Endo-SPONGE pulley system for the treatment of chronic anastomotic leakage after rectal resection.

A case report

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Livia Palmieri, Diletta Corallino, Ingrid Elva Cordova Herencia, Francesca Meoli, Alessandro M. Paganini

Department of General Surgery and Surgical Specialties "Paride Stefanini", Sapienza University, Rome, Italy

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AIM: *Anastomotic leakage (AL) after anterior rectal resection unresponsive to diverting ileostomy is difficult to manage. Endoscopic vacuum-assisted (E-VAC) wound closure system is a new approach based on co-axial sponge positioning under endoscopic control. If the abscess is not co-axial, however, endoscopic positioning is not feasible. Aim is to report an original method of sponge positioning.*
CASE EXPERIENCE: *A 62-year-old woman with chronic AL after anterior rectal resection for cancer was referred. AL had been treated with diverting ileostomy without healing. Due to the peri-rectal abscess anatomy, standard E-VAC positioning was not possible. A combined endoscopic-interventional radiology procedure for Endo-SPONGE® (B. Braun Aesculap AG, Germany) positioning was thus employed. Under general anesthesia, a guidewire was passed after small counter-incision on the left gluteus and through the left levator muscle, reaching the anastomotic dehiscence and rectal lumen through the chronic abscess. The guidewire was retrieved through the anus and connected to a long silk thread. By retracting the trans-gluteal guidewire, the silk thread was pulled through the abscess to exit from the gluteal skin incision. A tailored Endo-SPONGE® was then connected to the trans-anal silk thread. By pulling on the gluteal silk thread, the sponge was positioned inside the abscess. The silk thread remained in place under a medication for sponge replacements.*
DISCUSSION AND RESULTS: *Twelve Endo-SPONGE replacements under sedation were required until AL completely resolved after 35 days.*
CONCLUSION: *When traditional endoscopic sponge insertion into AL is not possible, this original "pulley system" proved effective for sponge introduction and replacement.*

KEY WORDS: Anastomotic leakage (AL), Anterior rectal resection, Endo-SPONGE, Endoscopic-Interventional radiology, Pulley system

Introduction

Anastomotic leakage (AL) after anterior rectal resection is the most dreaded complication [1,2], with an incidence rate ranging between 1% and 24% [3-4]. Patients who underwent neoadjuvant chemoradiotherapy (n-CRT) are reported to be at higher risk of AL [5,6]. The development of postoperative AL considerably increases postoperative morbidity and hospital stay, sometimes requiring additional surgical procedures for its resolution [7-15]. For this reason, in these patients a permanent stoma may be required in up to 25% of cases[4] with worsening quality of life.

Several approaches have been proposed for the treatment of AL that does not heal spontaneously after diverting ileostomy [16,17]. Endoscopic vacuum-assisted (E-VAC) wound closure system therapy is a new minimally invasive, well-tolerated alternative in patients not responding

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Correspondence to: Livia Palmieri, M.D., Department of General Surgery and Surgical Specialties "Paride Stefanini", Sapienza, University of Rome, Azienda Policlinico Umberto I, Viale del Policlinico 155, 00161 Rome, Italy (e-mail: livia.palmieri@alice.it)

to traditional treatments [18]. This device reduces the size of the abscess cavity until AL closure, thereby decreasing the risk of a permanent stoma [19]. However, if the position of the peri-rectal abscess is not co-axial with the axis of the rectum and colon, standard endoscopic E-VAC positioning may not be possible precluding its effective use and inherent benefits.

In the present case report, we describe the case of a woman with chronic postoperative AL after anterior rectal resection, in whom traditional endoscopic positioning of E-VAC therapy system was not possible due to the peculiar AL anatomy. In fact, the AL was in continuity with a blind-bottomed abscess cavity with long axis that was not co-axial with the rectal and colonic lumen and that was located in a dependent position with an acute angle. This prevented forward and reflexed view (retrovision maneuver) of the abscess cavity and standard positioning of the E-VAC therapy system.

