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Natural orifice transluminal endoscopic surgery and localized resection for colorectal neoplasia

Ronan A Cahill, Neil J Mortensen

Ronan A Cahill, Neil J Mortensen, Department of Colorectal Surgery, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, United Kingdom

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Correspondence to: Ronan A Cahill, MD, Department of Colorectal Surgery, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, United Kingdom. cahillra@gmail.com
Telephone: +44-1865-220937 Fax: +44-1865-851173

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Abstract

Modern methods of surgical intervention have the potential to provide effective, definitive management of early stage colorectal neoplasia by truly minimally invasive means. Margin-free clearance of early colonic neoplasia from within the intestinal lumen can already now be effected by endoscopic submucosal dissection in the colon and transluminal endoscopic microsurgery (TEM) in the rectum. Natural orifice transluminal endoscopic surgery (NOTES) offers the potential for providing transmural, full thickness excision as TEM does but at sites in the colon proximal to the rectum. The next conceptual advance required to make this practice an effective reality lies in evolving surgical regional staging strategies to effectively partner localized resective approaches and allow their deployment as definitive curative therapy. As the most compelling modality for nodal status ascertainment in the absence of lymphatic basin excision for other malignant disease processes, it seems timely to reconsider sentinel node biopsy in cancer of the colon and rectum. Whether by this means or indeed any other, such an ability to confidently identify patients with node negative disease would allow nascent innovative techniques flourish as definitive management for confined (N0) T1 and T2 cancers and so allow the application of available advanced tech-

nology for clinical benefit. Conversely, the development of a specific clinical niche for NOTES (whether, as here, for full thickness localized colonic excision or nodal staging alone) would greatly benefit the evolution and incorporation of this surgical strategy into clinical care paradigms.

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INTRODUCTION

As much as representing an alternative access route, natural orifice transluminal endoscopic surgery (NOTES) may prompt re-evaluation of the operative blueprint for intra-abdominal operations for colorectal neoplasia. This is because it poses a stimulating challenge to expert groups intent on surmounting the technical aspects of confined operative space but also, and, more importantly, as a means of making this potential advance relevant to clinical practice. By minimizing operative access alone, laparoscopy has already provided clear short-term benefits to patients in terms of postoperative pain and convalescence rates^[1-3]. Combining focused intra-abdominal operation with minimized access may add synergistically to patient outcome if oncological providence can be assured so that cure rates are not compromised. From the alternative perspective, exact replication

of the entire radical operation as conventionally performed is frustrating for the development of NOTES-type (and indeed single port laparoscopic) operations^[4]. Tailoring the operative approach to the individualized needs of any particular patient with colorectal cancer and thereafter specifically selecting the least invasive suitable approach seems likely to be the next major step change in surgical progress for this disease^[5].

LOCALISED FULL THICKNESS RESECTION OF THE COLON BY NOTES

Provision of a facility to provide full thickness, partial circumference localized resection of a segment of large intestine would seem an ideal niche for the nascent technique of NOTES as currently there is a gap between the capability to provide partial thickness mural resection by endoscopic means (i.e. mucosal and submucosal endoscopic dissection) and conventional radical operation (including resection of sites of potential but unproven nodal metastases). Transluminal endoscopic microsurgery (TEM) can provide partial circumference full thickness resection for the rectum^[6,7], but there is no similar approach available in clinical practice for the colon. However, selected expert groups have already developed methods and means of assuring safe resection of a segment of intestine in survival animal studies using NOTES approaches using both conventional and innovative technology. While the TEM platform can be adapted for use to provide rigid instrumentation through the rectum^[8], standard, flexible endoscopic and laparoscopic equipment can also be employed *via* combined transgastric and transcolonic routes to allow two expert surgeons to work in concert to provide full thickness segmental excision^[9]. By including the colotomy within the resected specimen, this approach leaves only the gastrotomy site as the single peritoneal access site. While further technological development to ensure safe visceral access sites is still required, there is sufficient promise in the techniques under evaluation to suggest this concern will be surmounted in the near future^[10]. In addition, many of the elements developed for employment in this method can be directly transposed to laparoscopic operations for benign disease^[11].

