

CLINICAL STUDY

New trends in criteria indicative of neoadjuvant oncological therapy of lower and middle rectal cancers

Martin KUKUCKA¹, Ludovit DANIHEL¹, Milan ORAVSKY¹, Matus RAJCOK¹, Michal BERNADIC², Paula KOVAROVA¹, Natalie BIRKNEROVA³, Marian CERNY⁴, Maria NOVISEDLA KOVA⁵, Miriam DRAHOKOUPILOVA⁵, Peter STEFANIK⁶, Milan SCHNORRER¹

IIIrd Department of Surgery Comenius University Bratislava, Slovakia. kukuckamartin@yahoo.com

ABSTRACT

The indication for primary surgical resection or neoadjuvant therapy in lower and middle rectal cancers is often disputable. The aim of the study was to evaluate the occurrence of local recurrence of rectal cancer as for a period of at least 4 years after radical resection. The second aim was to evaluate and compare the results of preoperative magnetic resonance (MR) staging with definitive histology.

From September 2013 to December 2017, we, at the 3rd Surgical Department Comenius University, Bratislava, prospectively evaluated patients with lower and middle rectal cancers with the distal tumor border being in a 12-cm distance from the anal verge. All patients underwent MR examination at the same MRI department and were operated on at the 3rd Surgical Department, Comenius University, Bratislava. Inclusion criteria included parameters based on MRI examination, i.e., T-staging of T1-T3b, negative extramural vascular infiltration (EMVI), negative circumferential margin (CRM), no mesorectal fascia infiltration with a distance of more than 2 mm. We did not take lymph node staging into account in the indication for primary surgical resection. We performed a radical primary resection procedure (R0 resection) in all patients. The group consisted of 87 patients, of whom 49 were men and 38 were women. The mean age of the patients was 66 years (min. 36 – max. 86 years).

Our study also shows significant differences in preoperative T and N staging as compared to definitive histology. The incidence of local recurrence during a period of at least 4 years after surgery was 6.76 %. Study also shows that the indication for preoperative radiotherapy for lower and middle rectal cancers based on N status is inaccurate and leads to unnecessary indications for preoperative radiotherapy which may decrease the patients' quality of life and increase the post-operative complications. We have also shown that leaving out the N-based radiotherapy from indications does not lead to an increase in the number of local recurrences in lower and middle rectal cancers (*Tab. 1, Fig. 5, Ref. 22*). Text in PDF www.elis.sk

KEY WORDS: rectal cancer, neoadjuvant therapy, local recurrence.

Introduction

Rectal cancer is one of the most common malignant diseases in the developed countries. In recent decades, the diagnosis of rectal cancer and its availability have significantly improved. As a result of that, we can choose a more favorable strategy for the treatment of rectal tumors and thereby improve the prognosis of patients. Despite the improvement in the availability of diagnosis-

tic and therapeutic options, rectal cancer represents a major social problem, and the patient's prognosis depends on the stage of the disease at the time of diagnosis (1–3).

Patients and methods

From September 2013 to December 2017, we prospectively followed and evaluated patients with tumors of the middle and distal parts of the rectum with the distal border of the tumor being in a 12-cm distance from the anal verge. Patients underwent preoperative MR staging at one workplace according to the latest recommendations of the MR protocol. The mechanical preparation of the bowel was not necessary for patients undergoing MR staging. Antispasmodics were administered to the patients before the MR examination in order to reduce the peristalsis of the bowel and reduce the occurrence of movement artifacts. MR protocol included views, particularly the sagittal T2 and axial T2, small field of view (FOV – Field-of-view) T2 through the tumor, axial, and coronal. To determine the stage of locally advanced rectal cancer,

¹IIIrd Department of Surgery Comenius University Bratislava, Slovakia, ²Department of Surgical Oncology, National Oncological Institute, Bratislava, Slovakia, ³Department of Clinical Biochemistry Charles University, University Hospital in Hradec Králové Czech Republic, ⁴Klinik für Allgemein-, Viszeral-, Thorax-, Adipositas-, Gefäß- und Kinderchirurgie, Passau, Germany, ⁵Department of Clinical Oncology, The Brothers of Saint John of God, Bratislava, Slovakia, and ⁶IInd Department of Surgery, Comenius University, Bratislava, Slovakia.

Address for correspondence: Martin KUKUCKA, MD, IIIrd Department of Surgery Comenius University Bratislava, Namestie SNP 10, SK-814 65 Bratislava, Slovakia.

