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Role of transanal endosonography in the staging of early rectal cancer

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Introduction

Over the last three decades, the management of rectal cancer has changed, reflecting a better pelvic anatomy knowledge. A refinement of surgical technique and advances in neoadjuvant and adjuvant therapy improved oncological and functional results. In rectal cancer, the local extent of disease, lymph node involvement, metastatic spread, and surgical technique significantly affects survival and clinical outcomes. Royal College of Radiologists recommendations suggest the use of high-resolution magnetic resonance imaging (MRI) to assess the circumferential resection margin and pelvic nodal involvement. Endorectal ultrasound (ERUS) is also recommended to determine tumor depth in order to asses an appropriate local resection. Both MRI and ERUS improve selection of patients suitable for local excision.

ERC

There is no consensus on the definition of Early Rectal Cancer (ERC). Several definitions of ERC based on microscopic and macroscopic findings have been proposed. The Kikuchi classification [1] aims to describe the depth of submucosal invasion in non-pedunculated lesions, by dividing the submucosa in 3 parts: sm1, sm2 and sm3 T1 cancers. Despite ERC is widely used to indicate submucosal cancers, with low risk of lymph node metastases [2], this definition does not reflect clinical implications related to management and long term outcomes of ERC.

European Association for Endoscopic Surgery clinical consensus conference defined ERC as a rectal cancer with good prognostic features that might be safely removed preserving the rectum. This way ERC has a very limited risk of relapse after local excision [3].

The preoperative staging must include digital examination, endoscopy, endosonography (EUS) and computed tomography (CT) and magnetic resonance imaging (MRI).
Total mesorectal excision (TME) is widely accepted as standard surgical practice for rectal cancer [4], it provides the best chance of a tumor-free circumferential resection margin [5].
Local recurrence is directly related to incomplete resection of the tumor [6, 7] and the most important parameter related to local recurrence is the distance between the tumor and the mesorectal fascia [8, 9].
Locally advanced rectal cancer with extramural spread (T3 tumor) has an high frequency of local recurrence and metastasis. Currently, the standard treatment for locally advanced rectal cancer consists of preoperative neoadjuvant concomitant radiation and chemotherapy (CRT) followed by standard resection of the rectum, with resection of the surrounding organs [10, 11].

Endoluminal Ultrasound

Endoluminal Ultrasound (ERUS) is an established modality to evaluate the integrity of the rectal wall. As advantages it includes the convenient accessibility because it is part of the initial assessment performed by the colorectal surgeon in conjunction with the digital rectal examination [12]. ERUS, although operator-dependent, can be performed with minimal bowel preparation and patient discomfort, and it is considered the most accurate method to stage local rectal cancer. It is performed using an high frequency (>7.5 MHz) endoluminal probes **[Fig.1]**.

ERUS permits to identify five layers, three hyperechoic lines represent interfaces to the anatomic layers, defined by the two hypoechoic lines. The first hyperechoic line represents the interface between the balloon and the mucosa. The second hypoechoic line is the mucosa, muscularis mucosa, and submucosa. The third hyperechoic line represents an interface between the submucosa and muscularis propria. The fourth hypoechoic line is the muscularis propria. The fifth hyperechoic line is related to an interface between the serosa and perirectal fat.

To study the rectal wall and the anal sphincter, several ultrasound probes have been developed; there are mechanical sector probes with a single transducer and linear or curved array probes. Some of these probes incorporate radial probes with a full 360-degree field of view despite of the limited field of view of 120 to 210 degrees of the other ones.
There are also probes that allow different images reconstruction: biplanar or tridimensional ones. Biplanar probes can

change the view from the axial plane to the longitudinal one and allow to perform Doppler study.
Tridimensional probes permit image reconstruction and rendering **[Fig.2]**. Tip colonoscope ultrasound probes (flexible echoendoscope) could raise 20 MHz transducers. Echoendoscope has the advantage to be more tolerate by the patient in order to the inferior dimension.
Rigid probes are oriented; this characteristic allows to identify the exact position of the lesion.