ONCOLOGICAL ASPECTS OF LOCALISED RESECTION

The current requirement for radical mesocolonic and mesorectal excision in combination with resection of the colorectal primary is predominantly based on the need to ensure nodal staging in every case and resection of all disease containing sites in node-positive patients. Despite advances in preoperative imaging, the majority of nodes bearing cancer deposits in colorectal cancer patients lie beneath the size threshold of resolution (5 mm) of both computerized tomograms and magnetic resonance imaging. Already, a small group of patients (10% of the total, a figure equating to 9555 people per year in England

alone and 11500 per year in the United Kingdom) are undergoing a full operation when their entire cancer burden is in fact potentially removable (and curable) by an endoscopic procedure that would not entail removal of any significant length of bowel and that could be performed potentially as a day-case procedure. This figure is set to increase with increasing awareness of early surveillance of higher risk groups (e.g. family history) while the advent of systematic wide-spread screening programmes is expected to further shift the incidence of node-negative disease up to 50%^[12,13]. If nodal status could be assured without radical surgery, the current requirement to perform radical mesenteric resection in every case may then be viewed as exposing the truly node negative patients to additional unnecessary risks of injury during their operation^[14].

Because of this, certain groups have already begun to suggest that limiting operative extent should indeed pay considerable dividend for the patient and indeed the health-care provider and reduce the relatively high morbidity rates associated with radical operation for early stage disease^[15]. Standard surgical staging alone in such node negative patients introduces increased intraoperative risks (e.g. injuries of root mesenteric and paracolic structures such as the ureters, para-aortic nerves and duodenum and spleen). As complete nodal resection requires high arterial ligation, this intraoperative step also induces ischemia on a wider area of intestine than would otherwise be induced by narrow margin excision of the primary lesion. Thus, such radical resection may be implicated at least theoretically in incidences of anastomotic leak (which remain unacceptably frequent across the spectrum of colorectal resection) and postoperative ileus (a major factor in both patient convalescence and hospital stay as well as a cause of readmission in enhanced recovery programmes). Furthermore, postoperative bowel dysfunction complicates patients' recovery after colorectal resection at least in the first postoperative year. Finally, operative extent and lymphatic clearance is directly related to the need for both temporary and permanent stoma formation in cancers of the rectum.

SENTINEL NODE BIOPSY AND COLORECTAL CANCER

Surgeons involved in the care of breast cancer^[16], melanoma^[17] and, more recently, early stage gastric cancer^[18] have recognized the concept of sentinel nodes (SNs) as first order draining nodes and therefore the first possible site of metastasis *via* lymphatic drainage from a primary tumor. Moreover, they have proved that the absence of metastases in these SNs is correlated with the absence of metastases in downstream lymph nodes. Embracing this concept has allowed selection of patients without nodal involvement for simplified operation in these specialties. In this way, for breast cancer, melanoma and, more recently, gastric cancer, surgeons have begun offering limited operations with functional preservation for those patients with node negative disease without oncological compromise.

By contrast, in colorectal cancer this concept has so far been confined to pathological upstaging after conventional operation. Return to its original purpose of selecting node negative patients and its use as an oncological support for minimal resective techniques could therefore pay dividends for selected patients with colorectal malignancy. Further confining lymphatic mapping to patients with early stage disease could also allow it to function with maximum efficiency and effectiveness as it is clear from experience in cancers at other sites, that this technique functions best in those whom can benefit from it the most (i.e. those with localized disease). Supportive evidence for this concept has already been provided by rigorous systematic reviews of the literature^[19] and secondary intention analysis of prospective, high quality databases^[20]. Experimental study has also demonstrated that lymphatic mapping and sentinel node excision can be performed with high accuracy without conventional operative approaches (see below). The proof of the validity of this premise now requires prospective a priori analysis in the clinical setting.

The immediate clinical niche for a minimally invasive approach to SN biopsy within the current clinical care setting is the after-treatment of patients undergoing endoscopic resection (either polypectomy or endoscopic mucosal/submucosal resection) of a lesion in their colon that is subsequently determined to be a completely excised invasive cancer. Conventionally, the gold standard further treatment for such patients is radical resection although this is usually overtreatment as most such patients have truly node negative disease. Sentinel node mapping and biopsy could provide a means for laparoendoscopic determination of nodal burden and hence obviate further radical operations in those proven node negative. For this indication, the ideal mapping agent would be injected immediately prior to the initial endoscopic resection. The agent would then persist both in the colon wall and in the first draining (“sentinel”) nodes and so allow subsequent laparoscopic detection of both the site of the primary and SNs. Analysis of nodes (ideally intraoperatively) would then allow determination of the oncological adequacy of the index procedure and indicate whether further resection is required.

