research article

Ultralow anterior resection with implantation of gentamicin-collagen sponge and no defunctioning stoma: anastomotic leakage and local cancer relapse

Tomasz Michalik[1], Rafał Matkowski[1,2], Przemyslaw Biecek[3], Jozef Forgacz[1], Bartlomiej Szynglarewicz[1,2]

[1] Department of Surgical Oncology, Lower Silesian Oncology Centre – Regional Comprehensive Cancer Centre, Wroclaw, Poland

[2] Department of Oncology, Faculty of Postgraduate Medical Training, Wroclaw Medical University, Wroclaw, Poland

[3] Faculty of Mathematics and Information Science, Warsaw University of Technology, Warsaw, Poland

Radiol Oncol 2019; 53(1): 77-84.

Received 7 November 2018
Accepted 10 January 2019

Correspondence to: Dr. Bartlomiej Szynglarewicz, Assoc. Prof.; Department of Oncology, Wroclaw Medical University, and Department of Surgical Oncology, Lower Silesian Oncology Centre - Regional Comprehensive Cancer Centre, Plac Hirszfelda 12, 53413 Wroclaw, Poland. Phone: +48 071 3689391; Fax: +48 071 3619111; E-mail: szynglarewicz.b@dco.com.pl

Disclosure: No potential conflicts of interest were disclosed.

Background. Anterior resection with total mesorectal excision (TME) of ultralow rectal cancer may result in the increased risk of the anastomotic leakage (AL). The aim of this study was to evaluate the usefulness of the gentamicin-collagen sponge (GCS) for the protection against symptomatic AL and investigate association between AL and local relapse (LR).

Patients and methods. A series of 158 patients with ultralow rectal cancer was studied. All the patients underwent R0 sphincter-saving TME with anastomosis wrapping using GCS. In none of the cases a temporary protective stoma was constructed.

Results. AL rate was 3.2% (5/158) while median time to AL diagnosis was 5 days following surgery (range 3-15). There was no postoperative and leakage-related mortality. Patient age > 75 years and smoking were independent risk factors related to significantly increased AL rate: 12.5% *vs.* 0.8% ($P = 0.0004$) and 5.7% *vs.* 0% $P = 0.043$), respectively. LR was observed in 12% of cases. It was highly significantly more common and developed earlier in patients who have had AL when compared with non-AL group: 80% *vs.* 9% ($P = 0.00001$) and 8.5 *vs.* 17 months ($P = 0.014$), respectively.

Conclusions. Anastomosis wrapping with GCS after anterior resection with TME is a safe procedure resulting in the low incidence of anastomotic leakage which may be also associated with decreased risk of local relapse.

Key words: rectal cancer; anterior resection; total mesorectal excision; anastomotic leakage; gentamicin-collagen sponge

Introduction

Because of effective local control, total mesorectal excision (TME) is nowadays the mainstay of curative treatment in rectal cancer. However, sphincter-saving TME may result in the increased risk of the anastomotic leakage (AL) due to the short rectal remnant and local oxygen tissue deficiency in anastomosis associated with the reduced distal blood supply. Moreover, this technique produces the large splinted cavity within the pelvis, conducive to the exudate retention and the formation of haematoma, which may become infected. Reported rates of AL following TME are up to even 23%, being influenced by several patient-, tumour- and treatment related factors.[1,2] As a result of even

minor leakage, local contamination at the perirectal area may be the cause of extra-abdominal infection. The presence of AL is closely associated with the increased risk of pelvic abscess, peritonitis and septicemia, which commonly require additional intervention, prolong hospital stay, limit the cost-effectiveness of treatment and may result in postoperative death. It impairs late functional results and probably oncological outcomes.[2]

On the other hand, the recent emergence of technologies such as resorbable implants offers new possibilities to protect the anastomosis and reduce the consequences of leakage. Hence we reported the wrapping of anastomosis with the gentamicin-collagen sponge (GCS) as a potential preventive manoeuvre against the AL – probably limiting the leakage intensity and reducing its clinical symptoms.[3,4] It encouraged us to continue the study with more patients and longer follow-up in order to obtain more reliable and objective results as well as for more robust statistics.

The aim of this study was to evaluate the possible impact of GCS on the risk of clinically symptomatic AL and investigate association between AL and local relapse.

