Which treatment for large rectal adenoma? Preoperative assessment and therapeutic strategy

Which treatment for large rectal adenoma? Preoperative assessment and therapeutic strategy.

Alberto Arezzo, Simone Arolfo, Francesca Cravero, Marco Migliore, Marco Ettore Allaix, Mario Morino

Department of Surgical Sciences, University of Torino, Italy

Correspondence and requests for reprints to :
Prof. Alberto Arezzo
Department of Surgical Sciences, University of Torino,
corso Dogliotti 14, 10126 Torino, Italy
mail: alberto.arezzo@unito.it
phone: +393358378243
fax: +390116336641

No conflict of interests, funding, grant equipment and drugs to declare

Abstract

In the present review the authors discuss the standard ways of preoperative work-up for a suspected large rectal non-invasive lesion, comparing East and West different attitudes both in staging and treatment. Looking at the literature and analyzing recent personal data, neither pit-pattern classification, nor EUS, nor biopsy histology, nor lifting sign verification, nor digital examination allow a specificity of more than three fourth of such cases.

The authors disquisition about which optimal treatment excludes a role for EMR for the impossibility to obtain a single en-bloc specimen, minimum requirement for a correct lateral and vertical margin assessment. For the same reason ESD should be preferred, although a recent meta-analysis of the literature defined that one fourth of patients undergoing ESD for a preoperatively assessed non-invasive large rectal lesion fail to receive an R0 en-bloc resection. This forces about 10% of patients treated by flexible endoscopy, to undergo abdominal surgery, which is about a fourth fold higher than TEM.

While awaiting further implementation of modern technologies both to improve staging and to reduce invasiveness, a full-thickness excision of the rectal wall by TEM still represents the standard treatment even for suspected benign diseases.

Keywords Rectal adenoma - Transanal Endoscopic Microsurgery - Endoscopic Submucosal Dissection - Endoscopic Mucosal Resection

Background

Incidence and screening

Colorectal cancer (CRC) is among the most common malignancies in the Western world. Rectal cancer accounts for approximately one third of all CRCs (1). The occurrence of CRC is preceded by a benign neoplasm. Early detection of rectal adenomas prevents the development of rectal cancer. Its removal therefore significantly contributes to the prevention of this disease (2).

Since early detection and removal of rectal adenomas prevents the occurrence of rectal cancer, CRC screening has been adopted in many western countries (3). When CRC screening was introduced, this inevitably lead to an increased detection of early rectal neoplasia (4). It is therefore expected that more rectal adenomas will need treatment in the forthcoming years. Consequently, the most appropriate therapy concerning efficacy, safety, quality of life and costs must be selected to deal with the observed increase in rectal adenomas. Large adenomas continue to represent a clinical challenge, generating scientific discussion, to which univocal answers are not yet available.

EAST / WEST, differences in classification

The reporting of High Grade Dysplasia (HGD) in adenomas has been a topic of ongoing debate. Although current guidelines refer to HGD as a feature of advanced adenomas, no histological criteria have been provided to establish reporting guidelines (5). Among reference pathology texts, the entity of HGD has not been clearly defined. The World Health Organization book on tumours of the digestive tract makes no mention of criteria for HGD, and the Armed Forces Institute of Pathology states that separations of low-grade dysplasia from HGD are superficial in nature because the two entities are part of a spectrum (6,7).

Histological definitions of HGD are essentially similar to adenomatous change with regard to cytological and architectural atypia, but more pronounced. Histological features including a cribriform glandular architecture have been suggested by some groups to represent intramucosal carcinoma; however, this may still be classified as HGD by other pathologists (6). The thresholds for diagnos-

ing HGD and intramucosal carcinoma also vary according to country. The Japanese literature focuses on nuclear features, while Western pathologists place more emphasis on invasion through the muscularis mucosae (8). This may account for the greater incidence of early carcinoma in the Japanese literature (8,9). Despite diagnostic ambiguity and inter-observer variability, HGD continues to be reported and influences patient management. An assessment of the prognosis for these patients is needed. This will help to define the role of HGD within the category of advanced adenoma to guide the clinical management. In the meanwhile, Japanese series of superficial colorectal lesions report a a much higher incidence of adenocarcinoma.