Case Experience

In April 2018, a 62-year-old female patient was admitted to our Department, presenting with chronic AL located at five centimeters from the anal verge, that had initially occurred after anterior rectal resection for carcinoma (cT3N0Mx) without diverting ileostomy performed elsewhere in June 2009, following n-CRT. Definitive histology was ypT2N0M0, G2. In October 2009, follow up computed tomography (CT) scan showed the presence of hepatic metastasis (segments VIII-IV), hence the patient underwent 4 + 2 chemotherapy cycles (FOLFIRI-AVASTIN protocol, Roche S.p.A., 4052, Basel, Switzerland). During follow up, in May 2010 the patient developed fever and abdominal pain, with increased neutrophils count. A diagnosis of AL was made by water-soluble enema showing pre-coccygeal and pre-sacral fluid collections (max diameter 9x8 cm). The patient underwent uneventful segment IV atypical liver resection and loop ileostomy creation. Next, the patient underwent six further chemotherapy cycles. In March 2011, a follow up CT scan confirmed persistence of the AL along the left postero-lateral wall of the anastomosis with a blind-bottomed abscess developing caudally with respect to the anastomosis, ending at the level of the left levator ani muscle plane.

In May 2016, with no evidence of cancer recurrence at long-term follow up, the patient was referred to our Unit for the treatment of the chronic AL, due to failure of the diverting ileostomy at obtaining resolution of the anastomotic dehiscence and consequent abscess. The patient was therefore possibly considered a suitable candidate for Endoluminal Vacuum Therapy (E-VAC) (Endo-SPONGE®, B. Braun Aesculap AG, Germany). The first attempt at endoscopic Endo-SPONGE placement failed because it was impossible to angulate the flexible endoscope into the abscess. In fact, the long axis of the abscess was not presacral and co-axial with the axis of the colon but described a very narrow angle in a dependent position with respect to the AL and pointing caudally towards the left gluteus (Fig. 1). The Endo-SPONGE® was therefore positioned by a combined endoscopic and interventional radiology procedure. With the patient under general anesthesia and in gynecological position with moderate Trendelemburg tilt of the operative table, a water-soluble enema fluoroscopy showed the direction of the abscess (Fig. 1). A guidewire was then passed by counter skin incision on the left gluteus and through the left levator ani muscle, reaching the anastomotic dehiscence and the rectal lumen through the course of the abscess under digital rectal examination. The guidewire was then pulled out through the anus and tied to a long silk U.S.P. #1 suture thread (Ethicon Inc., Johnson & Johnson, Somerville, NJ, USA). By retracting the trans-gluteal guidewire, the silk suture thread was pulled through the abscess and out from the gluteal skin incision. After slightly enlarging the gluteal skin incision, the suture thread was tied to the tip of a 3x4 mm non-disposable Volkmann sharp bone spoon curette (Moretti S.p.A., 52022, Cavriglia, Arezzo, Italy). Next, by pulling on the trans-anal portion of the suture thread, the bone spoon curette was driven through the skin and levator ani muscles plane (Fig. 2) and it was used for sharp curettage of the internal walls of the abscess. The bone spoon curette was then retrieved from the gluteal skin incision and disconnected from the suture thread. The irrigation set with

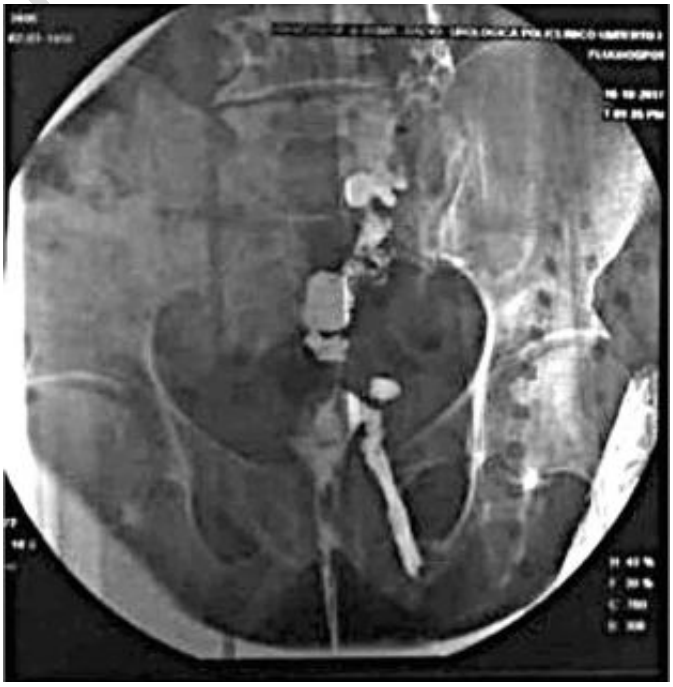

Fig. 1: Water-soluble contrast enema imaging of anastomotic dehiscence and perirectal abscess at the beginning of Endo-SPONGE® treatment.

