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Review

Natural orifice transluminal endoscopic surgery – here and now[☆]

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ABSTRACT

Natural Orifice Transluminal Endoscopic Surgery (NOTES) has captured the attention of physicians and patients alike. Although clinical experience remains limited as technological capacity lags somewhat behind concept, this revolutionary approach is already prompting reassessment of conventional surgical dogma. Indeed, this very aspect may in fact represent the greatest legacy of current endeavour aimed at progressing natural orifice intervention as the biological insights so gleaned may then be used to help hone standard operations further towards perfection. As a corollary, rather than viewing it as a mere means of reformatting laparoscopic operation without the abdominal wall access component, NOTES should be investigated fully from the perspective of how it may complement (rather than compete with) current conventional techniques. In this way patients may in due course be allowed benefit by selection of the procedure of 'best fit' from an expanded array of surgical interventions. A clear focus on identifying specific clinical niches that are currently imperfectly addressed would also considerably advance the rationale for new surgical innovations such as NOTES and allow them to be engineered in the directions most likely to result in therapeutic advance. Thus while NOTES approaches for operations for neoplasia of the colon and even rectum clearly require more nuanced deliberation and care than does for example cholecystectomy for uncomplicated cholelithiasis, the gain from such investment seems likely to more considerably aid both the development and stature of NOTES as well as providing the greater likelihood of clinical progress for our patients.

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'To Hope till hope creates, from its own wreck, the thing it contemplates.'

Demogorgon, Prometheus Unbound (1820): 4; 570–8.
Percy Bysshe Shelley.

Background

Natural Orifice Transluminal Endoscopic Surgery, or NOTES, conveys the concept of performing surgical operations within the abdominal or even thoracic cavities using access achieved

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via a natural orifice (i.e. the mouth, anus, urethra or vagina). While certain NOTES inspired procedures such as 'intra-luminal appendectomy' are feasible without luminal egress, most others involve visceral breach and exit (i.e. transgastric, transcolonic, transvisceral or transvaginal penetration). In exchange for the potential increased risk in infection rates inherent to such violation (due to perioperative contamination as well as the risk of visceral leakage due to incompetent access site closure), such approaches have been promoted as facilitating 'no (visible) scar' surgery. In this way, as much as offering cosmetic advantage, abdominal wall complications such as superficial surgical site infection as well as wound dehiscence and herniation should be obviated while the anterior peritoneal plane is preserved for any future operation. Indeed, natural orifice access may allow direct access to hitherto relatively inaccessible organs (e.g. approaching the body of the pancreas by entering the lesser sac via the posterior gastric wall). Finally, proponents hope that post-procedural pain may be markedly lessened while others tentatively propose that the need for general anaesthesia and, even, conventional theatre sterility protocols may be diminished. For these reasons, many view the emergence of NOTES as both a logical progression in the development of minimally invasive surgery and proof that 'human ingenuity and invention can continue to deliver more effective treatments by increasingly less invasive means'.¹

However, although NOTES possesses much intuitive appeal, claims regarding its potential have not gone unopposed. Some experts do not see it offering significant physical advantages over standard laparoscopic approaches and conceive it only in terms of presenting marginal cosmetic advantage.^{2,3} In addition, many fear that the clumsiness and imprecision of current instrumentation will lead to both operator distress and patient morbidity at least in the short-term. Certain experts have however gone further in insisting that the approach is 'ill-conceived', risk-prone' and, simply, defies 'good judgment, good sense and sound practice'⁴ while others perceive it only as a 'flout (of) long-established principles' and 'torture (of) convention'.⁵⁻⁷ The proposal of natural access surgery, has also been dismissed as a mere manifestation of 'panache'² and 'pandering to vanity' (of both patient and physician) as well as technical triumph that will be wrought primarily for commercial gain.⁸ It is certainly true that many claims surrounding NOTES have exceeded far beyond the actual current capability of the technique and too often authors have concluded their experience reports leaving much to 'future technological innovation' to address. Furthermore, while very many NOTES 'firsts' have been reported in experimental models (see Table 1) and, increasingly, in humans patients, most concern only replication of the corresponding laparoscopic intervention without the abdominal wall ingress. While useful in the establishment of proof of concept, such investigation is less valuable for the development of a specific niche for NOTES to progress as a distinct clinical specialty.