Preoperative Assessment

Numerous studies on histopathology of surgically resected specimens of early neoplasia have demonstrated that the vertical depth of tumour infiltration is the most important predictive parameter for lymph node metastases. According to these results, the risk can be negligible if a neoplasia is limited to the mucosa (10). In addition, the risk is also very low in well-differentiated colorectal adenocarcinoma with superficial invasion of the submucosa and no infiltration of lymphatic vessels.

Pit-pattern classification

The idea of observing the surface microstructure of colorectal epithelium is dated the 1970s, with the use of dissecting microscopes on resected specimens. It was Nishizawa in the early 1980s (11) who showed that the normal colonic mucosa, adenoma, and adenocarcinoma have their own characteristic surface structures. Already in the 1980s the development of magnifying fiber colonoscopes enabled the microstructure of the various colorectal lesions to be seen in vivo (12). Ten years later, the advent of commercially available high-resolution magnifying video colonoscopes stressed the study of the microstructures of colonic lesions (13). Expectations were that endoscopic pit-pattern classification could determine not only the lateral extent but also the depth of a lesion, this way contributing to the indication to local or radical excision.

Although it is true that a totally disorganized or a non structural pattern seems to correspond to carcinomas with a submucosal invasion, pit-pattern analysis failed to become a completely reliable method of pre-treatment classification and it is still routinely used only in eastern countries. In order

to improve the accuracy of diagnosis in vivo, it has been suggested to use natural or electronic chromoendoscopy techniques (NBI, FICE) with or without optical or electronic magnification. If these techniques have been used rarely in western countries so far as they are considered too burdensome for routine endoscopy, the progressive implementation and simplification of electronic endoscopy chrome on the new instruments should lead to more widespread use of this technique.

EUS

In a recent systematic review and meta-analysis, Puli (14) showed a pooled sensitivity of 88% - 95% for detecting T stage and of 99% for diagnosing depth of tumor invasion. However different studies (15,16) including a considerable number of patients from a multitude of centers revealed a uT-pT correspondence of less than 65%, demonstrating that, in clinical routine, the diagnostic accuracy of transrectal ultrasound in staging rectal carcinoma does not attain some very good results reported in the literature.

This is also our experience. To define a correct indication for local excision it is mandatory to know if the observed lesion invades the submucosal layer, and if it does, if this goes deeper than 1 mm below the *lamina propria*. This is probably too much to be asked to any in-vivo diagnostic tool. By reviewing our experience of the last five years, to be sure that no technology improvement could be responsible of changing results, we could verify that about one fourth of the lesions preoperatively assessed as uT0, i.e. limited to the mucosal layer where in fact invasive carcinomas.

Biopsy

Despite in Eastern countries the routine usage of magnification is assumed to reduce the requirement for biopsies, Western endoscopists tend to base treatment decisions largely on the size and the location of the tumor and on the histology of biopsy specimens, considering the Japanese classification too complex for practical use.

Nevertheless even the routine use of biopsy has certain limitations. Our experience of the last five years allows to define that almost half of the those neoplasms that resulted at definitive histology of the specimen invasive cancers, had a preoperative biopsy histology of dysplasia, in about 7% of

cases judged as low-grade, so that no grade of dysplasia detected at biopsy could be considered an assurance of not having to deal with an invasive cancer in the end.

Lifting sign

A sign endoscopic highly accurate to evaluate a possible invasion of cancer that affects the radical resection is the no-lifting sign after injection of saline into the submucosa below the polyp. When the lesion does not lift completely it is likely to have already passed the submucosa, preventing complete endoscopic excision of the lesion.