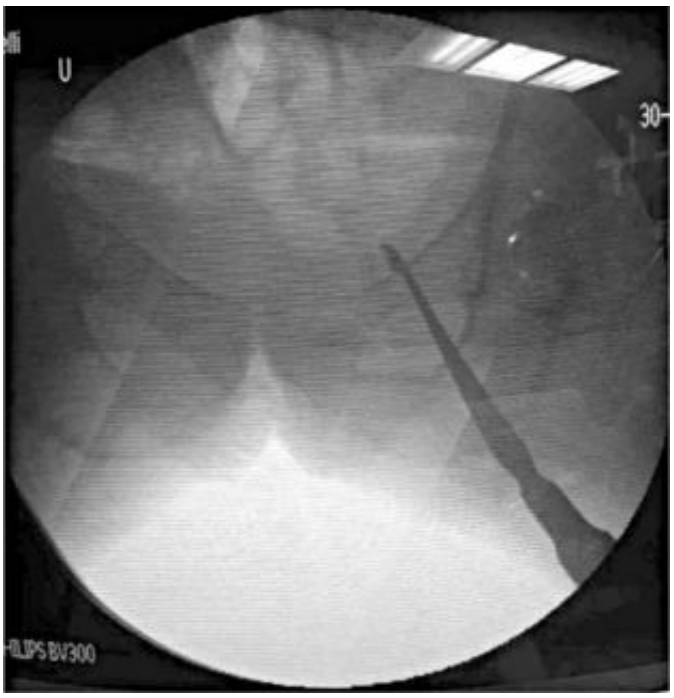

Fig. 2: Intraoperative fluoroscopy imaging of the bone spoon curette in place through the gluteal skin incision and through levator ani muscle plane, for curettage of the perirectal abscess cavity.

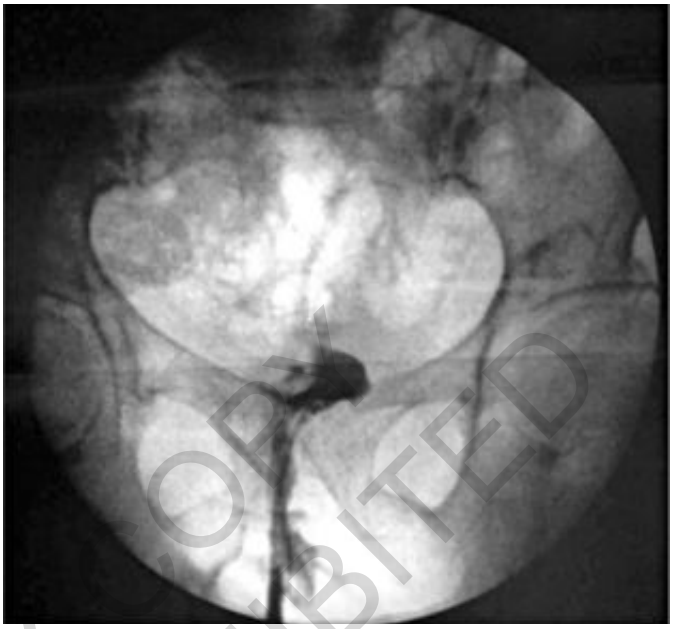

Fig. 3: Water-soluble contrast enema imaging showing healing of anastomotic dehiscence and perirectal abscess at the end of Endo-SPONGE® treatment.