Clinical impact of NOTES in general

NOTES however is already having an impact on clinical practice helped markedly by the fact that, notwithstanding

the above comments, NOTES-framed concepts and proposals are generally being received with an air of inquisitiveness not afforded laparoscopy and indeed endovascular operations when these innovations were first proposed. Indeed, probably due to the establishment of these latter techniques against the expectations of many, even the harshest criticisms of NOTES have tended to be tempered with an unwillingness to totally dismiss the concept.⁴ This combined with considerable, burgeoning interest among allied specialties (particularly gastroenterology) have meant that basic studies and proof of concept models have been embraced by many surgical and gastroenterological journals with a vigour somewhat greater than the scientific rigour of their execution would suggest appropriate. The initial publication base has though at least been marked by an egalitarianism in that such is the novelty of this approach no-one group can specifically claim special expertise based on prior credentials.

Because of NOTES, many surgical units are looking anew at endoscopic techniques and undertaking specific training in flexible endoscopy. Considerable interest in laparoendoscopic techniques has also been generated and surgeons are seriously deliberating means of minimising trocar number by exploring means such as natural orifice specimen extraction and innovative retraction devices. Although reduced port number may be primarily for cosmetic advantage in many general surgical operations, there is consensus that real advantage accrues to bariatric patients if abdominal wall ingress is minimised. Single port laparoscopic surgery has also received a considerable boost with many now viewing it as a stepping stone towards NOTES operations rather than focussing on it purely as an end in itself. Gastroenterologists too have been encouraged to become increasing adventurous in outlook and look set to glean considerable advancement in equipment innovation for their endoluminal procedures as much as their trans-luminal aspirations.

However, while much is made of the technological advances required to enable NOTES to become a clinical reality, only relatively recently have determined attempts been made to specifically site NOTES and NOTES-type interventions within clinical care pathways (rather than mere recreation of the laparoscopic equivalent) so that the benefits for patients of this revolutionary approach are maximised.^{3,9} Given the limitations of NOTES procedures in providing for standard operative manoeuvres such as triangulation and the constraints of working via confined access routes, there is considerable incentive to return to the base operative blueprint to distil the intervention to its core surgical and, where neoplastic disease is concerned, oncological essence. Clear identification of specific areas to direct NOTES advancement for clinical gain could concentrate the developmental effort and engineer specific domains for this innovative access route. Conversely, such reappraisal could have considerable reciprocal swash onto standard laparoscopic and even open approaches. Clear refocus on the biological aim of surgical intervention may therefore present the most important initial value of NOTES's emergence and perhaps even may provide its greatest legacy should NOTES per se either not progress or be superseded by another disruptive technology.

Table 1 – List of procedures reported to have been performed by NOTES-techniques both in clinical and experimental settings.

NOTES procedures performed to date

Diagnostic laparoscopy	Staging	Liver biopsy
	peritoneoscopy	
Cholecystectomy	Splenectomy	Ventral hernia repair
Gastrojejunostomy	Pyloroplasty	Tubal ligation
Pseudoappendicectomy	Localised colectomy	Segmental colectomy
Nephrectomy	Adrenalectomy	Distal pancreatectomy
Gastric sleeve resection	Wedge gastrectomy	Heller's myotomy
Pleural cavity biopsy	Myocardial injection	Diaphragm pacing

Potential impact of NOTES on colorectal surgery

The conceptual separation of colonic surgery into distinct components in colorectal surgery is most easily realised in the approach to excisional surgery for benign disease. Inclusion of the mesenteric resection with the colonic specimen is one of the main limitations on NOTES-type operations because of its need for both wide tissue retraction and major vessel ligation as well as its tendency to increase specimen bulk. Simplification of operative intent therefore would greatly facilitate the performance of the operation via a minimum access route- in the case of resection for diverticular and inflammatory bowel disease, a pericolic line of dissection minimises specimen size, avoids the encounter of major calibre vessels and relieves the need for retraction to access the mesenteric base.¹⁰ Equally, the facility to perform the operation with lesser operative insult may encourage reassessment of the indication for intervention. The current trend in the surgical management of diverticular disease has been to opt for conservative management in the majority of cases due to the risks of surgical intervention. Reducing these risks may shift the focus to intervention for subjective complaints and quality of life issues rather than on objective parameters based on the perspective of the health care provider (i.e. readmission rates).¹¹ Such reappraisal of indication for intervention on the basis of new operative approaches has precedent in the fields of endovascular repair for thoracic and abdominal aortic aneurysms and, more recently, of minimally invasive parathyroidectomy for asymptomatic primary hyperparathyroidism.