Although not ideal, due to the limits of other criteria to assess correct indication for local excision, as exposed above, the lifting sign still remains at least in Western countries, a routine procedure. As not all the neoplasms that infiltrate up the submucosal layer are good indication for local excision, and the risk of deep margin infiltration of the specimen increases, the lifting of the neoplasm does not assure that the endoscopic local excision would be considered curative.

Digital examination

At least in the low and mid rectum, digital examination can easily replace the need to inject lifting agents into the submucosa to exclude infiltration of the muscular layer. With similar accuracy, this easy manouvre allows also to detect the consistency of the lesion, the distance from the anal verge and the location along the circumference which might help during the dissection manouvre both endoscopic and by transanal surgery.

The role of Transanal Endoscopic Microsurgery

Almost 30 years ago, transanal endoscopic microsurgery (TEM) revolutionized the technique and outcomes of transanal surgery, first becoming the standard of treatment for large rectal adenomas (17-19), then offering a possibly curative treatment for early rectal cancer (20), and finally generating discussion on its potential role in combination with neoadjuvant therapies for the treatment of more invasive cancer (21-23). TEM afforded the advantage of combining a less invasive transanal approach with low recurrence rates thanks to enhanced visualization of the surgical field, which allows more precise dissection.

Under general anesthesia a dedicated rectoscope of 12 or 20 cm in length (Richard Wolf GmbH Knittlingen, Germany) or 7 or 15 cm in length (Karl Storz GmbH Tuttlingen, Germany) is inserted within the rectum to assure proper visualization of the lesion. The rectoscope is fixed to the operating table by a supporting device, providing the opportunity to reposition the rectoscope during ongoing surgery. The rectal cavity is insufflated with CO2 by a combined endosurgical unit to achieve constant distension for appropriate visualization of the rectal adenoma. The combined endosurgical unit further regulates irrigation and suction, thereby maintaining a constant intra rectal pressure. With the use of a binocular stereoscopic eyepiece for three-dimensional view (Richard Wolf GmbH) or a forward oblique telescope (Karl Storz GmbH) a magnified view is being created for visualization of the lesion. With various HF monopolar and bipolar instruments, needle diathermy, tissue handling forceps, needle holder, suction probe, injection needle, clip applicator) the rectal lesion will be dissected.

Supporters of the TEM technique praise the excellent exposure of the rectum and the minimal invasiveness, as opposed to conventional surgical techniques (24-26). Besides, recurrence rates after TEM appear to be lower when compared to conventional surgical transanal excision (27).

Originally developed for the treatment of large villous adenomas, due to the observation of a consistent number of disregarded malignant lesions with unexpected low tendency to recurrence or progressive disease, in few years TEM gained consideration as a suitable curative treatment for early rectal carcinoma, thus contributing to the identification of pathology risk factors for invasiveness and recurrence (28). While till 1989 Gerhard Buess had forced to radical surgery any patient who resulted affected at definitive pathology by a malignant disease, the observation of the scarce or null tendency to recur of those patients with non-invasive disease according to Hermanek (28) who refused major abdominal surgery after TEM, convinced him of the potentials of a local treatment even for selected malignant diseases.

Although initially described as a technique for submucosal dissection (mucosal excision), partial-wall excision (limited to part of the muscular layer) or full-thickness excision of the rectal wall, the difficulty in preoperative assessment of suspected benign lesions, together with the need of reaching disease-free dissection margins for an appropriate staging of the disease, suggested to perform only full-thickness excisions, removing the rectal wall till the perirectal fat. Even the opening of

the peritoneum which was considered in former times a good reason to perform only partial-wall excision to avoid intra-operative complications, is now considered routine (29) so that TEM is addressed as a potential platform towards the abdominal cavity for Natural Orifices Transluminal Endoscopic Surgery (NOTES) procedures (30).