A second role for NOTES with considerable clinical resonance is in the upgrading of endoscopic resective techniques to a definitive surgical treatment of localised (N0) colorectal primary lesions with diameters within their effective range. This would probably entail a combined NOTES/laparoendoscopic approach. Indeed laparoscopic assistance in intraluminal resection has already been advocated by certain experts^[21]. As well as determining the appropriateness of endoscopic resection in the selected case, peritoneal access would also provide a ready means for performing full-thickness localised resection of the primary. Thirdly, proof of capability could subsequently be applied to advancing the role of minimized access operations such as single port operations and ultimately perhaps pure NOTES-type procedures^[22].

SENTINEL NODE BIOPSY AND NOTES

Considerable preclinical work has been expended to demonstrate the feasibility and safety of sentinel node biopsy from the colonic mesentery by NOTES^[23]. Both the concept and practice of the use of the surgical access technique are straightforward either as a nodal biopsy technique alone or in combination with a NOTES segmental resective technique^[24]. A transgastric approach is made to allow a double channel flexible endoscope to access the peritoneum. Thereafter, an intraluminal magnetic frame allows display of the sigmoid colon and mesentery, allowing the *in situ* peritoneoscope to observe the performance of lymphatic mapping by a sigmoidoscope. Choice of a mapping agent that is rapidly taken up by the lymphatics allows the NOTES optic to follow the efferent lymphatics in real-time so that the first order draining node(s) is identified. Thereafter, the sentinel node(s) can be “cherry-picked” from the mesentery and retrieved to the exterior for analysis by either standard pathological evaluation or possibly by rapid intraoperative RT-PCR determination. Additionally, innovative optical biopsy technologies such as Optical Coherence Tomography may in future allow direct *in situ* analysis of nodal status^[25].

CONCLUSION

These developments in surgical capability and shifts in patient demographics mean that there is now, as never before, an opportunity to consider a range of resective options depending on stage of disease at presentation. An ability to confidently direct NOTES development towards the resection of the primary alone, rather than including resection of nodal sites of unproven dissemination, would greatly simplify its progression by sharpening its focus. In addition, a means to ensure correct nodal staging ahead of operative resection would therefore greatly enhance the evolution of the discipline of colorectal surgery overall. Whether or not this role can be fulfilled to absolute satisfaction by SN biopsy is at the moment unproven. Even if definitively proven as not suitable for routine clinical use in this field, the admission that operative surgical extent could be individualized to the disease stage of the patient at presentation would encourage additional work in this field to focus on the basic issues presented here and to work to hone the current surgical paradigm. Therefore, the most important issues are the acceptance of the concept of moving towards individualized surgical extent of resection and the need for appropriate, assiduous evaluation of the potential of new technologies to make this a reality.