More provocatively NOTES may encourage useful re-evaluation in the surgical care pathway for early stage colon cancer. Indeed its advent may represent the beginning of an era of individualisation of surgical strategy for this disease. The contemporary paradigm for colon cancer is rooted in the era where only one operative access (i.e. laparotomy) gave rise to one gold standard operation (i.e. radical segmental colectomy including en bloc mesenteric resection) for every case. This operation was well suited for the address of symptomatic presentations of colorectal malignancy wherein the majority of patients have locally advanced disease. The routine employment of radical mesenteric excision for early stage cases was further justifiable because the operation for

removal of the primary lesion was performed most efficiently by laparotomy (i.e. inclusion of mesenteric excision added little significant additive morbidity or operative effort). As a nascent technology confounded early by misleading reports of oncological complications (such as port site metastases), laparoscopic resections were also best advanced within the standard paradigm and therefore best proven initially by its ability to replicate surrogate markers of adequacy (i.e. specimen lengths and mesenteric lymph node quantity).

However increasing proportions of patients are now diagnosed with early localised disease as a result of increased patient and physician awareness and increased access to highly sensitive non-operative modalities of colorectal examination. Furthermore, the advent of systematic widespread screening programmes is expected to shift the incidence of node-negative disease from 10% of the current total to 50% within the coming few years. Improved outcomes as well as improved insights into 'at risk' populations (mostly as a result of family history and genetic screening) have also increased the numbers of patients undergoing surveillance in order to determine pre-regional neoplastic disease. In tandem with this, the facility to excise early colorectal primary lesions without transgression of the colonic wall is increasingly feasible. As much as Transanal Endoscopic Microsurgery (TEM) is proving its ability to provide margin free resection of rectal lesions so too are advanced endoscopic techniques such as Endoscopic Submucosal Dissection (ESD) for lesions in the colon. Specifically formatted NOTES operations are also developing to allow full-thickness transmural resection of localised lesions.¹² Both the two former interventions are however particularly attractive for the patient as they preserve the colonic wall (the risk of colotomy is putatively similar to that of colonic anastomosis). Therefore, as never before, there is now an opportunity to consider a range of resective options for significant numbers of patients so that the operative approach is tailored to the individualised needs of any particular patient (Fig. 1).

The limiting factor of these technologies is however the current inability to provide for regional staging ahead of or at the same time as address of the primary. Therefore these interventions are currently confined to benign lesions or those at least risk of lymphatic metastases. However it is worth considering that, although the risk of dissemination rises with the degree of mural invasion, the majority of early T-stage tumours do not have lymph node involvement (see Table 2). Whatever the benefits of lymphadenectomy in patients with nodal disease, en bloc mesenteric resection confers no therapeutic benefit in those with truly lymph node negative disease. Given that efficient address of the primary lesion may no longer require recourse to conventional means of resection, such nodal staging may now be viewed as risking increased intraoperative (e.g. injuries of root mesenteric and paracolic structures such as the ureters, para-aortic nerves and even the duodenum and spleen) and postoperative (e.g. ileus and bowel dysfunction) complications. As complete nodal resection requires high arterial ligation, such a task also likely impacts upon anastomotic complications given that this intraoperative step induces ischemia on a wider area of intestine than would otherwise be induced by narrow margin excision of the primary lesion. Furthermore, it is becoming