TABLE 1. Baseline characteristics

Characteristics	n (%)
Gender Female / Male	92 (58) / 66 (42)
Age (years) Mean ± SD / median / range	67.1 ± 9.8 / 68 / 34-85
Comorbidity Diabetes / Cardiovascular disease	13 (8) / 40 (25)
Smoking Yes / No	87 (55) / 71 (45)
Obesity Yes / No	31 (20) / 127 (80)
Preoperative radiotherapy Yes / No	65 (41) / 93 (59)
Operating time (minutes) Mean ± SD / median / range	118.9 ± 24.8 / 120 / 45-190
Level of anastomosis (cm) Mean ± SD / median / range	5.4 ± 1.1 / 5.0 / 3-7
Blood transfusion Yes / No	24 (15) / 134 (85)
Postoperative fever Yes / No	9 (6) / 149 (94)
T stage T1T2 / T3	95 (60) / 63 (40)
N status N- / N+	91 (58) / 67 (42)

Patients and methods

Patients

A series of 158 patients with T1-T3 and N-/N+ ultra-low rectal cancer (below 8 cm from the anal verge) without distant metastases (M0) who underwent anterior resection with curative intent at the Lower Silesian Oncology Centre – Regional Comprehensive Cancer Centre in the years 2006 - 2012 was studied. None of them was in poor general condition, had anaemia or was treated with steroids. Patients underwent pre-operative bowel preparation with 4 L polyethylene glycol solution 1 day before surgery. All patients received prophylactic systemic antibiotic therapy in a perioperative intravenous injection within 30 minutes of the skin incision (cefotaxime 1000 mg i.v. followed by a supplementary dose 12 h later; metronidazole 500 mg i.v. followed by two more supplementary doses every 8 h) and anticoagulant therapy with low molecular weight heparin. All the patients underwent traditional open surgery through a midline laparotomy incision. All analysed patients fulfilled the following study inclusion criteria: the lack of intraoperative bowel perforation, total integrity of doughnuts after retrieval of the stapler and complete integrity of the anastomosis examined by transanal air insufflation with the anastomosis immersed in warm normal saline solution.

Patients data, tumour-related factors and treatment characteristics are shown in Table 1.

Treatment

Sixty-five (41%) patients with T3 and / or N+ tumours in MRI or endorectal ultrasound received preoperative five-day scheduled high-dose radiation with a total dose of 25 Gy in a daily fractions of 5 Gy. Since in our institution the use of preoperative chemotherapy was limited to T4 tumours (combined with long-term radiation), it was not administered in the analysed group. The upper limit of all the pelvic fields was at the L5-S1 level and the lower one was 5 cm below the tumour. Radiotherapy was followed by surgery within 7 days. All patients were operated on strictly according to the TME with complete peri-rectal tissue removal by sharp dissection of pelvic fascia under the direct vision between parietal and visceral surface to the levators. Inferior mesenteric vessels were ligated high at their origin. Splenic flexure of the colon was mobilized to relieve a tension. Minimum 1 cm distal margin was achieved. Straight end-to-end anastomosis with double-stapling technique

was constructed. Although routine pelvic drainage in colorectal surgery has not been justified in randomised controlled trials, it is routinely used in our institution after anterior resection because we believe it may act as an early detector of anastomotic leakage. Thus, a silastic pelvic drainage was placed in all of the analysed patients using a closed, gravitational no-suction method.

GCS implantation

Technique of GCS implantation has already been presented by us in details elsewhere.[5] Briefly, anastomosis was wrapped with 10 x 10 x 0.5 cm sponge containing 130 mg of gentamicin sulfate and 280 mg purified bovine tendon type I collagen which was applied deeply into pre-sacral area to the levators level. GCS was formed and pressed to the bowel wall (Figure 1). Special effort was made for its adequate location and stability.[5] During the all postoperative hospital stay a close patient examination was performed several times a day in order to identify any clinical symptoms suspicious of the leakage. AL was considered to be present if any of the following features were noticed: the presence of peritonitis caused by anastomotic dehiscence, the presence of feculent substances and gas from the pelvic drain or the presence of pelvic abscess with the demonstration of leakage by transrectal examination, endoscopy, contrast enema, endorectal ultrasound or CT scanning.

Follow-up

During the postoperative follow-up physical examination (with digital rectal examination and CEA measuring) was scheduled every three months for the first two years, at 6-months intervals for the next three years, and once a year thereafter. Abdominal and pelvic imaging was performed every six months. Colonoscopy was performed after 1 year and then every three years. Any symptoms potentially related to LR were a subject of investigation with colonoscopy and CT or MRI. LR was defined as local cancer recurrence regardless of the presence or absence of distant metastases.