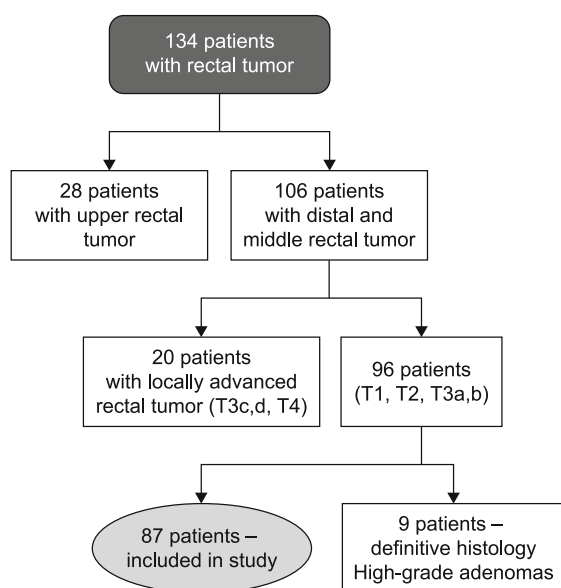


Fig. 1. Selection of patients included in the study.

the contrast agent gadovist was used as part of the MR examination. Patients were primarily operated in the T1-T3b stage according to MR, with a tumor in the distance of more than 2 mm from the mesorectal fascia without EMVI, while the N status was not taken into account. All patients were operated on at the 3rd Surgical Department, Comenius University, Bratislava. We performed a radical R0 resection of the rectum in all monitored patients. The first aim of our prospective study was to compare the TN stage assessed on the basis of the preoperative MR examination with the findings of definitive histology. The second aim was to evaluate the occurrence of local recurrence of rectal cancer as for a period of at least 4 years after the operation and to evaluate the long-term survival of the entire group of patients. Patients were informed about the nature of the study and the therapeutic procedure which they agreed to. In total, 87 patients were included in the study, of whom 49 were men and 38 were women. The average age of the patients was 66 years (min. 36 – max. 86 years). Abdominoperineal resection according to Miles was performed in 13 patients (14.9 %). The remaining 74 patients (85.1 %) were treated with anterior low

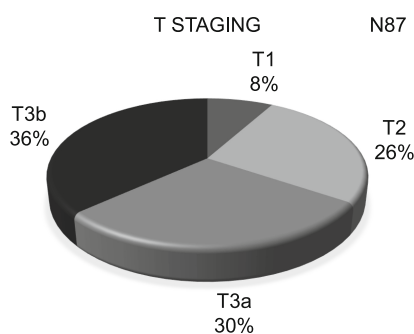


Fig. 2. Preoperative T staging according to magnetic resonance (n=87).

resection according to Dixon. The presented set of 87 patients in the studies was selected from 134 patients. Patients with cancer of the upper rectum, patients in the T4 stage of the disease, patients with a tumor distance of less than 2 mm from the mesorectal fascia, and patients with a positive EMVI were not included in the study. Nine patients whose definitive histology showed adenoma with high-grade dysplasia (HGD) were not included in the study (Fig. 1).

All patients were dispensarised at the oncological department the Brothers of Saint John of God in Bratislava. Patients underwent regular check-ups after 3, 6 and 12 months after surgery, then once a year. As part of the dispensary, patients underwent a control colonoscopic examination 12–18 months after the operation.

Results

Comparison of T MR staging results with definitive histology

Of the group of 87 patients primarily operated on for middle or distal rectal tumors, 7 patients (8 %) were in stage T1, 23 patients (26 %) in stage T2, 25 patients (30 %) in stage T3a and 32 patients (36 %) in stage T3b according to MR (Fig. 2).

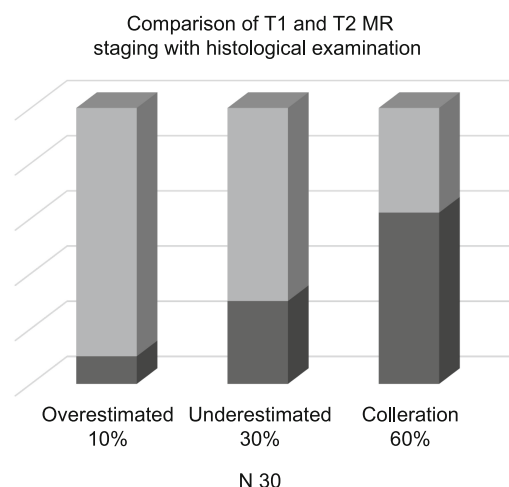


Fig. 3. Comparison of T1 and T2 MR staging with histopathology examination (n=30).