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REFERENCES

- 1 **Tjandra JJ**, Chan MK. Systematic review on the short-term outcome of laparoscopic resection for colon and rectosigmoid cancer. *Colorectal Dis* 2006; **8**: 375-388
- 2 **Schwenk W**, Haase O, Neudecker J, Müller JM. Short term benefits for laparoscopic colorectal resection. *Cochrane Database Syst Rev* 2005; CD003145
- 3 **Murray A**, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, Krukowski Z, Vale L, Grant A. Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation. *Health Technol Assess* 2006; **10**: 1-141, iii-iv
- 4 **Cahill RA**, Marescaux J. Natural orifice transluminal endoscopic surgery (N.O.T.E.S.) for oncologic disease. *Surg Oncol* 2009; **18**: 91-93
- 5 **Cahill R**, Lindsey I, Cunningham C. NOTES for colorectal neoplasia--surgery through the looking glass. *Gut* 2009; **58**: 1168-1169
- 6 **Bretagnol F**, Merrie A, George B, Warren BF, Mortensen NJ. Local excision of rectal tumours by transanal endoscopic microsurgery. *Br J Surg* 2007; **94**: 627-633
- 7 **Tytherleigh MG**, Warren BF, Mortensen NJ. Management of early rectal cancer. *Br J Surg* 2008; **95**: 409-423
- 8 **Whiteford MH**, Denk PM, Swanström LL. Feasibility of radical sigmoid colectomy performed as natural orifice transluminal endoscopic surgery (NOTES) using transanal endoscopic microsurgery. *Surg Endosc* 2007; **21**: 1870-1874
- 9 **Leroy J**, Cahill RA, Perretta S, Forgione A, Dallemagne B, Marescaux J. Natural orifice transluminal endoscopic surgery (NOTES) applied totally to sigmoidectomy: an original technique with survival in a porcine model. *Surg Endosc* 2009; **23**: 24-30
- 10 **Perretta S**, Sereno S, Forgione A, Dallemagne B, Coumaros D, Boosfeld C, Moll C, Marescaux J. A new method to close the gastrotomy by using a cardiac septal occluder: long-term survival study in a porcine model. *Gastrointest Endosc* 2007; **66**: 809-813
- 11 **Leroy J**, Cahill RA, Asakuma M, Dallemagne B, Marescaux J. Single-access laparoscopic sigmoidectomy as definitive surgical management of prior diverticulitis in a human patient. *Arch Surg* 2009; **144**: 173-179; discussion 179
- 12 **Fazio L**, Cotterchio M, Manno M, McLaughlin J, Gallinger S. Association between colonic screening, subject characteristics, and stage of colorectal cancer. *Am J Gastroenterol* 2005; **100**: 2531-2539
- 13 **Pignone M**, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; **137**: 132-141
- 14 **Cahill RA**. Regional nodal staging for early stage colon cancer in the era of endoscopic resection and N.O.T.E.S. *Surg Oncol* 2009; **18**: 169-175
- 15 **Cahill RA**, Leroy J, Marescaux J. Localized resection for colon cancer. *Surg Oncol* 2009; **18**: 334-342
- 16 **Mabry H**, Giuliano AE. Sentinel node mapping for breast cancer: progress to date and prospects for the future. *Surg Oncol Clin N Am* 2007; **16**: 55-70
- 17 **Balch CM**, Morton DL, Gershenwald JE, McMasters KM, Nieweg OE, Powell B, Ross MI, Sondak VK, Thompson JF. Sentinel node biopsy and standard of care for melanoma. *J Am Acad Dermatol* 2009; **60**: 872-875
- 18 **Kitagawa Y**, Saikawa Y, Takeuchi H, Mukai M, Nakahara T, Kubo A, Kitajima M. Sentinel node navigation in early stage gastric cancer--updated data and current status. *Scand J Surg* 2006; **95**: 256-259
- 19 **Cahill RA**, Leroy J, Marescaux J. Could lymphatic mapping and sentinel node biopsy provide oncological providence for local resectional techniques for colon cancer? A review of the literature. *BMC Surg* 2008; **8**: 17
- 20 **Cahill RA**, Bembenek A, Sirop S, Waterhouse DF, Schneider W, Leroy J, Wiese D, Beutler T, Bilchik A, Saha S, Schlag PM. Sentinel node biopsy for the individualization of surgical strategy for cure of early-stage colon cancer. *Ann Surg Oncol* 2009; **16**: 2170-2180
- 21 **Cahill RA**, Asakuma M, Perretta S, Leroy J, Dallemagne B, Marescaux J, Coumaros D. Supplementation of endoscopic submucosal dissection with sentinel node biopsy performed by natural orifice transluminal endoscopic surgery (NOTES) (with video). *Gastrointest Endosc* 2009; **69**: 1152-1160
- 22 **Cahill RA**, Lindsey I, Cunningham C. Address of early stage primary colonic neoplasia by N.O.T.E.S. *Surg Oncol* 2009; **18**: 163-168
- 23 **Cahill RA**, Perretta S, Leroy J, Dallemagne B, Marescaux J. Lymphatic mapping and sentinel node biopsy in the colonic mesentery by Natural Orifice Transluminal Endoscopic Surgery (NOTES). *Ann Surg Oncol* 2008; **15**: 2677-2683
- 24 **Cahill RA**, Perretta S, Forgione A, Leroy J, Dallemagne B, Marescaux J. Multimedia article. Combined sentinel node biopsy and localized sigmoid resection entirely by natural orifice transluminal endoscopic surgery: a new challenge to the old paradigm. *Dis Colon Rectum* 2009; **52**: 725
- 25 **Cahill RA**, Asakuma M, Trunzo J, Schomisch S, Wiese D, Saha S, Dallemagne B, Marks J, Marescaux J. Intraoperative virtual biopsy by fibered optical coherence tomography (OCT) at natural orifice transluminal endoscopic surgery (NOTES). *J Gastrointest Surg* 2010; **14**: 732-738

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