Statistical analysis

Data was collected in a prospective manner and then retrospectively analysed. In each case following parameters were recorded: patient age, gender, comorbidity (diabetes and cardiovascular disease), obesity (body mass index > 30 kg/m^2), smoking status, preoperative radiotherapy, level of anastomosis from the anal verge (cm), blood transfusion, presence of postoperative fever (> 37.5 Celsius degrees), T stage and N status. The median and range values as well as the mean values with their standard deviations were calculated when appropriate. Incidence and rates of AL and LR were calculated. Correlation between categorical variables was assessed using chi-square test with correction for continuity while between continuous variables using *T*-test. Multivariate analysis was performed with the use of multiple logistic regression. The statistical significance was assumed at p value < 0.05. Statistical analysis was performed by a professional statistician (PB) using R-software ver. 3.2 (free environment for statistical computing and graphics).

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board. This research was financed through a statutory subsidy by the Minister of Science and Higher Education as a part of the research grant ST.C280.17.010 (record number in the Simple System).

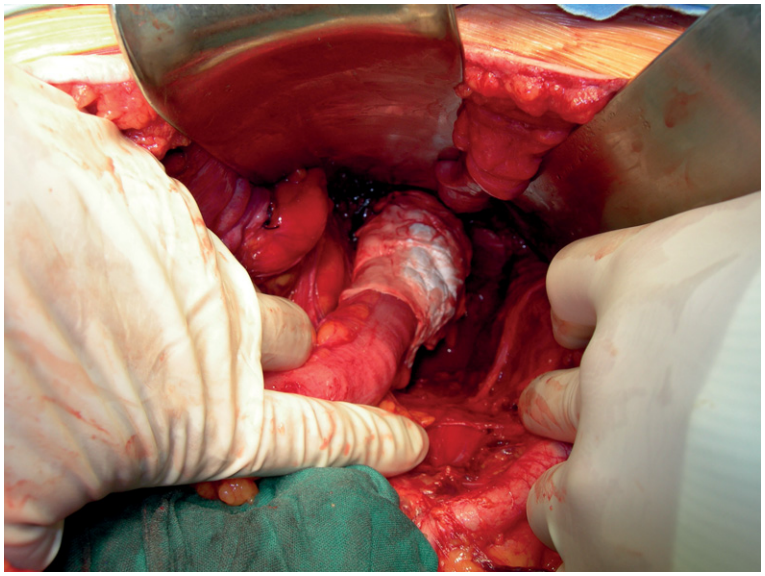

FIGURE 1. Anastomosis wrapping with GCS.

Results

GCS was applied without any technical difficulties and was well tolerated. Neither sponge-related adverse reaction nor drain blockage were noticed. AL developed in 5 patients giving the AL rate of 3.2%

TABLE 2. Uni – and multivariate analysis of anastomotic leakage incidence

Variables	Patients with leakage n (%)	Univariate analysis *P* - value	Multivariate analysis *P* - value
Gender			
Female	2 (2.2)	0.4010	-
Male	3 (4.5)		
Age			
≥ 75	4 (12.5)	0.0007	0.0004
< 75 years	1 (0.8)		
Diabetes			
Yes	1 (7.7)	0.3303	-
No	4 (2.8)		
Cardiovascular disease			
Yes	1 (2.5)	0.7811	-
No	4 (3.4)		
Smoking			
Yes	5 (5.7)	0.0401	0.043
No	0 (0)		
Obesity			
Yes	2 (6.5)	0.2435	-
No	3 (2.4)		
Preoperative radiotherapy			
yes	3 (4.6)	0.4053	-
no	2 (2.2)		
Level of anastomosis			
> 5	1 (1.5)	0.3289	-
≤ 5 cm	4 (4.3)		
Blood transfusion			
yes	1 (4.2)	0.7607	-
no	4 (3.0)		
Postoperative fever			
yes	0 (0)	0.5765	-
no	5 (3.4)		
T stage			
T1T2	3 (3.1)	0.9953	-
T3	2 (3.2)		
N status			
N-	3 (3.3)	0.9119	-
N+	2 (3.0)		

(5/158). In all the cases it was associated with clinical symptoms: peritonitis and pelvic abscess in one patient each, and gas or feculent discharge from pelvic drain in three patients. The median time to the diagnosis of AL was 5 days (range: 3-15) following surgery. Two patients (one with peritonitis and one with abscess) underwent surgical re-intervention: peritoneal lavage and defunctioning transversostomy. Three remaining patients had only minor AL without peritonitis and abscess and were effectively treated with pelvic lavage through the drain, total parenteral nutrition and antibiotic therapy. There was no leakage-related mortality. All resolution of AL was confirmed by endoscopy or contrast enema.