ERUS accuracy for T staging varies between 69% and 97%. It is presently the most accurate imaging modality for the assessment of tumor ingrowth into rectal wall layers [13, 14]. Rectal ultrasound T staging accuracy may be improved by the new 3D −16 MHz probes. Higher frequency ultrasound probes are available, but have not yet been investigated. It is expected that the 20 MHz or even higher frequencies probes introduction will lead to an higher investigation accuracy in T0-T2 cancers. ERUS has a 82–93% accuracy to reveal the depth of invasion, although overstaging has been reported. Assessment of lymph node involvement is less reliable, with reported accuracy of 65–81% [15].

Metastatic lymph nodes can be detected from reactive ones because of their hypoechoic and irregular ultrasound features. In a 11 studies meta-analysis [16], sensitivity was shown to be affected by T stage. ERUS is very accurate for staging superficial rectal tumors but is not so useful to stage advanced rectal cancer [17]. The overall staging accuracy is 69%, because the limited depth of acoustic penetration prevents accurate assessment of local tumor extent in bulky T3 and advanced rectal cancers. Although endoluminal US is very accurate to stage superficial rectal cancer, it is less suitable to evaluate the mesorectal excision plane.

Moreover, endoluminal US is limited in differentiating the T2 from the initial T3 stage. On the other hand, the overall accuracy of endoluminal US in N staging varies from 64% to 83% [18] **[Fig. 3]**.

Discussion

A meta-analysis evaluated the accuracy of ERUS on T stage rectal cancers differentiation, with a sensitivity and specificity for T1 stage of 87.8 and 98.3%, respectively, decreasing to 80.5 and 95.6% for T2, 96.4 and 90.6% for T3, 95.4 and 98.3% for T4 [19]. Data from a 90 studies meta-analysis showed that ERUS and MRI have a similar sensitivity (94%) in defining parietal involving disease although ERUS was more specific to asses neoplastic infiltration (86 vs 69%) [20].

Even if ERUS is an operator-dependent technique, this could be an important advantage in expert hands [21, 22]. According to the results of a Hungarian study [23 - 24], the learning curve is relatively short, in fact after 30 examinations it is possible to safely evaluate the invasion of rectal tumors.

Flexible probes have several advantages compared to the rigid ones, in fact, due to their smaller diameter, they are able to pass the recto-sigma joint, pandering the physiological bowel curvatures, and studying even more proximal colonic tract. Despite this, a study seems to support rigid probes in terms of accurate staging T and N [23]. Rigid probes are preferable to flexible ones even for their lower cost and better accuracy [25]. ERUS should be performed before biopsy, as scars and deformations make interpretation more difficult.

The differentiation between T0 and T1 stage is a challenge, in fact, 56.6% of adenomas

and 30.7% of in situ carcinomas are staged as uT1, while nearly half of pT1 carcinomas are interpreted as uT0. This is a known examination limit, that has no impact on the therapeutic program, since both T0 and T1 tumors are treated with minimally invasive surgery. Glensy et al., in a series of 62 patients considered eligible for TEM, reported 95% ERUS with 3 overstaging patients and none understaging [26]. In another study, 210 pT0-pT1 patients were subjected to local excision or radical surgery; preoperative staging with ERUS was corrected in 187 cases (89%) and only 9 patients were overstaged (T2-T3) [27].

T1 cancers with deep submissive invasion, and the most advanced lesions, are most important to correctly be identified. In fact, the ERUS differentiation between sm1, sm2, sm3 is very hard to detect when the tumor reaches the muscle layer [28]. Lymph node metastases increase with the Kikuchi stage, with a 1-3% risk for submucosal layer sm1, 8% for sm2 and 23% for sm3 lesions. Low-risk ERC may be treated endoscopically or with a transanal procedure. Transanal excision or transanal endoscopic microsurgery may be inadequate for high-risk ERCs and adjuvant chemoradiotherapy may be appropriate.

There is a low rate of recurrence after local surgery for low-risk ERCs but this increases to up to 29% for high-risk cancers [29]. The endoscopic piecemeal removal of large sessile or flat polyps with conventional polypectomy or endoscopic mucosal resection (EMR), although it is less invasive, is known to be associated with an high local recurrence rate of 14%-19.5% [30, 31].