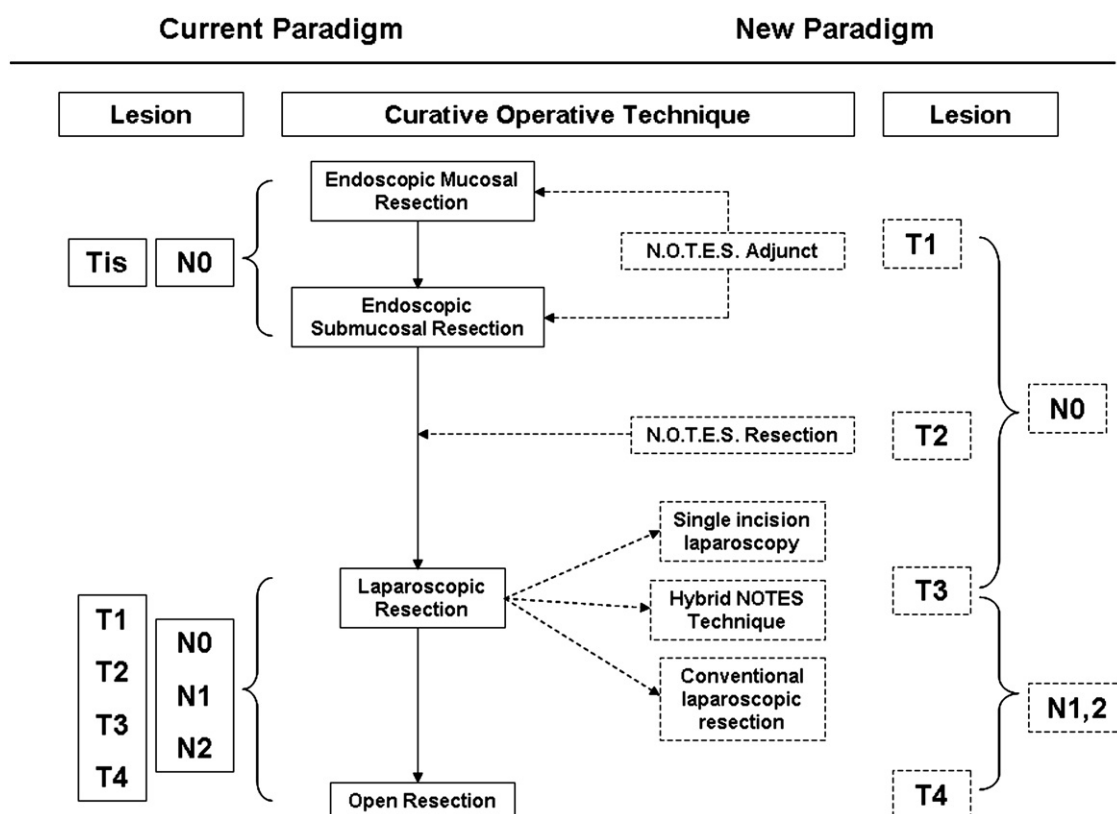


Fig. 1 – Illustrative figure demonstrating how NOTES intervention could alter the standard paradigm for the clinical care of patients with colon cancer by facilitating individualisation of resection extent (from Ref. 28).

increasingly clear that standard mechanisms for lymph node harvest and examination have clear deficiencies and, despite being the current ‘gold standard’, lack standardisation.^{13–16} Exact replication of the entire operation is frustrating for the development of NOTES-type and single port operations and in fact may not be necessary for the patient without node metastases. An ability to confidently direct their development towards the excision of the primary alone, rather than including resection of nodal sites in the absence of regional dissemination, would greatly simplify their progression by sharpening their focus.

Other surgical specialities have already grasped the basic tenets of these arguments and harnessed technology to ensure appropriate resection extent for their patients. Their employment of the sentinel node concept as the first order draining node(s) most likely to contain disseminating tumour

cells has been proven to allow selection of patients without nodal involvement for simplified operation. Furthermore, this modality also provides tissue for direct analysis from nodes lying beneath the threshold of identification by radiological imaging (70% of nodes containing metastases in those with T1 or T2 lesions are less than 5 mm in diameter). In this way, surgery for breast cancer, melanoma and, more recently, gastric cancer have begun offering limited operation with functional preservation for those patients with node negative disease without oncological compromise. In contrast, such sentinel node mapping in colorectal cancer has been confined to date only for the purposes of pathological upstaging after conventional operation has been performed. Realisation that sentinel node mapping can be performed independently (perhaps even by NOTES^{17,18}) to excision of the primary, may return the concept to its original purpose in this disease (i.e. selection of node negative patients) and its use as an oncological support for minimal resective techniques could therefore pay dividends for patients with colorectal malignancy.¹⁹ Further the confinement of lymphatic mapping to patients with early stage disease should allow this technique to function with maximum efficiency and effectiveness as it is clear from prior experience that sentinel node mapping functions best in those with localised disease (also those likely to benefit the most from its deployment).²⁰

There are two means of utilising the ‘sentinel node concept’ for selection of node negative colonic neoplasia. The first is to employ a NOTES or more likely initially a single port

Table 2 – Incidence of lymph node metastases associated with early stage neoplasia and colon. sm denotes the level of submucosal invasion present.