Univariate analysis demonstrated that patient age > 75 years and smoking were significantly related to the increased AL rate: 12.5% *vs*. 0.8% (p = 0.0007) and 5.7% *vs*. 0 (p = 0.0401), respectively. Influence of patient gender, diabetes and cardiovascular disease, obesity, preoperative radiotherapy, operating time, level of the anastomosis, blood transfusion, postoperative fever, T stage and N status on AL rate did not reach statistical significance. In multivariate analysis patient age > 75 years was identified as the most important independent risk factor for clinical AL (p = 0.0004). However, the negative impact of smoking was also significant (p = 0.043). Results are presented in Table 2.

Twenty-three patients were lost from follow-up. In the remaining 135 patients median follow-up (mean ± SD; range) was 61 months (64.8 ± 32.5; 16-134). LR developed in 12% of patients (16/135). In 12 cases was resectable, in 5 patients with curative intent. Median interval (mean ± SD; range) to LR was 14 months (15.9 ± 6.3; 7-28). 25% of patients (4/16) with LR had AL after TME while just 0.8% in non-recurrent group (1/119). 88% of LR (14/16) developed in 24 months. LR was observed in 80% of patients with postoperative AL (4/5) while only 9% of patients without AL (12/130); the difference was highly significant (p = 0.00001). Time to LR was significantly shorter in AL group when compared with patients without leakage; median (mean ± SD; range): 8.5 (9.1 ± 2.1; 7-12) *vs*. 17 (18.9 ± 6.1; 10-28) months (p = 0.014).

Discussion

Due to high risk of long duration of procedure, bacteria migration, toxin translocation, possibility of contamination and the presence of malignancy, effective antibiotics in colorectal cancer surgery are needed for the prophylaxis and treatment. Gentamicin is the one of the most often used antimicrobial agents. However, recent studies clearly show that systemic administration of gentamicin results in only borderline effectiveness and does not achieve levels above minimum inhibitory concentration in serum, subcutaneous tissue, epiploic fat and bowel wall.[6] In addition, although blood transfusions are not often required in modern colorectal surgery (as observed in our series), intravenously administered fluids can strongly decrease gentamicin concentrations. Local application of gentamicin provides sufficient drug dosage that can reduce the incidence of infections, lowers the risk of antibiotic resistance by reducing the need for long-term systemic therapy and carries a low risk of toxicity.[7] Collagen seems to be one of the most favourable matrix for controlled local drug delivery because of its bio-compatibility and well-established safety profile.[8] Its usage as a carrier has

positive effect on wound healing and eliminates the need of re-operation because the implant is fully resorbable. Collagen causes faster coagulation to stop bleeding and reduces the risk of hematoma or seroma formation that can in turn accelerate bacterial proliferation. The breakdown of the GCS by macrophage collagenases increases the number of collagen fibres released, which attracts fibroblasts and stimulates the fibroblasts to proliferate and lay down new collagen in the healing process.[9] Drugs are released from a collagen matrix by a combination of diffusion and natural enzymatic breakdown of the collagen matrix, which provides rapid (diffusion) and prolonged (breakdown of the matrix) drug release.[10] Moreover, immune response against collagen implants are uncommon.[11,12] Hence, GCS is used to improve wound healing and for prophylaxis of infections following surgery, including gastrointestinal operations.[3]

Features affecting AL rates in our series are not surprising. Older age is mentioned among the most frequent factors.[1] Negative impact of smoking is also well documented. It increases a risk of AL mainly by affecting small vessels and causing tissue hypoxia, which compromises the healing of anastomosis.[2] The other factors, including preoperative radiotherapy and anastomosis level did not reach statistical significance in our series. The use of covering stoma remains controversial and more individual approach is needed. However, our findings suggest that it still can be worth considering in well-selected high-risk cases, such as older and smoking patients.