syringe and cap that is included in the Endo-SPONGE® kit was employed for irrigation of the abscess with Hydrogen Peroxide (FARMAC-ZABBAN, 40012, Calderara Di Reno, Bologna, Italy) through the gluteal skin incision, to remove necrotic debris after sharp curettage of the internal walls of the abscess. The trans-anal suture thread was then tied to the open-pore polyurethane ether Endo-SPONGE®, which had been tailored to the size of the peri-rectal abscess based on the water-soluble enema fluoroscopy imaging. By pulling on the trans-gluteal suture thread by means of this "pulley system", the sponge and joined redon drain were pulled through the anus and through the AL until the sponge was correctly positioned inside the abscess, with its connected redon drain routed through the anus. The redon drain was then connected to the Y-shaped connecting tube with Luerlock attachment on REDYROB® Trans Plus bottle (B. Braun Aesculap AG, Germany), establishing the negative pressure of -1 (120 mmHg, "low pressure") while the trans-gluteal suture thread remained in place under a medication. The patient was discharged home with the Endo-SPONGE® and REDYROB® Trans Plus bottle suction system in place and returned as an outpatient to have the system replaced under sedation every 72 hours. Twelve consecutive Endo-SPONGE replacements in the operative room were required, with no need for fluoroscopic or endoscopic control. At each replacement session, the curettage procedure with bone spoon curette was repeated over and over again, and the sponge was progressively trimmed smaller and smaller, until the abscess and AL completely healed after 35 days, as demonstrated by water-soluble contrast enema imaging (Fig. 3). The patient is now undergoing anal sphincter biofeedback rehabilitation, due to the long period of fecal diversion with consequent sphincter hypotonicity, while waiting for ileostomy closure.

Discussion

After failure of conservative treatment with diverting stoma creation, in this patient closure of a chronic AL and healing of a chronic perirectal abscess with Endo-SPONGE® system positioning and subsequent replacements was eventually obtained in a little more than one month.

The Endo-SPONGE system reduces the duration of hospital stay as compared to other more invasive alternatives[20]. In the literature, several possible more or less invasive therapeutic approaches are reported, including local repair of the fistula (transanal, transvaginal, or trans-perineal approaches), use of biomaterials (fibrin glue, collagen fistula plug and huge variety of biosynthetic products), tissue transposition repairs and trans-abdominal surgery[21-26]. The multiplicity of treatment options gives evidence of the difficulties that may be encountered in

obtaining successful management of this condition. All of these options may have good success rates, but often at the cost of an additional complex surgical procedure coupled with the need for faecal diversion, which also requires an additional surgical procedure for its closure [21-26].

In this case, the Endo-SPONGE® system proved to be comfortable and well tolerated by the patient. Once the "pulley system" was established, sponge replacement was simple and straightforward in an outpatient setting, although perfomed under sedation in the operating room. This method provides continuous and effective drainage of the fistula with debridement and consecutive mechanical reduction of the abscess cavity volume, until closure of the abscess is obtained [3,20]. The sponge open-pore structure in combination with negative pressure provides a very effective method of drainage, without damage to the neighboring structures, and enhances the formation of granulation tissue in the abscess cavity [19,27]. The topical negative pressure is applied uniformly to every point on the inner surface of the abscess cavity [18,27].

In this patient, due to the peculiar anatomy of the abscess with respect to the axis of the colon and rectum, devising and application of the "pulley system" was of primary importance for resolution of the abscess. This was obtained after creation of a left gluteal skin counter-incision and passing through the left levator ani muscles plane, thereby temporarily transforming the chronic abscess into a colo-cutaneous fistula for transcutaneous sharp curettage and cleansing of the internal walls of the abscess, and replacements of the sponge. To the best of our knowledge, this is the first "pulley system" devised for E-VAC sponge positioning and replacement [18,27,28] when the abscess cannot be reached under endoscopic control due to its peculiar anatomy with respect to the axis of the rectum. It is obviously necessary to carefully evaluate the anatomy of the peri-anastomotic abscess and the general and local conditions to select the patients who can take advantage of Endo-SPONGE treatment [29].