Early stage	Colon cancer (Refs ^{23–27})
T1 Overall	7–15%
sm1	3–4.2%
sm2	8–21.3%
sm3	23–38.5%

type intervention to 'cherry-pick' the sentinel node from the colonic mesentery in support of an ESD-type procedure.²¹ This would allow direct analysis of the node(s) most likely to harbour lymphatic dissemination and so encourage the endoscopist to proceed with intraluminal excision of the primary with confidence. The crucial issue here is ensuring high sensitivity of detection to minimise the risk of overlooking additional sentinel nodes (the median being two) and so dual mapping agents with assiduous preoperative and intraoperative scrutiny for their identification is required. This seems likely to require both fluorescent and radioisotope mapping. The second approach involves extending the concept to that of a 'sentinel basin' as first proposed by Kitagawa and is more suitable for support of localised transmural resections. This concept assumes that in cases where the true sentinel node is not mapped due to obstruction by tumour metastases (as occurs in approximately 40% of false negative cases), the alternative node drainage is likely to lie within the same lymphatic delta rather than being anatomically distant. In cases where a segment of bowel is being removed, the entire mesentery does not need preservation- the central issue is preservation of feeding arterial blood supply to the remaining colon. There is likely to be little additive morbidity from clearing the mesenteric segment containing both the mapped node as well as the 'original' sentinel node while preserving the vascular scaffold (see Fig. 2). Employing sophisticated means of intraoperative optical ('augmented reality' or 'virtual') analysis of entire portions of the mesentery in situ by means such as catheter-based Optical

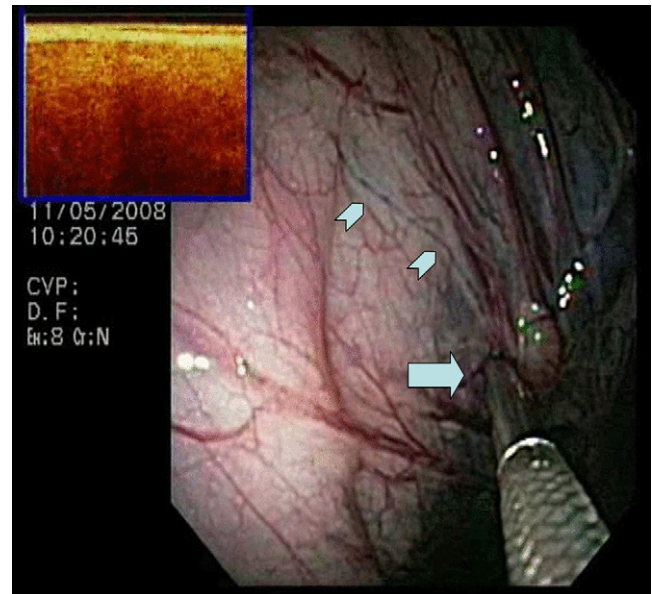


Fig. 3 – Photograph demonstrating virtual biopsy of a sentinel node by employing catheter-based Optical Coherence Tomography (this 'OCT' probe has been inserted down the working channel of a standard gastroscope which has been advanced into the peritoneum transgastrically as a NOTES peritoneoscope²⁹). [The blue chevrons show the course of the blue stained lymphatic afferent channel to the sentinel node which is indicated by the blue arrow].