Interestingly, the incidence of AL among the patients in our group seems to be relatively low when compared to the 10 - 13.7% incidence reported by others.[14-18] Only few papers concerning the use of GCS in colorectal surgery have been published as yet. In the recent multi-centre randomized trial enrolling 602 patients, Bennett-Guerrero and coworkers from a SWIPE 2 trial group found GCS not effective at preventing surgical-site infection, either superficial or deep: 20.3% *vs*. 13.6% (p = 0.03) and 8.3% *vs*. 6.0% (p = 0.26), respectively.[19] On the other hand, there is a growing body of data, including findings from randomized studies that support the use of GCS following high-risk colorectal procedures in order to reduce post-operative morbidity rate, wound healing time and length of hospital stay. Rutten and Nijhuis observed that the application of systemic antibiotics plus GCS *vs*. systemic antibiotics alone significantly decreased the incidence of abdominal wound infections (5.6% *vs*. 18.4%; p = 0.01) as well as the median hospital stay (13.8 *vs*. 16.3 days; p = 0.015).[20] Nowacki *et al*. reported a lower post-operative complications rate at 30 days (20.7% *vs*. 37.5%; p < 0.05). Sub-group analysis also revealed that the difference was maintained in high-risk patients, i.e. those with surgery exceeded 3 hours and those who experienced intraoperative bowel perforation: 19.2% *vs*. 40.8% (p = 0.03) and 20.0% *vs*. 57.9% (p = 0.01), respectively.[21] Multicenter trial by Gruessner and colleagues demonstrated significantly decreased rate of perineal wound infections and secondary complications with infection after abdomino-perineal excision if GCS was used: 6.1% *vs*. 20.8% and 6% *vs*. 21%, respectively. In addition, patients with GCS had a much greater reduction in the number of pathogens in the post-operatively obtained wound secretion samples (p = 0.013).[22] De Bruin *et al*.. studied the effect of GCS on postoperative outcome in patients undergoing abdomino-perineal excision following short-term neoadjuvant radiotherapy (5 Gy x 5 days to a total dose 25 Gy). They demonstrated lower rates of total and deep wound infection rates as well as higher rates of primary wound healing when GCS was applied: 16% *vs*. 57% (p = 0.01), 5% *vs*. 29% (p = 0.05), and 84% *vs*. 43% (p = 0.01), respectively. The patients with GCS also had significantly shorter mean hospital stay, i.e. 15 *vs*. 25 days.[23]

Discrepancies in AL rates among the series of patients following anterior resection with TME and GCS implantation may be caused by many reasons. Firstly, a distribution of AL risk factors could substantially differ. Secondly, the site of GCS implantation is not standardized: wound, upon the closed fascia or pelvic cavity, around the anastomosis (as in the present study).[19, 20, 21] The other possible reason may be the different definition of clinical AL.[24] However, still little is known about the impact of GCS on anastomosis healing. Although some studies suggest positive effect of local gentamicin on collagen content and metabolism, there are conflicting data regarding this subject. Quicker mucosal, muscular and extra-cellular matrix repair was noticed in experimental study by Mutter and colleagues.[25] Binnebosel *et al*. reported that intra-abdominal application of gentamicin can enhance the healing of anastomosis and increase the collagen type I/III in rats.[26] On the other hand, Vaneerdeweg *et al*. did not observe any significant influence of GCS on symptomatic AL rate in animal models.[27] This topic warrants further investigation.

A meta-analysis of the recent studies demonstrates that the cumulative risk of local recurrence following curative R0 anterior resection with TME

varies from 1% to 13.5%. The risk mainly depends on the tumour stage, histological differentiation, nodal status, and the circumferential resection margin.[28] We observed much higher incidence of LR in AL group. However, number of patients with AL was too small to obtain a robust statistics and draw a significant conclusion. Possible association between AL and colorectal cancer recurrence is a subject of intensive research. Sammour *et al*. did not notice a significant difference in LR as well as 5-year overall and cancer-specific survival with regard to AL after rectal cancer resection.[29] In contrast, a negative impact of AL on LR and overall survival was reported by others.[30] Mirnezami *et al*. reviewed 21 studies (21,902 patients) and found that LR as well as cancer specific mortality was significantly higher after AL.[31] Similar findings were reported by Lu *et al*.[32] In the meta-analysis of 14 studies (11,353 patients) made by Wang and colleagues AL was significantly related to increased LR rates and decreased both overall and cancer-specific survival.[33] Postulated mechanism of LR after AL is associated with the fact that leakage may lead to the penetration and implantation of extraluminal tissue by previously exfoliated rectal cancer cells which still may be present in the lumen of the bowel despite routine rectal wash out. In addition, AL causes pelvic infection, which may enhance proliferation, migration and invasion capacities of cancer cells.[33]