A recent systematic review (31) analysed the treatment for large (> 2 cm) rectal adenomas, comparing the safety and effectiveness of EMR and TEM, assuming that the potential lower morbidity of EMR may become irrelevant if EMR is less effective. The study showed a recurrence rate at 3 months as high as 11.2% after piece-meal EMR for colorectal lesions, which dropped to 1.5% after further endoscopic treatment at 3 months. Authors claimed that this demonstrated the equivalent effectiveness of the endoscopic EMR technique compared to TEM, while EMR results safe.

Unfortunately the study has several methodological flaws, being the major: 1) all but one endoscopic series included only benign lesions, which suggests an evident selection of cases based on post-operative histology; 2) most of the TEM series included cases that were operated using a partial wall excision technique and not a full-thickness, as suggested by most expert authors (32). The authors are to be congratulated for conducting parallel to this, the TREND study, a prospective randomized trial which seems imperative before making recommendations concerning the treatment of large rectal suspected adenomas.

Nevertheless, as the correct preoperative assessment of sessile rectal lesions is so much inaccurate, and the main reliable criteria for assessing a curative resection is the pathology analysis of the en-bloc specimen which should preferably correspond to an attempted R0 resection, so to be able to define both lateral and deep resection margins. For this it reason seems more reasonable that the aim of an endoscopic resection of a non-invasive rectal lesion today should be to use an ESD technique. In the absence of comparative studies, we have recently performed a single-arm meta-analysis of case series as the only available evidence. We defined strict inclusion criteria, limiting the analysis to lesions >2 cm according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines (33), suspected non-invasive by preoperative assessment and excluded all TEM series including preoperatively assessed malignant lesions and not performed full-thickness.

We could demonstrate an R0 resection achieved by ESD in 74% of patients compared to 89% by TEM. This probably reflected on the consistently higher need of further abdominal surgery in the ESD group, despite the rate of unpredicted invasive cancers treated in the two groups was comparable. In other words TEM when performed full-thickness for suspected non-invasive rectal lesions, seems to represent a consistent advantage compared to ESD, about fourfold, when considering the need for further surgery for oncologic reasons.

Complications of the two techniques are equal for incidence, being reported in about 5% of cases, and requiring further surgical treatment in about 1.5% of cases. This, despite it has to be said that complications after TEM, although extremely rare, are generally more severe, including full thickness dehiscence of the rectal suture line, and even in rare cases recto-vaginal fistulas.

Finally, even more today, cost-effectiveness plays a crucial role in deciding which therapy strategy. While TEO is performed in a standard OR, ESD requires an advanced endoscopic room with anesthesist. The time for a TEM procedure is about 60 minutes, while 100 minutes for an ESD, so that, even considering the increased costs of a OR environment, costs are almost the same. On the other side the cost of a TEO equipment including its support arm and the dedicated 5 mm optics is about 12.500 euros once for ever, having almost no need of service, while a standard ESD procedure is currently performed by using a special knife and a monopolar grasper for coagulation, which cost about 500 euros each. This means that having completed about 12 cases the costs are equivalent and any further case would represent an extra cost for those centers routinely performing ESD. This, not taking into account the increased need of further surgery after ESD for oncologic reasons.

Recently, the development and marketing of single-port devices, allowed the description and diffusion of a new surgical technique, which combines single-port access with the principles of transanal excision. A confusing nomenclature for the technique, including different acronyms such as TransAnal Mini-Invasive Surgery (TAMIS) (34,35), Transanal Single-Port Microsurgery (TSPM) (36), Transanal Endoscopic Video-Assisted surgery (TEVA) (37), and SILSTEM (38), has been adopted. In all these procedures, a single-incision laparoscopic surgery port is introduced into the anal canal, followed by transanal excision using standard laparoscopic instruments. The supposed benefits of a cheaper technique induced the publication of several case series which reported