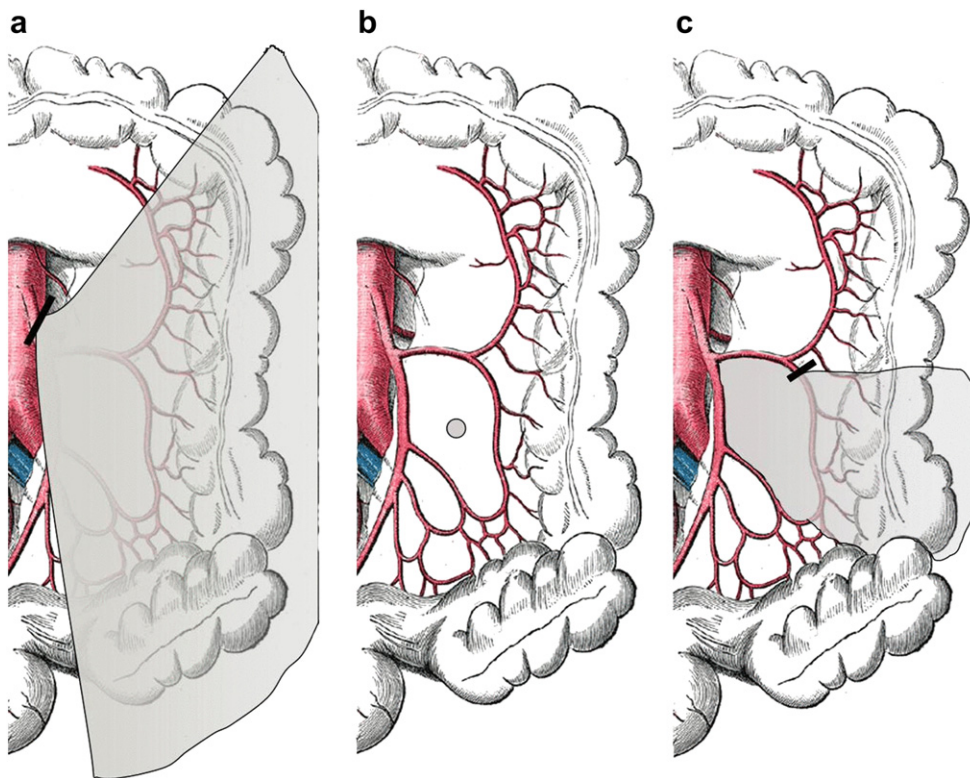


Fig. 2 – Illustrations demonstrating the approaches to sentinel node mapping in the left mesocolon by showing (a) standard radical mesenteric resection, (b) sentinel node 'cherry-picking' and (c) 'sentinel basin' excision. The thick black line represents the level of arterial ligation, the grey area the specimen for resection.

Coherence Tomography (see Fig. 3) could allow overlapping of these concepts by allowing examination of a wide portion of the mesentery without resection and therefore reduce the necessity to deliberately confine focus to a limited region.

Conclusion

While minimisation of abdominal wall ingress is of value particularly in obese patients, entire focus of NOTES on the visible scar aspect of surgery tends to undervalue the potential of the technique. Instead greater utility may be ascribed this revolutionary approach if it is grasped as the spur to reappraise the technical building blocks of surgical intervention. Refocusing on the biological requirement of the operation may then allow simplified operation in line with advanced technological capability for the benefit of patients and advance of the overall science of surgery. Therefore, while the instruments and devices needed to enable NOTES become a reality are in development, equal endeavour and effort needs to be applied in determining and even developing appropriate and useful indications for such intervention. This needs honest reassessment of imperfections and flaws in current operative approaches so that this new approach evolves to deliver the progress in care that we, and our patients, need.

Using NOTES-type operations to maximise the application of accepted endoscopic techniques such as ESD and even perhaps TEM is a particularly exciting area both for this nascent surgical approach and its more established endoluminal counterparts.^{3,22} In particular, performing sentinel node biopsy from the colonic mesentery in order to augment the oncological providence of such advanced intraluminal endoscopic procedures could allow these techniques reach their maximum utility by increasing the proportion of patients with early stage disease suitable for such intervention. Furthermore, such a straight forward procedure as nodal biopsy would seem to lie much more readily within the capability of transmural approaches (at least initially) than more complex intra-abdominal procedures. Proof of effective experience in such procedures would also provide a much stronger basis for advancing NOTES operations towards provision of full-thickness resection colotomy for therapy of more advanced lesions. Finally verification of the oncological premise of such an approach would have considerable impact on standard or even open operations. Minimisation of the operative extent even with local segmental resection but avoiding base mesenteric resection could have considerable benefit for patients regardless of the operative access employed.