Our study has some important limitations. Firstly, a severe weakness of this paper is an incomplete investigation of oncological outcomes. Only local recurrence analysis was completed. Survival analysis was not performed and, as a consequence, neither 5-year overall survival nor disease-free survival rates were demonstrated. Secondly, due to low AL rate some findings are based on the comparison of small groups. Even if the results are significant, their statistical power is low and conclusive statement cannot be drawn. Thirdly, this is just an observational study and a single-institution case series. Consequently, one cannot be certain that our results will be repeatable in another setting. Moreover, during the study period, GCS wrapping of an anastomosis in patients that have undergone restoration of bowel continuity after ultra-low rectal cancer resection was considered standard management and in accordance with the department policy. Therefore, it is not possible to compare these results to a control group operated on in the same time period without the use of GCS. We previously observed an anastomosis failure in 10.6%-12.6% of patients after sphincter-preserving TME.[3,4] Present results look favourable when compared to this historical cohort operated on by the same surgical team at the same institution. However, comparisons to historical series have no statistical power and no significant conclusion can be drawn. Ultimately, we will never be certain if these superior results are a consequence of the usage of GCS or whether they can be attributed to the impact of surgical technique or patient selection.

Our findings suggest that low rate of symptomatic AL might be at least partially influenced by GCS application following TME. GCS can reduce tissue exudation and fluids accumulation at the pelvis cavity and has a local anti-bacterial and haemostatic activity. Hence, it is possible that GCS can secure the anastomosis area. On the other hand, potential benefit from GCS may also be associated with the ability to diminish dehiscence range and its severe consequences, limit pelvic abscess formation, peritonitis and septicemia without the impact on sub-clinical failure. That may be the possible reason of favourable clinical course of the leakage occurred in analysed group.

Based on our previous studies and recent findings the wrapping of an anastomosis with GCS remains the standard management after low anterior rectal cancer resection in our institution. Keeping the risk of AL at the lowest possible level improves local cancer control and the patient's quality of life.[31-33] However, there are still some interesting points waiting to be explored. Nowacki *et al*. observed in a randomised trial a significantly reduced rate of distant metastases in patients with GCS after TME with preoperative radiotherapy compared to a control group without GCS.[21] These surprising findings were also demonstrated in a confirmatory study from the same institution with the median follow-up of 80 months.[36] These results are difficult to explain, in particular, the fact that there were no significant differences in overall and disease-free survival rates. Apart from the assessment of oncological outcomes, a detailed cost-effectiveness analysis as well as a long-term evaluation of conceivable late side effects (anastomosis stricture, persistent anterior resection syndrome) are other interesting topics worth to be explored in the future.[37-40]

Acknowledgements

Authors would like to thank Mr Jacob Bronowicki for his kind assistance in revising the English of this manuscript.