technical feasibility and low morbidity. Unfortunately, after an initial enthusiasm, reports about its feasibility were at least contraddictory. There are in fact at least three reports of the use of single-port devices for transanal endoscopic surgery in which their use is not always possible (39-41), either because the lesion was judged too close, or because the single-port device did not reach sufficient intrarectal retractor expansion, or due to an insufficient stability. We confirmed this impression in an ex-vivo trial performed at our institution, and recently published (42). In a dedicated trainer box for transanal procedures, no difference was observed between the two techniques regarding the accuracy of dissection, but dissection and suturing were significantly quicker in the TEM group and in 3 out of 10 cases in the SILS group, completing the suture was not considered possible, and the procedures were terminated by TEM. Moreover, here again cost-effectiveness should also be taken into account. We believe that there is no discussion that a TEO instrumentation is much cheaper than the routine use of any single-port device. Single-port devices in fact are affordable for a cost of at least 360 euros each, provided that standard laparoscopic instruments are used, while the cost of a 30° 5 mm 50 cm in length optics accounts for about 5.700 euros. In other words, having completed 18 cases the costs are equivalent and any further case would represent an extra cost for those centers routinely using single-port devices. This, not taking into account the need of specific automated suturing and knot forming devices, as underlined by some authors, all extremely expensive, nor the fact that while TEM/TEO is a true single surgeon procedure, TAMIS always requires two scrubbed surgeons at the OR table.

Discussion

Our recent experience demonstrates the difficulty to reliably assess malignancy in large superficial rectal lesions. For this reason the aim of any kind of resection should be the one to send to the pathologist an integer en-bloc specimen containing the lesion. This cannot be achieved by piecemeal EMR, and for this reason, due to the high percentage of malignancies encountered among suspected benign lesions, this technique should not be practiced in presence of better alternatives. Among endoscopic techniques ESD aims at achieving an en-bloc resection, with the advantage of no need of general anesthesia and prolonged hospitalization. Unfortunately the rate of unsuccess-

ful R0 en-bloc resections achieved by ESD is higher than one fourth, not comparable to TEM standard which is about one tenth.

For this reason, it is our opinion that the difficulty to reliably assess malignancy in large superficial rectal lesions is also a major point in favor of a full thickness excision of the lesion which today can only be achieved through transanal surgery. In fact, the risk of infiltration of the vertical margin is the only risk factor for recurrence (33).

Further analyses would have been of extreme interest, such as influence on anal continence and rectal function, sexual and urinary dysfunction, quality of life, but the lack of sufficient data on these topics forced us to stop.

Notwithstanding the above-mentioned limitations, we can conclude that, based on evidence of our review and analysis, TEM achieves a higher rate of en-bloc and R0 excision. As a consequence, full-thickness rectal wall excision by TEM reduces significantly the need for further abdominal treatment according to oncologic criteria. Thus, the way in which these results will ultimately translate into common daily clinical practice remains unclear. No randomized, head-to-head comparisons between TEM and ESD have been performed. Our review clearly highlights the importance of a large randomized study to obtain unbiased results on the effectiveness and safety of these two strategies in patients with large rectal lesions preoperatively assessed as adenomas or superficial neoplasms. In the meanwhile, we have opened a large multicentric international registry (www.temendo.zapto.org) for monitoring results of the different techniques described above for the cure of suspected rectal adenomas.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan;63(1):11–30.

2. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N. Engl. J. Med. 1993 Dec 30;329(27):1977–81.

3. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastro-enterology. 2003. pp. 544–60.

4. van Rijn AF, Dekker E, Kleibeuker JH. [Screening the population for colorectal cancer: the background to a number of pilot studies in the Netherlands]. Ned Tijdschr Geneeskd. 2006 Dec 16;150(50):2739–44.

5. Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'brien MJ, Levin B, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin. 2006. pp. 143–59–quiz184–5.

6. Rex DK, Goldblum JR. Pro: Villous elements and high-grade dysplasia help guide post-polypectomy colonoscopic surveillance. Am. J. Gastroenterol. 2008 Jun;103(6):1327–9.