The first data on the treatment of AL with the Endo-SPONGE® system are reported by Nagell *et al.* in 2006 [28]. The mean healing time was 51 days in four patients treated by a sponge in comparison to 336 days in 10 patients treated conservatively by trans-rectal drainage. Weidenhagen *et al.* [27], between 2002 and 2005 treated 97 patients with AL after anterior resection, 43 patients with Endo-SPONGE® and 54 conservatively. The average healing time was 33.5 days in patients with Endo-SPONGE®, versus 81 days in the control group treated by diverting stoma creation. In 2009, von Berstoff *et al.* [30] reported 23 patients who had complete healing of the dehiscence with Endo-SPONGE®, in a series of 26 patients (88.5%). An Italian study by Strangio *et al.* [3] also reported an 88% success rate in their patients, with a median healing time of 28 days. These authors also performed a literature review, reporting on a total of 174 patients including their series. Complete healing of the abscess cavity was achieved in 94.3% of patients, with a success rate ranging from 56.6 to 100%, over a treatment duration time of 34 days (range 1-221) and with a median of 11 replacement procedures (range 1-41). In a more recent publication, Milito *et al.* [20] reported their experience in 14 patients with AL treated with Endo-SPONGE®. The median duration of therapy was 35 days, with 3-14 sponge replacements per patient. The median healing time was 37 days with no intraoperative complications.

Conclusion

Endo-SPONGE® is a minimally invasive, safe and effective procedure for the management of AL. However, positioning of the device may not always be possible in relation to the anatomy of the abscess, which may be difficult to reach under endoscopic control. The "pulley system" devised by the authors proved to be a valid option for successful treatment of this patient.

Riassunto

OBIETTIVI: La deiscenza anastomotica è la complicanza più temuta dopo resezione anteriore del retto, per il cui trattamento sono stati proposti vari approcci, sia conservativi che chirurgici. Il trattamento endoscopico con il sistema E-VAC è un'alternativa poco invasiva e ben tollerata dal paziente, basato sul posizionamento endoscopico della spugna. Tuttavia, se l'ascesso non risulta essere co-assiale rispetto all'asse del retto e del colon, il posizionamento endoscopico può non essere possibile. L'obiettivo di questo case report è mostrare un metodo alternativo di posizionamento del sistema E-VAC.

CASE REPORT: Riportiamo il caso di una donna di 62 anni con deiscenza anastomotica cronica a cinque centimetri dal margine anale, dopo radio-chemioterapia neoadiuvante e resezione anteriore del retto per adenocarcinoma e successiva chemioterapia per metastasi epatiche. La deiscenza anastomotica non si era risolta dopo ileostomia derivativa confezionata al momento della resezione epatica. In questo caso il posizionamento del sistema E-VAC in maniera tradizionale non era possibile a causa dell'anatomia della fistola. Il lume del retto e la fistola presentavano un angolo acuto di 20° diretto caudalmente, che non consentiva il posizionamento e la sostituzione del sistema per via endoscopica in retrovisione. La paziente è stata quindi candidata al posizionamento del sistema Endo-SPONGE® (B. BraunAesculap AG, Germany) mediante procedura combinata endoscopica e radiologica interventistica. Dopo aver effettuato un Rx-clisma opaco con gastrographin ed aver identificato il tramite ascessuale, un filo guida è stato fatto passare da contro-incisione sul gluteo sinistro attraverso il piano

degli elevatori, fino a raggiungere il lume del retto attraverso l'ascesso. Estratto per via trans-anale, il filo guida è stato legato ad un filo di seta che è stato fatto passare attraverso l'ascesso e recuperato dalla contro-incisione glutea. Questo sistema "a carrucola" ha consentito di guidare il passaggio di un cucchiaio di Volkmann percutaneo, per curettage delle pareti dell'ascesso, e di praticare lavaggi con acqua ossigenata. Con lo stesso sistema, la spugna Endo-SPONGE® sagomata è stata connessa al filo-guida di seta, retraendo il quale la spugna si posizionava perfettamente per via trans-anale nel tramite ascessuale. Sono state necessarie dodici sostituzioni consecutive dell'Endo-SPONGE® ogni 72 ore per raggiungere la completa risoluzione della fistola in 35 giorni.

DISCUSSIONE: Senza il sistema "a carrucola" descritto non sarebbe stato possibile posizionare il dispositivo in aspirazione continua.

CONCLUSIONE: Per quanto ne sappiamo, questo è il primo "sistema a carrucola" riportato in letteratura per il posizionamento della spugna Endo-SPONGE® di poliuretano.

References

1. Shalaby M, Thabet W, Rulli F, Palmieri F, Saraceno F, Capuano I, Buonomo O, Giarratano G, Petrella G, Morshed M, Farid M, Sileri P: *Anastomotic leakage following laparoscopic resection of low and midrectalcancer*. AnnItalChir, 2019; 90:57-67.