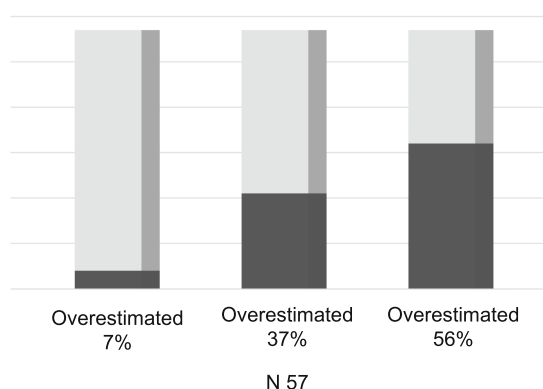


Fig. 4. Comparison of T3-staging on MRI with histopathologic examination findings (n=37).

Tab. 1. Comparison of N-staging on MRI with histopathologic examination findings (n87).

N 87 (59 N+, 28 N0)	
N0 (28) Underestimated	2 patients (7%)
N0 (28) Correlation	26 patients (93%)
N+ (59) Underestimated	3 patients (5%)
N+ (59) Correlation	21 patients (36%)
N+ (59) Overestimated (N1, N2)	35 patients (59%), 3 patients with positive lymph nodes – N2 tumors on MR
N+ (59) Overestimated	32 patients (54.2%) overestimated with negative lymph nodes

Of the group of 7 patients with a T1 tumor, the consistency in findings, as compared between preoperative staging and definitive histopathological findings, was present in 6 patients. In one patient, the results were underestimated, and definitive histology showed the stage of disease to be T3.

In the group of 23 patients with a T2 tumor, the consistency in findings, as compared between preoperative staging and definitive histopathological examination, was present in 12 patients. The results were overestimated in 3 cases where definitive histology showed T1 tumors. Eight patients had underestimated preoperative MR staging results and histology showed the stage of rectal tumors to be T3 (Fig. 3).

Of the group of 57 patients in the T3 MR stage (25 patients with T3a and 32 patients with T3b), the consistency in findings, as compared between preoperative staging and definitive histopathological examination, was present in 32 patients (56 %). Results were overestimated in 21 patients (37 %). Results were underestimated in 4 patients (7 %) (Fig. 4).

Comparison of N MR staging results with definitive histology

In a group of 87 patients primarily operated on for middle and distal rectal tumors, there were 28 patients in the N0 preoperative MR staging, and 59 patients were in the N+ stage. Of the group of 28 patients in the N0 stage, the consistency in findings was present in 26 patients (93 %), while in 2 patients (7 %), the results were underestimated (Tab. 1). Of the group of 59 patients in the

N+ stage (N1, N2), the findings were consistent in 21 patients were evaluated (36 %), while the results of 3 patients (5 %) were underestimated, and those of 35 patients (59 %) were overestimated. What is more, 32 of these patients (54.2 %) had negative lymph nodes on definitive histopathological examination. (Table 1) The average number of examined lymph nodes in the histological preparation was 16.81 (min. 12 – max. 32).

Evaluation of immediate postoperative complications of patients – anastomotic leak.

The most feared complication in the immediate postoperative period in rectal surgery is the dehiscence, an anastomotic leak, in which the infectious intestinal content escapes outside the intestinal lumen. In many cases, the anastomotic leak leads to immediate reoperation of the patient with the necessity of a stoma. In certain cases, the anastomotic leak is treated conservatively. In our group, 74 patients underwent a low rectal resection, the remaining patients underwent an operation according to Miles. An anastomotic leak was noted in 6 patients (8.1 %). Reoperation was necessary in 3 patients (4.1 %), the remaining 3 patients (4.1 %) were managed conservatively.

Occurrence of local recurrence in a period for at least 4 years after surgery

In the group of 87 patients, 8 patients died due to dissemination of the underlying disease, but no local rectal recurrence was found. Three patients died of other, mainly cardiovascular causes. Two patients could not be traced as they failed to comply with regular check-ups. Out of 74 long-term monitored patients in whom histological examination confirmed rectal adenocarcinoma, local recurrence of the disease was recorded in 5 patients in a period for at least 4 years after the operation, which represents 6.76 %. Of the 5 patients with local recurrence, 2 patients were in N0 stage on the preoperative MR staging, the remaining 3 patients were in N+ stage of the disease on the preoperative MRI. Definitive histology of patients with local recurrence showed T1, N0 stage in 1 patient, T2, N0 stage in 3 patients and T3, N0 stage of disease in 1 patient. R0 resection was performed in all patients with local recurrence, and the occurrence of local recurrence was recorded within 2 years of the operation.

Evaluation of overall survival

In the studies, we evaluated the duration of overall survival using the Kaplan-Meier curve (Fig. 5). The minimum patient follow-up time was 4.17 years, the maximum patient follow-up time was 9.02 years. The average follow-up period of the patients was 6.75 years.

