode identification and analysis during the surgical procedure. To be able to perform it we will use the One step nucleic acid Amplification (OSNA) system for example. This system canallow to identify positive lymphnodes and has been shown to upstage normal pathological staging in different colorectal papers[18-20].

We will design a study to perform a careful pathological examination that will identify, map and remove marked nodes for histopathology, immunocytochemistry and OSNA (trisection). This protocol will permit to assess the efficacy of the node trisection. Concordance between the three methods need to be studied. The putative sentinel node will be compared with the whole lymph node burden and its potential for prediction of true lymph node status assessed.

A predictive score will be developed. Only then will the feasibility of in theatre node biopsy and OSNA be tested.

Once the proof of principle established, a real time (during surgery) lymphnodes analysis with the OSNA system will be possible, tagged lymphnodes will be tested in theatre in real time with OSNA. It will allow to give informations about the real time needed to perform the test during surgery

All specimens will be sent for histological examination. In addition to standard histological examination, the first draining nodes will fine immunohistochemical analysis in the case of any being negative on initial conventional examination but where metastases are present in the non-sentinel nodes. These nodes will be more extensively examined than it is usually by routine testing.

This is a potentially game changing project. Lymph node mapping is in its infancy and real time nodal molecular assessment is right on the cutting edge of pathology advances. If successful we would be able to establish the principle of safe tailored surgery with smaller resections for patients without cancer in their lymph nodes.

Transversal applications:

The development in the field of lymphnode mapping is going very fast and even if we focus our main interest on colorectal disease, this could potentially lead to further application in other organs such as the liver, pancreas or stomach for example.

A robotic application is possible with this technology, the firefly near infrared system on the robot comes from the Novadaq company and is therefore fully similar.

7. Conclusion:

The use of Indocyanine green and the near infrared technology allows to increase the reality in a way that was never possible before. There is a broad development of those techniques in the operating field and that will lead to major change in the management we have of our patients, being able to identify problems before they are visible on normal light, and to prevent unexpected complications.

Our experience with the microvascularisation assessment is already very valuable and we need to have prospective randomised studies to be able to prove the benefit over the normal visual assessment. The first draining lymphnode concept is relevant from a clinical point of view, with no available alternatives and allow to tailor the surgery the patient needs according to labelling of the Lymphnodes in real time. Current application is carried in our institution and has already allowed improvement in patient's care.

New biomarkers are emerging and will certainly increase the labelling specificity of one or the other structure we want to have a better perception.

The Near infrared technology will be able in the future to better outline the way we perform endoscopy, surgery and therefore to improve significantly patient outcomes and hospital costs.

8. Additional Material:

- Published as a video (CDI-00731-2013) in Colorectal disease

Near infrared (NIR) laparoscopic assessment of perfusion sufficiency of digestive anastomosis

F.Ris, R. Hompes, I. Lindsey, C. Cunningham, N.J. Mortensen and R. Cahill

Onlinelibrary.wiley.com/journal/10.1111/(ISSN) 1463-1318

Http://vimeo.com/84463618

- Accepted for publication in Clinics in colorectal surgery

Enhanced reality and intraoperative imaging in colorectal surgery

F Ris, T. Yeung, R. Hompes, N Mortensen

9. References:

Most of the references are already cited in the presented articles.

1. Vignali A, Gianotti L, Braga M, Radaelli G, Malvezzi L, Di Carlo V. Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. Dis Colon Rectum 2000;**43**(1): 76-82.

2. Ishii M, Tanaka E, Imaizumi T, Sugio Y, Sekka T, Tanaka M, Yasuda M, Fukuyama N, Shinozaki Y, Hyodo K, Tanioka K, Mochizuki R, Kawai T, Mori H, Makuuchi H. Local VEGF administration enhances healing of colonic anastomoses in a rabbit model. Eur Surg Res 2009;**42**(4): 249-257.

3. Attard JA, Raval MJ, Martin GR, Kolb J, Afrouzian M, Buie WD, Sigalet DL. The effects of systemic hypoxia on colon anastomotic healing: an animal model. Dis Colon Rectum 2005;**48**(7): 1460-1470.

4. Grommes J, Binnebosel M, Klink CD, von Trotha KT, Schleimer K, Jacobs MJ, Neumann UP, Krones CJ. Comparison of intestinal microcirculation and wound healing in a rat model. J Invest Surg 2013;**26**(1): 46-52.

5. Bertelsen CA, Andreasen AH, Jorgensen T, Harling H, Danish Colorectal Cancer G. Anastomotic leakage after curative anterior resection for rectal cancer: short and long-term outcome. Colorectal Dis 2010;**12**(7 Online): e76-81.

6. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis 2009;**11**(4): 354-364; discussion 364-355.

7. Killeen S, Mannion M, Devaney A, Winter DC. Complete mesocolic resection and extended lymphadenectomy for colon cancer: a systematic review. Colorectal Dis 2014.

8. Hashiguchi Y, Hase K, Ueno H, Mochizuki H, Shinto E, Yamamoto J. Optimal margins and lymphadenectomy in colonic cancer surgery. Br J Surg 2011;**98**(8): 1171-1178.

9. Cahill RA, Anderson M, Wang LM, Lindsey I, Cunningham C, Mortensen NJ. Near-infrared (NIR) laparoscopy for intraoperative lymphatic road-mapping and sentinel node identification during definitive surgical resection of early-stage colorectal neoplasia. Surg Endosc 2011.

10. Reuthebuch O, Haussler A, Genoni M, Tavakoli R, Odavic D, Kadner A, Turina M. Novadaq SPY: intraoperative quality assessment in off-pump coronary artery bypass grafting. Chest 2004;**125**(2): 418-424.

11. Kubota K, Kita J, Shimoda M, Rokkaku K, Kato M, Iso Y, Sawada T. Intraoperative assessment of reconstructed vessels in living-donor liver transplantation, using a novel fluorescence imaging technique. J Hepatobiliary Pancreat Surg 2006;**13**(2): 100-104.

12. Allison AS, Bloor C, Faux W, Arumugam P, Widdison A, Lloyd-Davies E, Maskell G. The angiographic anatomy of the small arteries and their collaterals in colorectal resections: some insights into anastomotic perfusion. Ann Surg 2010;**251**(6): 1092-1097.

13. Liu DZ, Mathes DW, Zenn MR, Neligan PC. The application of indocyanine green fluorescence angiography in plastic surgery. J Reconstr Microsurg 2011;**27**(6): 355-364.

14. Onoda S, Azumi S, Hasegawa K, Kimata Y. Preoperative identification of perforator vessels by combining MDCT, doppler flowmetry, and ICG fluorescent angiography. Microsurgery 2013.

15. Ris F, Hompes R, Lindsey I, Cunningham C, Mortensen NJ, Cahill RA. Near Infra-red (NIR) laparoscopic assessment of the adequacy of blood perfusion of intestinal anastomosis. Colorectal Dis 2014.

16. Sherwinter DA, Gallagher J, Donkar T. Intra-operative transanal near infrared imaging of colorectal anastomotic perfusion: a feasibility study. Colorectal Dis 2013;**15**(1): 91-96.

17. Jafari MD, Lee KH, Halabi WJ, Mills SD, Carmichael JC, Stamos MJ, Pigazzi A. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. Surg Endosc 2013.

18. Croner RS, Schellerer V, Demund H, Schildberg C, Papadopulos T, Naschberger E, Sturzl M, Matzel KE, Hohenberger W, Schlabrakowski A. One step nucleic acid amplification (OSNA) - a new method for lymph node staging in colorectal carcinomas. J Transl Med 2010;**8**: 83.

19. Visser M, Jiwa M, Horstman A, Brink AA, Pol RP, van Diest P, Snijders PJ, Meijer CJ. Intra-operative rapid diagnostic method based on CK19 mRNA expression for the detection of lymph node metastases in breast cancer. Int J Cancer 2008;**122**(11): 2562-2567.

20. Yamamoto H, Sekimoto M, Oya M, Yamamoto N, Konishi F, Sasaki J, Yamada S, Taniyama K, Tominaga H, Tsujimoto M, Akamatsu H, Yanagisawa A, Sakakura C, Kato Y, Matsuura N. OSNA-based novel molecular testing for lymph node metastases in colorectal cancer patients: results from a multicenter clinical performance study in Japan. Ann Surg Oncol 2011;**18**(7): 1891-1898.

Acknowledgment:

I would like to thank my wife Sabrina and my children Ludovic and Clémentine for their support during the redaction of this thesis.

I would like to thank Professor Morel giving the necessary support and infrastructure to allow development of new technologies in our institution.

I would like to thank Professor Neil Mortensen, Professor Ronan Cahill and all the colorectal consultants in Oxford, especially Mr Roel Hompes for sharing their views on those project and allowing me to be part of it from the beginning at the level of a fellow, as well as to continue to have regular collaborations and discussions together among those projects.

Thank as well to all the fellows, registrars, clinical staff or scrub nurses in Oxford or Geneva supporting this research and looking for all new developments and possible applications to improve the patient's care.