2. Paliogiannis P, Attene F, Scognamillo F, Trignano E, Torre C, Pulighe F, Trignano M: *Conservative management of minor anastomotic leakage after open elective colorectal surgery*. Ann Ital Chir, 2012; 83(1):25-8.

3. Strangio G, Zullo A, Ferrara EC, Anderloni A, Carlino A, Jovani M, Ciscato C, Hassan C, Repici A: *Endo-sponge therapy for management of anastomotic leakagesafter colorectal surgery: A case series and review of literature*. Dig Liver Dis, 2015; 47(6):465-69. doi: 10.1016/j.dld.2015.02.007.

4. Lee WS, Yun SH, Roh YN, Yun HR, Lee WY, Cho YB, Chun HK: *Risk factors andclinical outcome for anastomotic leakage after total mesorectal excision forrectal cancer*. World J Surg, 2008; 32(6):1124-129. doi:10.1007/s00268-007-9451-2.

5. Branagan G, Finnis D: *Wessex colorectal cancer audit working group; prognosis after anastomotic leakage in colorectal surgery*. Dis Colon Rectum, 2005; 48(5):1021-26.

6. Batista Rodríguez G, Balla A, Corradetti S, Martinez C, Hernández P, Bollo J, Targarona EM: *What have we learned in minimally invasive colorectal surgery from NSQIP and NIS large databases? A systematic review.* Int J Colorectal Dis, 2018; 33(6):663-81. doi: 10.1007/s00384-018-3036-34.

7. D'Ambrosio G, Paganini AM, Balla A, Quaresima S, Ursi P, Bruzzone P, Picchetto A, Mattei FI, Lezoche E: *Quality of life in non-early rectal cancer treated by neoadjuvant radio-chemotherapy and endoluminal loco-regional resection (ELRR) by transanal endoscopic microsurgery (TEM) versus laparoscopic total mesorectal excision*. Surg Endosc, 2016; 30(2):504-11. doi: 10.1007/s00464-015-4232-8.

8. Mussetto A, Arena R, Buzzi A, Fuccio L, Dari S, Brancaccio ML, Triossi O: *Long-term efficacy of vacuum-assisted therapy (Endo-SPONGE(®)) in largeanastomotic leakages following anterior rectal resection*. Ann Gastroenterol, 2017; 30(6):649-53. doi: 10.20524/aog.2017.0194.

9. D'Ambrosio G, Balla A, Mattei F, Quaresima S, De Laurentis F, Paganini AM: *Quality of Life after Endoluminal Loco-Regional Resection (ELRR) by Transanal Endoscopic Microsurgery (TEM).* Ann Ital Chir, 2015; 86(1):56-60.

10. D'Ambrosio G, Paganini AM, Guerrieri M, Barchetti L, Lezoche G, Fabiani B, Lezoche E: *Minimally invasive treatment of recto-vaginal fistula*. Surg Endosc, 2012; 26(2):546-50. doi: 10.1007/s00464-011-1917-5.

11. Biviano I, Balla A, Badiali D, Quaresima S, D'Ambrosio G, Lezoche E, Corazziari E, Paganini AM: *Anal function after endoluminallocoregional resection by transanal endoscopic microsurgery and radiotherapy for rectal cancer.* Colorectal Dis 2017; 19(6):O177-O185. doi: 10.1111/codi.13656.

12. Balla A, Quaresima S, Smolarek S, Shalaby M, Missori G, Sileri P: *Synthetic versus biological mesh-related erosion after laparoscopic ventral mesh rectopexy: A systematic review*. Ann Coloproctol, 2017; 33(2):46-51. doi: 10.3393/ac.2017.33.2.46.

13. Lezoche E, Feliciotti F, Paganini AM, Guerrieri M, De Sanctis A, Campagnacci R, D'Ambrosio G: *Results of laparoscopic versus open resections for non-early rectal cancer* in *patients with a minimum follow-up of four years.* Hepatogastroenterology, 2002; 49(47):1185-90.

14. Quaresima S, Balla A, D'Ambrosio G, Bruzzone P, Ursi P, Lezoche E, Paganini AM.: *Endoluminal loco-regional resection by TEM after R1 endoscopic removal or recurrence of rectal tumors*. Minim Invasive Ther Allied Technol, 2016; 25(3):134-40. doi: 10.3109/13645706.2016.1145125.