Endoscopic submucosal dissection (ESD) is a novel technique that was originally developed in Japan more than 10 years ago. ESD was developed to achieve an en bloc mucosal resection with wider margins [32, 33, 34]. Currently, an increased number of endoscopists throughout the world have acquired this skill and have published promising outcomes of ESD [35-40]. The recent retrospective analysis reported by Kiriyama et al [41] compared ESD for colorectal intramucosal or slightly submucosal invasive cancers versus low anterior rectal resection (LAR) for T1 cancer. This study demonstrated a lower complication rate in the ESD group. Another similar prospective study also compared ESD for adenoma or T1 cancer with less than SM-s (superficial submucosal invasion) vs LAR for SM-d (deep submucosal invasion) [42]. Until now, no worldwide consensus has been adopted about the endoscopic treatment (i.e., ESD) of benign colorectal neoplasms [43]. From the very beginning of the development of colorectal ESD, the procedure was performed primarily by gastroenterologists.

No published data exists to compare clinical outcomes of ESD vs LAR when both procedures were performed by the same group of surgeons. Surgeons who can perform both procedures may be in an advantageous position in that they can balance the risks and benefits of the endoscopic approach vs the surgical approach **[Fig. 4].**

Conclusions

The advent of two-dimensional and, most recently, three-dimensional ERUS technique significantly improved the diagnostic accuracy in pre- and post-operative staging of rectum cancers. In fact, it allowed to overhead many limitations related to traditional diagnostic imaging.

However, the choice of the most suitable therapy for these tumors is increasingly affected by the depth of infiltration rather than the size of the neoplasm. Depending on the correct staging, the therapeutic decision, and consequently the prognosis, is crucial. It is very important to state which professional character is suitable to stage and treat the disease: the advent of the new diagnostic and therapeutic options (ERUS, TEM, ESD) increased the importance of the surgical role instead of a previous radiologist commitment.

Endoscopists usually carry out endoscopic removal with piecemeal resection, at the same time of the diagnosis without a biopsy result. This technique does not ensure complete removal of the lesion, it does not provide a specimen orientation, and a proper margin evaluation, due to the coagulation artifacts, making the pathological report very hard.

Advanced tumors currently require multidisciplinary management. The use of neoadjuvant therapies, such as pre- or intra-operative radiotherapy, has led to a dramatic reduction in abdominal-perineal amputation interventions that forced patients to a definitive colostomy. The benefit of sphincter conservation interventions are the reductions of incidence of local recurrences, the increase long-term survival, and quality of life. The expansion of ERUS is mandatory because has proved to be sensitive, feasible, tolerated by the patient and not excessively expensive.

The limits of the ERUS can be overcome by the use of other diagnostic investigations such as CT scan and MRI when the ultrasound image could be doubtful or difficult to be understood.

Figures

Fig. 1

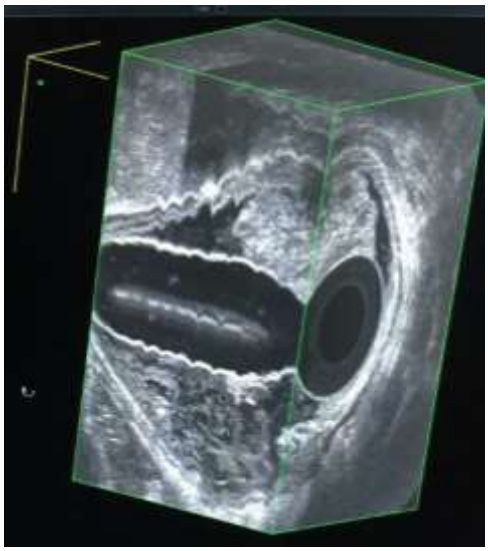

Fig. 2:

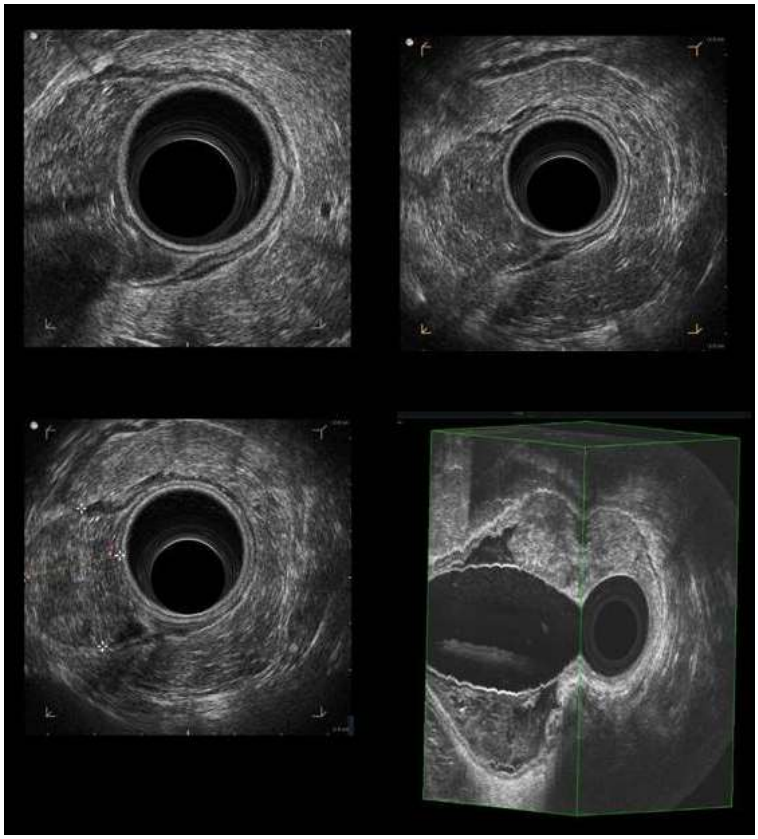

Fig. 3

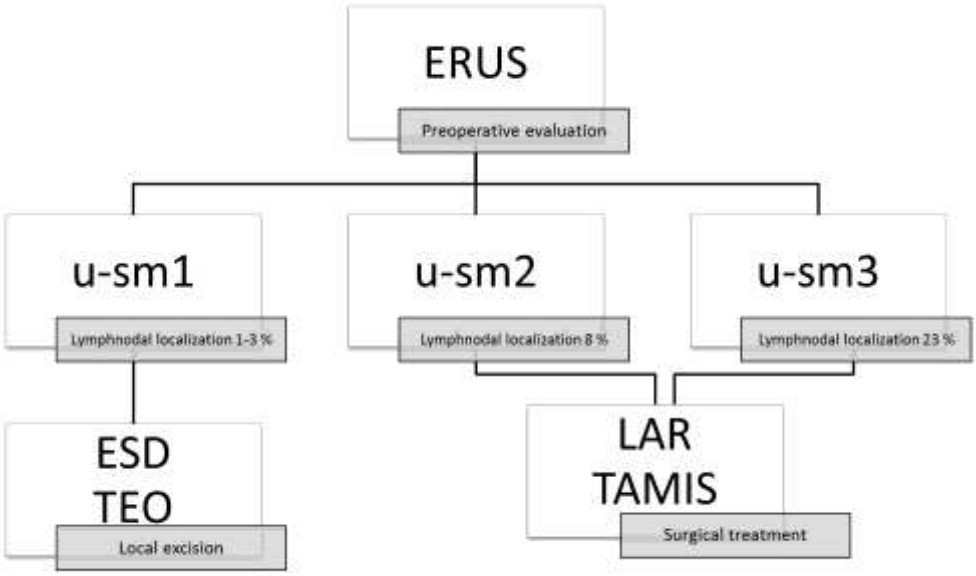
ERUS
Preoperative evaluation
u-sm1
Lymphnodal localization 1-3 %
u-sm2
Lymphnodal localization 8 %
u-sm3
Lymphnodal localization 23 %
ESD
TEO
Local excision
LAR
TAMIS
Surgical treatment

Fig. 4

Bibliography

1. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T, Uchida Y (1995), *Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines*. Dis Colon Rectum 38:1286-1295

2. Kitajima K, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajioka Y, Watanabe H, Watanabe T, Muto T, Nagasako K (2004) *Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study.* J Gastroenterol. 39:534-543

3. M Morino, M Risio, S Bach, R Beets-Tan, K Bujko, Y Panis, P Quirke, B Rembacken, E Rullier, Y Saito, T Young-Fadok, ME Alliax, Eary *Rectal Cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference*, Surgical Endoscopy 2015 V29 Issue 4 755-773