References

1. Gessler B, Eriksson O, Angenete E. Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. *Int J Colorectal Dis* 2017; **32:** 549-56. doi: 10.1007/s00384-016-2744-x
2. Taflampas P, Christodoulakis M, Tsiftsis DD. Anastomotic leakage after low anterior resection for rectal cancer: facts, obscurity, and fiction. *Surg Today* 2009; **39:** 183-8. doi: 10.1007/s00595-008-3835-2
3. Szynglarewicz B, Matkowski R, Forgacz J, Pudelko M, Grzebieniak Z. Anastomosis wrapping with gentamicin-containing collagen sponge in rectal cancer patients following sphincter-preserving total mesorectal excision without defunctioning stoma. *Case Rep Clin Pract Rev* 2006; **7:** 267-71.
4. Szynglarewicz B, Matkowski R, Gisterek I, Włodarska-Polińska I, Kasprzak P, Sydor D, et al. Implantation of gentamicin-containing collagen sponge following anterior resection for rectal carcinoma: can it decrease the leakage risk? *Colorectal Dis* 2007; **9 (Suppl 3):** O19.
5. Szynglarewicz B, Ekiert M, Forgacz J, Matkowski R. Can gentamicin-containing collagen sponge be used for the protection against leakage following low anterior resection with total mesorectal excision? *Tech Coloproctol* 2014; **18:** 767-8. doi: 10.1007/s10151-014-1139-7
6. Markantonis SL, Kostopanagiotou G, Panidis D, Smirniotis V, Voros D. Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. *Clin Ther* 2004; **26:** 271-81. doi: 10.1016/S0149-2918(04)90025-2
7. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis* 1987; **155:** 93-9. doi: 10.1093/infdis/155.1.93
8. Ruszczak Z, Friess W. Collagen as a carrier for on-site delivery of antibacterial drugs. *Adv Drug Deliv Rev* 2003**; 55:** 1679-98. doi: 10.1016/j.addr.2003.08.007.
9. Chvapil M. Collagen sponge: theory and practice of medical application. *J Biomed Mater Res* 1977; **11:** 721-41. doi: 10.1002/jbm.820110508
10. Waldvogel FA. Future perspective of aminoglycoside therapy. *J Antimicrob Chemother* 1984; **13:** 75-8. doi: 10.1093/jac/13.suppl_A.73
11. Anselme K, Bacques C, Charriere G, Hartmann DJ, Herbage D, Garrone R. Tissue reaction to subcutaneous implantation of collagen sponge. A historical, ultrastructural, and immunological study. *J Biomed Mater Res* 1990; **24:** 689-703. doi: 10.1002/jbm.820240605
12. Kinel FA, Ciaccio LA, Henderson SB. Sustained release preparations, XVI: Collagen as a drug carrier. *Arch Pharm* 1984; **317:** 657-61. doi: 10.1002/ardp.19843170802
13. De Bruin AFJ, Gosselink MP, van der Harst E, Rutten HJT. Local application of gentamicin collagen implants in the prophylaxis of surgical site infections following gastrointestinal surgery: a review of clinical experience. *Tech Coloproctol* 2010; **14:** 301-10. doi: 10.1007/s10151-010-0593-0
14. Frouws MA, Snijders HS, Malm SH, Liefers GJ, Van de Velde CJH, Neijenhuis PA, et al. Clinical relevance of a grading system for anastomotic leakage after low anterior resection: analysis from a National Cohort Database. *Dis Colon Rectum* 2017; **60:** 706-13. doi: 10.1097/DCR.0000000000000800
15. Rutkowski A, Olesiński T, Zając L, Bednarczyk M, Szpakowski M. The risk of anastomotic leakage after anterior resection – retrospective analysis of 501 rectal cancer patients operated on without protective stoma. *Minerva Chir* 2017; **72:** 491-8. doi: 10.1001/2013.jamasurg.2
16. Snijders HS, van den Broek CB, Wouters MW, Meershoek-Klein Kranenbarg E, Wiggers T, Rutten H, et al. An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? *Eur J Surg Oncol* 2013; **39:** 715-20. doi: 10.1016/j.ejso.2013.03.025
17. Wang L, Gu J. Risk factors for symptomatic anastomotic leakage after low anterior resection for rectal cancer with 30 Gy/10 f/2 w preoperative radiotherapy. *World J Surg* 2010; **34:** 1080-5. doi: 10.1007/s00268-010-0449-9
18. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. *JAMA Surg* 2013; **148:** 65-71. doi: 10.1001/2013.jamasurg.2
19. Bennett-Guerrero E, Pappas TN, Koltun WA, Fleshman JW, Lin M, Garg J, et al. Gentamicin-collagen sponge for infection prophylaxis in colorectal surgery. *N Engl J Med* 2010; **363:** 1038-49. doi: 10.1056/NEJMoa1000837
20. Rutten HJ, Nijhuis PH. Prevention of wound infection in elective colorectal surgery by local application of a gentamicin-containing collagen sponge. *Eur J Surg Suppl* 1997; **578:** 31-5. PMID: 9167147
21. Nowacki MP, Rutkowski A, Oledzki J, Chwalinski M. Prospective, randomized trial examining the role of gentamycin-containing collagen sponge in the reduction of postoperative morbidity in rectal cancer patients: early results and surprising outcome at 3-year follow-up. *Int J Colorectal Dis* 2005; **20:** 114-20. doi: 10.1007/s00384-004-0632-2