15. Quaresima S, Balla A, Franceschilli L, La Torre M, Iafrate C, Shalaby M, Di Lorenzo N, Sileri P: *TransanalMinimally Invasive Surgery for RectalLesions*. JSLS, 2016; 20(3). pii: e2016.00032. doi: 10.4293/JSLS.2016.00032.

16. Mileski WJ, Joehl RJ, Rege RV, Nahrwold DL: *Treatment of anastomotic leakagefollowing low anterior colon resection.* Arch Surg, 1988; 123(8):968-71.

17. Swain BT, Ellis CN: *Fibrin glue treatment of low rectal and pouch-analanastomotic sinuses*. Dis Colon Rectum, 2004; 47(2):253-55.

18. Borejsza-Wysocki M, Szmyt K, Bobkiewicz A, Malinger S, Świrkowicz J, HermannJ, Drews M, Banasiewicz T: *Endoscopic vacuum-assisted closure system (E-VAC): Case report and review of the literature.* WideochirInne Tech Maloinwazyjne, 2015; 10(2):299-310. doi: 10.5114/wiitm.2015.52080.

19. Bemelman WA: *Vacuum assisted closure in coloproctology. Tech Coloproctol.* 2009; 13(4):261-63. doi: 10.1007/s10151-009-0543-x.

20. Milito G, Lisi G, Venditti D, Campanelli M, Aronadio E, Grande S, Cabry F, Grande M: *Endoluminal vacuum therapy as treatment for anastomotic colorectalleakage*. Surg Technol Int, 2017; 30:125-30.

21. Abu Gazala M, Wexner SD: *Management of rectovaginal fistulas and patient outcome.* Expert Rev Gastroenterol Hepatol. 2017; 11(5):461-71. doi: 10.1080/17474124.2017.1296355.

22. Gessler B, Eriksson O, Angenete E: *Diagnosis, treatment, and*

consequences of anastomotic leakage in colorectal surgery. Int J Colorectal Dis, 2017; 32(4):549-56. doi: 10.1007/s00384-016-2744-x

23. Thornton M, Joshi H, Vimalachandran C, et al.: *Management and outcome of colorectal anastomotic leaks*. Int J Color Dis. 2011; 26(3):313-20. doi: 10.1007/s00384-010-1094-3.

24. Nachiappan S, Askari A, Malietzis G, et al.: *The impact of anastomotic leak and its treatment on cancer recurrence and survival following elective colorectal cancer resection*. World J Surg, 2015; 39(4):1052-. doi: 10.1007/s00268-014-2887-2.

25. Matthiessen P, Hallbook O, Rutegard J, et al.: *Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: A randomized multicenter trial*. Ann Surg, 2007; 246(2):207-14. doi: 10.1097/SLA.0b013e3180603024.

26. Kingham TP, Pachter HL: *Colonic anastomotic leak: risk factors, diagnosis, and treatment*. J Am Coll Surg, 2009; 208(2):269-78. doi: 10.1016/j.jamcollsurg.2008.10.015.

27. Weidenhagen R, Gruetzner KU, Wiecken T, Spelsberg F, Jauch KW: *Endoscopicvacuum-assisted closure of anastomotic leakage following anterior resection ofthe rectum: a new method.* Surg Endosc, 2008; 22(8):1818-25.

28. Nagell CF, Holte K: *Treatment of anastomotic leakage after rectal resectionwithtransrectal vacuum-assisted drainage (VAC): A method for rapid control ofpelvic sepsis and healing.* Int J Colorectal Dis, 2006; 21(7):657-60.

29. Arezzo A, Miegge A, Garbarini A, Morino M: *Endoluminal vacuum therapy foranastomotic leaks after rectal surgery*. Tech Coloproctol, 2010; 14(3):279-81. doi: 10.1007/s10151-010-0569-0.

30. von Bernstorff W, Glitsch A, Schreiber A, Partecke LI, Heidecke CD: *ETVARD (endoscopic transanal vacuum-assisted rectal drainage) leads to complete but delayed closure of extraperitoneal rectal anastomotic leakage cavities following neoadjuvant radiochemotherapy.* Int J Colorectal Dis, 2009; 24(7):819-25. doi: 10.1007/ s00384-009-0673-7.