4. Capussotti L (2011) *Surgical treatment of colorectal liver metastases*. Springer Verlag Edition

5. Tepper JE, O'Connell M, Niedzwiecki D et al (2002) *Adjuvant therapy in rectal cancer: Analysis of stage, sex, and local control. Final report of Intergroup 0114*. J Clin Oncol 20:1744-1750

6. MacFarlane JK, Ryall RDH, Heald RJ (1993) *Mesorectal excision for rectal cancer*. Lancet 341:457-460

7. Kapiteijn E, Marijnen CAM, Nagtegaal ID et al (2001) *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer*. New Engl J Med 345:638-646

8. Giordano P, Efron J, Vernava AM et al (2006) *Strategies of follow-up for colorectal cancer: a survery of American Society of Colon and Rectal Surgeons*. Tech Coloproctol 10:199-207

9. Anthony T, Simmang C, Hyman N et al (2004) *Practice Parameters for the Surveillance and Follow-Up of Patients With Colon and Rectal Cancer*. Dis Colon Rectum 47:807-817

10. Cali RL, Pitsch RM, Thorson A et al (1993) *Cumulative incidence of metachronous colorectal cancer*. Dis Colon Rectum 36:388-393

11. Lopez-Kostner F, Fazio VW, Vignali A et al (2001) *Locally recurrent rectal cancer: predictors of success of salvage surgey*. Dis Colon Rectum 44:173-178

12. Garcia Aguilar J, Cromwell JW, Marra C et al (2001) *Treatment of locally recurrent rectal cancer*. Dis Colon Rectum 41:1743-1748

13. Elias D, Sideris L, Pocard M et al (2004) *Results of R0 resection for colorectal liver metastases associated with extrahepatic disease*. Ann Surg Oncol 11:274-280

14. Kelly H, Goldberg RM (2005) *Systemic therapy for metastatic colorectal cancer: current opinions, current evidence*. J Clin Oncol 23:4553-60

15. Balch GC, De Meo A, Guillem JG: *Modern management of rectal cancer. A 2006 update*. World J Gastroenterol 2006; 12: 3186–3195

16. Baca B, Beart RW, Etzioni DA (2011) *Surveillance after colorectal cancer resection: a systematic review.* Dis Colon Rectum 54:1036-1048

17. Jeffery M, Hickey BE, Hider PN (2007) *Follow-up strategies for patients treated for non-metastatic colorectal cancer.* Cochrane Database of Systematic Reviews 1 CD002200

18. Langenhoff BS, Krabbe PF, Ruers TJ (2009) *Efficacy of follow-up after surgical treatment of colorectal liver metastases.* Eur J Surg Oncol 35:180-186

19. Puli SR, Bechtold ML, Reddy JB, Choudhary A, Antillon MR, Brugge WR. *How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review.* Ann Surg Oncol 16:254–265, 2009

20. Bipat S, Glas AS, Slors FJM, et al. *Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, MR imaging – a meta-analysis.* Radiology, 2004; 232:773-783

21. RG Landmann, WD Wong, J Hoepfl et al., *"Limitations of ERC nodal staging may explane failure after local excision"* Disease of Colon Rectum, Vol 50, No.10 – 1520-1525, 2007

22. BJ Carmody, DP Otchy, *Learning curve of transrectal ultrasound*. Disease of Colon Rectum, Vol 42, No 2, 143-147, 2000

23. A. Fabian, R. Bor, K, Farkas, A. Balint, A. Milassin, M. Rutka, L. Tiszlavycz, T. Whitmann, et al., "*Rectal tumor staging with endorectal ultrasound: is there any differences between Eastern and Western european countries?*", Gastroenterology Research and Practice, 2016

24. JCM Li, SYW Liu, AWI Lo et al., *The learning curve for endorectal ultrasonography in rectal cancer staging*. Surgical Endoscopy, Vol 24, No 12, 3054-3059, 2010

25. SR Steele, MJ Martin, RJ Place, *Flexible endorectal ultrasound for predicting pathologic stage of rectal cancers*. The American Journal of Surgery, Vol 184, No 2, 126-130, 2002

26. Glensy, AM PullyblanK, MG Thomas, *The role of colonscopic endoanal ultrasound (EUS) in selecting patients suitable for resection by transanal endoscopic microsurgery (TEM).* Colorectal dis, 7:148-150, 2005