7. Aust DE. [WHO classification 2010 for the lower gastrointestinal tract: what is new?]. Pathologe. 2011 Nov;32 Suppl 2:326–31.

8. Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, et al. Differences in the diagnostic criteria used by Japanese and Western pathologists to diagnose colorectal carcinoma. Cancer. 1998 Jan 1;82(1):60–9.

9. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut. 2000 Aug;47(2):251–5.

10. Fujishiro M. Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms. World J. Gastroenterol. 2008 Jul 21;14(27):4289–95.

11. Nishizawa M, Okada T, Sato F, Kariya A, Mayama S, Nakamura K. A clinicopathological study of minute polypoid lesions of the colon based on magnifying fiber-colonoscopy and dissecting microscopy. Endoscopy. 1980 May;12(3):124–9.

12. Tada M, Kawai K. Research with the endoscope: new techniques using magnification and chromoscopy. Clin Gastroenterol. 1986 Apr;15(2):417–37.

13. Kudo S, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, et al. Colorectal tumours and pit pattern. J. Clin. Pathol. 1994 Oct;47(10):880–5.

14. Puli SR, Reddy JBK, Bechtold ML, Choudhary A, Antillon MR, Brugge WR. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta-analysis and systematic review. Ann. Surg. Oncol. 2009 May;16(5):1255–65.

15. Marusch F, Koch A, Schmidt U, Zippel R, Kuhn R, Wolff S, et al. Routine use of transrectal ultrasound in rectal carcinoma: results of a prospective multicenter study. Endoscopy. 2002 May;34(5):385–90.

16. Marusch F, Ptok H, Sahm M, Schmidt U, Ridwelski K, Gastinger I, et al. Endorectal ultrasound in rectal carcinoma--do the literature results really correspond to the realities of routine clinical care? Endoscopy. 2011 May;43(5):425–31.

17. Buess G, Hutterer F, Theiss J, Böbel M, Isselhard W, Pichlmaier H. [A system for a transanal endoscopic rectum operation]. Chirurg. 1984 Oct;55(10):677–80.

18. Røkke O, Iversen KB, Ovrebø K, Maartmann-Moe H, Skarstein A, Halvorsen JF. Local resection of rectal tumors by transanal endoscopic microsurgery: experience with the first 70 cases. Dig Surg. 2005;22(3):182–9–discussion189–90.

19. Dias AR, Nahas CSR, Marques CFS, Nahas SC, Cecconello I. Transanal endoscopic microsurgery: indications, results and controversies. Tech Coloproctol. 2009 Jun;13(2):105–11.

20. Endreseth BH, Myrvold HE, Romundstad P, Hestvik UE, Bjerkeset T, Wibe A, et al. Transanal excision vs. major surgery for T1 rectal cancer. Dis. Colon Rectum. 2005 Jul;48(7):1380–8.

21. Lezoche E, Guerrieri M, Paganini AM, Baldarelli M, De Sanctis A, Lezoche G. Long-term results in patients with T2-3 N0 distal rectal cancer undergoing radiotherapy before transanal endoscopic microsurgery. Br J Surg. 2005 Dec;92(12):1546–52.

22. Lezoche E, Guerrieri M, Paganini AM, Feliciotti F. Long-term results of patients with pT2 rectal cancer treated with radiotherapy and transanal endoscopic microsurgical excision. World J Surg. 2002 Sep;26(9):1170–4.

23. Borschitz T, Heintz A, Junginger T. Transanal endoscopic microsurgical excision of pT2 rectal cancer: results and possible indications. Dis. Colon Rectum. 2007 Mar;50(3):292–301.

24. Winde G, Nottberg H, Keller R, Schmid KW, Bünte H. Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection. Dis. Colon Rectum. 1996 Sep;39(9):969–76.