22. Gruessner U, Clemens M, Pahlplatz PV, Sperling P, Witte J, Rosen HR; Septocoll Study Group. Improvement of perineal wound healing by local administration of gentamicin-impregnated collagen fleeces after abdominoperineal excision of rectal cancer. *Am J Surg* 2001; **182:** 502-9. doi: org/10.1016/S0002-9610(01)00762-0
23. De Bruin AFJ, Gosselink MP, Wijffels NAT, Coene PP, van der Harst E. Local gentamicin reduces perineal wound infection after radiotherapy and abdominoperineal resection. *Tech Coloproctol* 2008; **12:** 303-7. doi: 10.1007/s10151-008-0440-8
24. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery* 2010; **147:** 339-51. doi: 10.1016/j.surg.2009.10.012
25. Mutter D, Aprahamian M, Tiollier J, Sonzini P, Marescaux J. Evaluation of human collagen biomaterials in the healing of colonic anastomoses in dogs. *Eur J Surg* 1997; **163:** 287-95. PMID: 9161827
26. Binnebosel M, Junge K, Kaemmer DA, Krones CJ, Titkova S, Anurov M, et al. Intraperitoneally applied gentamicin increases collagen content and mechanical stability of colon anastomosis in rats. *Int J Colorectal Dis* 2009; **24:** 433-40. doi: 10.1007/s00384-008-0614-x
27. Vaneerdeweg W, Hendriks JM, Lauwers PR, Ieven M, Eyskens EJ. Effect of gentamycin-containing sponges on the healing of colonic anastomosis in a rat model of peritonitis. *Eur J Surg* 2000; **166:** 959-62. doi: 10.1080/110241500447137
28. Wang XT, Li DG, Li L, Kong FB, Pang LM, Mai W. Meta-analysis of oncological outcome after abdominoperineal resection or low anterior resection for lower rectal cancer. *Pathol Oncol Res* 2015; **21:** 19-27. doi: 10.1007/s12253-014-9863-x
29. Sammour T, Hayes IP, Jones IT, Steel MC, Faragher I, Gibbs P. Impact of anastomotic leak on recurrence and survival after colorectal cancer surgery: a BioGrid Australia analysis. *ANZ J Surg* 2018; **88:** E6-E10. doi: 10.1111/ans.13648
30. Du P, Burke JP, Khoury W, Lavery IC, Kiran RP, Remzi FH, et al. Factors associated with the location of local rectal cancer recurrence and predictors of survival. *Int J Colorectal Dis* 2016; **31:** 825-32. doi: 10.1007/s00384-016-2526-5
31. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg* 2011; **253:** 890-9. doi: 10.1097/SLA.0b013e3182128929
32. Lu ZR, Rajendran N, Lynch AC, Heriot AG, Warrier SK. Anastomotic leak after restorative resections for rectal cancer compromise cancer outcomes and survival. *Dis Colon Rectum* 2016; **59:** 236-44. doi: 10.1097/DCR.0000000000000554
33. Wang S, Liu J, Wang S, Zhao H, Ge S, Wang W. Adverse effect of anastomotic leakage on local recurrence and survival after anterior resection for rectal cancer: a systematic review and meta-analysis. *World J Surg* 2017; **41:** 277-84. doi: 10.1007/s00268-016-3761-1
34. Szynglarewicz B, Grzebieniak Z, Forgacz J, Pudelko M, Rapala M. Anastomotic leakage following anterior resection and total mesorectal excision in case of rectal carcinoma- prospective evaluation of the incidence, risk factors and protective methods. *Pol Przegl Chir* 2006; **78:** 1-12.
35. Szynglarewicz B, Matkowski R, Maciejczyk A, Piotr Kasprzak, Daniel Sydor, Józef Forgacz, et al. Neoadjuvant radiotherapy and anastomosis dehiscence after total mesorectal excision for stage II and III rectal cancer. *Rep Pract Oncol Radiother* 2007; **12:** 87-93. doi: org/10.1016/S1507-1367(10)60044-2
36. Rutkowski A, Pietrzak L, Krynski J, Zajac L, Bednarczyk M, Olesinski T, et al. The gentamicin-collagen implant and the risk of distant metastases of rectal cancer following short-course radiotherapy and curative resection: the long-term outcomes of a randomized study. *Int J Colorectal Dis* 2018; **33:** 1087-96. doi: 10.1007/s00384-018-3045-3

37. Lee SY, Kim CH, Kim YJ, Kim HR. Anastomotic stricture after ultralow anterior resection or intersphincteric resection for very low-lying rectal cancer. *Surg Endosc* 2018; **32:** 660-6. doi: 10.1007/s00464-017-5718-3

38. Ekkarat P, Boonpipattanapong T, Tantiphlachiva K, Sangkhathat S. Factors determining low anterior resection syndrome after rectal cancer resection: A study in Thai patients. *Asian J Surg* 2016; **39:** 225-31. doi: 10.1016/j.asjsur.2015.07.003

39. Chen TY, Wiltink LM, Nout RA, Meershoek-Klein Kranenbarg E, Laurberg S, Marijnen CA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clin Colorectal Cancer* 2015; **14:** 106-14. doi.org/10.1016/j.clcc.2014.12.007

40. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg* 2012; **255:** 922-8. doi: 10.1097/SLA.0b013e31824f1c21