27. PG Doornebosh, PJB Bronkhorst, WCJ Hop, et al., *The role of ERUS in therapeutic decision-making for local vs. transabdominal resection of rectal tumors*. Disease of colon and rectum 51:38-42, 2008

28. L. Zorcolo, G. Fantola, F. Cabras, L. Marongiu, G. D'Alia, G. Casula, University of Cagliari, *Preoperative staging of patient with rectal tumors suitable for transanal endoscopic*

microsurgery (TEM): comparison of endorectal ultrasound and histopathologyc findings. Surgical Endoscopy, 23:1384-1389, 2009

29. Tytherleigh MG, Warren BF, Mortensen NJMcC. *Management of early rectal cancer*. Br J Surg 2008; 95: 409–23

30. Saito Y, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fujii T. *Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection.* Surg Endosc 2010; 24: 343-352

31. Lim TR, Mahesh V, Singh S, Tan BH, Elsadig M, Radhakrishnan N, Conlong P, Babbs C, George R. *Endoscopic mucosal resection of colorectal polyps in typical UK hospitals.* World J Gastroenterol 2010; 16: 5324-5328

32. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. *Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video)*. Gastrointest Endosc 2007; 66: 966-973

33. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. *Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases*. Clin Gastroenterol Hepatol 2007; 5: 678-83

34. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D, Yokota T. *A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases*. Gastrointest Endosc 1999; 50: 560-563

35. Saito Y, Sakamoto T, Fukunaga S, Nakajima T, Kiriyama S, Matsuda T. *Endoscopic submucosal dissection (ESD) for colorectal tumors*. Dig Endosc 2009; 21 Suppl 1: S7-12

36. Niimi K, Fujishiro M, Kodashima S, Goto O, Ono S, Hirano K, Minatsuki C, Yamamichi N, Koike K. *Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms*. Endoscopy 2010; 42: 723-729

37. Nishiyama H, Isomoto H, Yamaguchi N, Fukuda E, Ikeda K, Ohnita K, Mizuta Y, Nakamura T, Nakao K, Kohno S, Shikuwa S. *Endoscopic submucosal dissection for colorectal epithelial neoplasms.* Dis Colon Rectum 2010; 53: 161

38. Zhou PH, Yao LQ, Qin XY, Xu MD, Zhong YS, Chen WF, Ma LL, Zhang YQ, Qin WZ, Cai MY, Ji Y. *Advantages of endoscopic submucosal dissection with needle-knife over endoscopic mucosal resection for small rectal carcinoid tumors: a retrospective study*. Surg Endosc 2010; 24: 2607–2612

39. Probst A, Golger D, Arnholdt H, Messmann H. *Endoscopic submucosal dissection of early cancers, flat adenomas, and submucosal tumors in the gastrointestinal tract.* Clin Gastroenterol Hepatol 2009; 7: 149-155

40. Hong MJ, Kim JH, Lee SY, Sung IK, Park HS, Shim CS. *Prevalence and clinical features of coagulation syndrome after endoscopic submucosal dissection for colorectal neoplasms*. Dig Dis Sci 2015; 60: 211-216

41. Kiriyama S, Saito Y, Yamamoto S, Soetikno R, Matsuda T, Nakajima T, Kuwano H. *Comparison of endoscopic submucosal dissection with laparoscopic-assisted colorectal surgery for earlystage colorectal cancer: a retrospective analysis*. Endoscopy 2012; 44: 1024-1030

42. Nakamura F, Saito Y, Sakamoto T, Otake Y, Nakajima T, Yamamoto S, Murakami Y, Ishikawa H, Matsuda T. *Potential perioperative advantage of colorectal endoscopic submucosal dissection versus laparoscopy-assisted colectomy*. Surg Endosc 2015; 29: 596-606

43. Jang JH, Balik E, Kirchoff D, Tromp W, Kumar A, Grieco M, Feingold DL, Cekic V, Njoh L, Whelan RL. *Oncologic colorectal resection, not advanced endoscopic polypectomy, is the best treatment for large dysplastic adenomas*. J Gastrointest Surg 2012; 16: 165-71; discussion 171-2