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REFERENCES

- Swain P. A justification for NOTES–natural orifice transluminal endosurgery. *Gastrointest Endosc* 2007;**65**:514–6.
- Hunter JD. Invited critique on ‘Marescaux J, Dallemagne B, Perretta S, Wattiez A, Mutter D, Coumaros D. Surgery without scars: report of transluminal cholecystectomy in a human being. *Arch Surg* 2007; 142:823–826’. *Arch Surg* 2007;**142**:826–7.
- Rosch T. Who votes for NOTES. *Gut* 2008;**57**:1481–6.
- Buess G, Cuschieri A. Raising our heads above the parapet: ES not NOTES. *Surg Endosc* 2007;**21**:835–7.
- Hookey LC, Ellis R. Natural orifice transluminal endoscopic surgery (NOTES): what are we getting into? *Can J Gastroenterol* 2007;**21**:423–4.
- Feretic C, Kalantzopoulos D, Koulouris P, Kolettas C, Archontovasilis F, Chandakas S, et al. Endoscopic transgastric procedures in anesthetized pigs: technical challenges, complications, and survival. *Endoscopy* 2007;**39**:394–400.
- Buyske J. Natural orifice transluminal endoscopic surgery. *JAMA* 2007;**298**:1560–1.
- de la Fuente SG, Demaria EJ, Reynolds JD, Portenier DD, Pryor AD. New developments in surgery: Natural Orifice Transluminal Endoscopic Surgery (NOTES). *Arch Surg* 2007;**142**:295–7.
- Cahill RA, Marescaux J. NOTES and Oncologic surgery. *Surg Oncol* 2009;**18**:91–3.
- Leroy J, Cahill R, 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**:173–9.
- Forgione A, Leroy J, Cahill R, Bailey C, Simone M, Mutter D, et al. Prospective evaluation of functional outcome after laparoscopic sigmoid colectomy for prior diverticulitis. *Ann Surg* 2009;**249**:218–24.
- 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, <http://www.ncbi.nlm.nih.gov/pubmed/18814015?tool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=8>.
- Cahill RA, Leroy J, Marescaux J. Localised resection for colon cancer. *Surg Oncol* 2009;**18**:334–42.
- Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer. *Ann Surg* 2006;**244**:602–10.
- Steele GJ. Colorectal cancer. In: McKenna RJ, Murphy GP, editors. *Cancer surgery*. Philadelphia: Lippincott; 1994. p. 125–84.
- Joseph NE, Sigurdson ER, Hanlon AL, Wang H, Mayer RJ, MacDonald JS, et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. *Ann Surg Oncol* 2003;**10**:213–8.
- 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**:2677–83.
- Cahill RA, Asakuma M, Peretta S, Dallemagne B, Marescaux J. Gastric lymphatic mapping for sentinel node biopsy by Natural Orifice Transluminal Endoscopic Surgery (NOTES). *Surg Endosc* 2009;**23**:1110–6.

19. Meijerink WJ, van der Pas MH, van der Peet DL, Cuesta MA, Meijer S. New horizons in colorectal cancer surgery. *Surg Endosc* 2009;**23**:1–3.
20. Cahill RA, Leroy J, Dallemagne B, Marescaux J. Could sentinel node biopsy provide the oncological propriety for endoscopic resection of early stage colon cancer? *BMC Surgery* 2008;**8**:17.
21. Cahill RA, Asakuma M, Perretta S, Leroy J, Marescaux J, Coumaros D. Sentinel node biopsy by NOTES in support of endoscopic submucosal dissection (ESD) for the colon and stomach (with video). *Gastrointest Endosc* 2009;**69**:1152–60.
22. Takeuchi H, Kitagawa Y. Sentinel node biopsy without scars: does natural orifice transluminal endoscopic surgery herald a new era for early GI cancer? *Ann Surg Oncol* 2008;**15**:2639–40.
23. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002;**45**:200–6.
24. Wang HS, Liang WY, Lin TC, Chen WS, Jiang JK, Yang SH, et al. Curative resection of T1 colorectal carcinoma: risk of lymph node metastasis and long-term prognosis. *Dis Colon Rectum* 2005;**48**:1182–92.
25. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T, et al. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. *Dis Colon Rectum* 1995;**38**:1286–95.
26. Sakuragi M, Togashi K, Konishi F, Koinuma K, Kawamura Y, Okada M, et al. Predictive factors for lymph node metastasis in T1 stage colorectal carcinomas. *Dis Colon Rectum* 2003;**46**:1626–32.
27. Tominaga K, Nakanishi Y, Nimura S, Yoshimura K, Sakai Y, Shimoda T. Predictive histopathologic factors for lymph node metastasis in patients with nonpedunculated submucosal invasive colorectal carcinoma. *Dis Colon Rectum* 2005;**48**:92–100.
28. Cahill RA, Lindesay I, Cunningham C. NOTES and colorectal cancer. Surgery through the looking glass. *Gut* 2009;**58**:1168–9.
29. Cahill RA, Asakuma M, Trunzo J, Schomisch S, Wiese D, Saha S, et al. Intraperitoneal virtual biopsy by fibered optical coherence tomography (OCT) at natural orifice transluminal endoscopic surgery (NOTES). *J Gastrointest Surg* 2009 (Epub ahead of press).