25. Lin G-L, Meng WCS, Lau PYY, Qiu H-Z, Yip AWC. Local resection for early rectal tumours: Comparative study of transanal endoscopic microsurgery (TEM) versus posterior transsphincteric approach (Mason's operation). Asian J Surg. 2006 Oct;29(4):227–32.

26. Doornebosch PG, Tollenaar RAEM, Gosselink MP, Stassen LP, Dijkhuis CM, Schouten WR, et al. Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer. Colorectal Dis. 2007 Jul;9(6):553–8.

27. Middleton PF, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. Dis. Colon Rectum. 2005 Feb;48(2):270–84.

28. Hermanek P, Guggenmoos-Holzmann I, Gall FP. Prognostic factors in rectal carcinoma. A contribution to the further development of tumor classification. Dis. Colon Rectum. 1989 Jul;32(7):593–9.

29. Morino M, Allaix ME, Famiglietti F, Caldart M, Arezzo A. Does peritoneal perforation affect short- and long-term outcomes after transanal endoscopic microsurgery? Surg Endosc. 2013 Jan;27(1):181–8.

30. Morino M, Verra M, Famiglietti F, Arezzo A. Natural Orifice Transluminal Endoscopic Surgery (NOTES) and colorectal cancer? Colorectal Disease. 2011 Nov 21;13:47–50.

31. Barendse RM, van den Broek FJC, Dekker E, Bemelman WA, de Graaf EJR, Fockens P, et al. Systematic review of endoscopic mucosal resection versus transanal endoscopic microsurgery for large rectal adenomas. Endoscopy. 2011 Nov;43(11):941–9.

32. Guerrieri M, Baldarelli M, de Sanctis A, Campagnacci R, Rimini M, Lezoche E. Treatment of rectal adenomas by transanal endoscopic microsurgery: 15 years' experience. Surg Endosc. 2010 Feb;24(2):445–9.

33. ~~33.~~ Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int. J. Clin. Oncol. 2012. pp. 1–29.

34. Atallah S, Albert M, Larach S (2010) Transanal minimally inva- sive surgery: a giant leap forward. Surg Endosc 24:2200–2205

35. Lim SB, Seo SI, Lee JL, Kwak JY, Jang TY, Kim CW, Yoon YS, Yu CS, Kim JC (2012) Feasibility of transanal minimally inva- sive surgery for mid-rectal lesions. Surg Endosc 26:3127–3132

36. Lorenz C, Nimmesgern T, Back M, Langwieler TE (2010) Transanal single port microsurgery (TSPM) as a modified tech- nique of transanal endoscopic microsurgery (TEM). Surg Innov 17:160–163

37. Ragupathi M, Haas EM (2011) Trans-anal endoscopic video- assisted excision: application of single-port access. JSLS 15: 53–58

38. Hayashi S, Takayama T, Yamagata M, Matsuda M, Masuda H (2013) Single-incision laparoscopic surgery used to perform transanal endoscopic microsurgery (SILSTEM) for T1 rectal cancer under spinal anesthesia: report of a case. Surg Today 43(3):325–328

39. Van den Boezem PB, Kruyt PM, Stommel MW, Tobon Morales R, Cuesta MA, Siestes C (2011) Transanal single-port surgery for the resection of large polyps. Dig Surg 28:412–416

40. Barendse RM, Doornebosch P, Bemelman W, Fockens P, Dekker E, de Graaf E (2012) Transanal employment of single access ports is feasible for rectal surgery. Ann Surg 256:1030–1033

41. Barendse RM, Doornebosch PG, Bemelman WA, Fockens P, Dekker E, de Graaf EJ (2012) Transanal single-port surgery: selecting a suitable access port in a porcine model. Surg Innov 19:323–326

42. Rimonda R, Arezzo A, Arolfo S, Salvai A, Morino M. TransAnal Minimally Invasive Surgery (TAMIS) with SILS™ Port versus Transanal Endoscopic Microsurgery (TEM): a comparative experimental study. Surg Endosc. 2013 May 1. [Epub ahead of print]