Discussion

Surgery dominates in the treatment of rectal cancer. The surgical procedure itself is the basis of the curative treatment of rectal

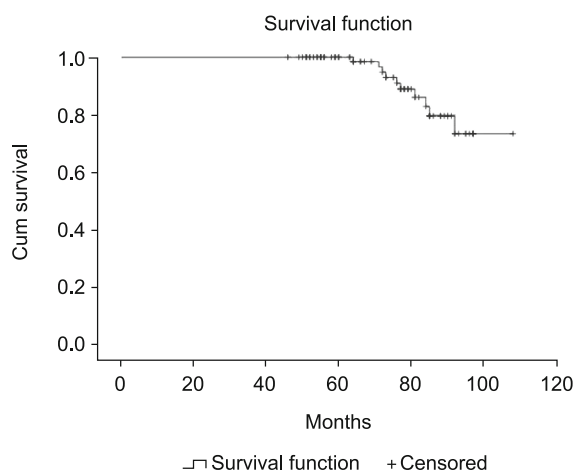


Fig. 5. Overall survival of patients whose definitive histology showed Kaplan-Meier adenocarcinoma (n=87).

cancer (1, 4, 5). Neoadjuvant therapy is indicated for patients with advanced rectal cancer (4–6). As part of the optimal management of patients with rectal cancer, it is necessary to distinguish between patients who are more suitable for primary surgical resection and those who benefit from neoadjuvant therapy. Neoadjuvant therapy often increases the percentage of curable resections, while it is not possible to determine the sensitivity of the tumor to neoadjuvant therapy. Today, it is not clearly proven whether neoadjuvant therapy significantly reduces the occurrence of local recurrences (8). The critical moment occurs when patients are indicated for neoadjuvant therapy in stages II and III according to the UICC classification. The imperfection of the classification consists in including patients with positive lymph nodes in stage III of the disease, while the T stage of the disease is not taken into account (9–10). Based on the latest ESMO recommendations from 2017, the primary surgery is recommended for stage T3aN1 of rectal cancer with an intact mesorectal fascia; NCCN (National Comprehensive Cancer Network) guidelines remain more restrained. Patients with locally advanced rectal tumor (T3c – T4 stage) are clearly indicated for neoadjuvant therapy (9–10).

Nowadays, in clinical practice in the treatment of rectal cancer, there is an effort to judiciously and purposefully refer patients to radiotherapy in order to avoid the increase in the number of complications related to radiotherapy (3, 11, 12). The issue is primarily focused on the treatment of the middle and lower parts of the rectum; for tumors further than 12 cm from the anus, we follow the therapeutic scheme for the treatment of the colon, and patients undergo primary surgery without prior neoadjuvant treatment. This procedure is also based on the guidelines of the American Gastroenterology Society, which considers the rectum to reach only up to a distance of 12 cm from the anus (3, 4, 12). At the time of our study, patients were indicated for radiotherapy based on classifying the patients with positive lymph nodes as being in stage III of the disease, while the T stage of the disease is not taken into account (1, 2, 6). In our study, we relied on knowledge from the OCUM and MERCURY studies, as well as from other foreign studies (12–15). In recent years, the treatment scheme has been slowly modified in favor of primary surgical resection, which can be seen in the latest ESMO recommendations from 2017, where primary surgical resection is also possible provided that strict selection criteria are applied and total mesorectal excision is of a very good quality (16–18). At our workplace, we primarily operate on patients in the T3b stage, however, patients indicated for surgery had to meet strict selection criteria. The aim of our study was to compare the definitive histopathological findings with the preoperative TNM staging and demonstrate that the indication of patients for radiotherapy based on preoperative N status is debatable and imprecise. In our group of primarily operated patients, the results of 35 patients (59 %) were overestimated during the preoperative N-staging, while up to 32 patients (54.2 %) had negative nodes on definitive histopathological examination. Today's trend in the treatment of rectal cancer is to try to maximally maintain the comfort of life at low risk of recurrence of the disease. Neoadjuvant therapy is of great importance in the treatment of patients with rectal cancer but patients who would benefit from this treatment

must be carefully selected. It is also necessary to pay attention to undesirable effects of this therapy that can lead to inflammatory changes, irritable bowel, reduced sexual function, and urological complications (3, 12, 13, 16, 17, 19). In our study, local recurrence was recorded in 5 patients (6.76 %), of whom 2 patients had N0 stage preoperatively and 3 patients had N1 stage on MRI. Definitive histology in these patients showed 1xT1, N0, 1xT2, N0 and 3xT3, N0 and the patients would not be indicated for radiotherapy based on the criteria valid at the time. In the literature, the incidence of local recurrence, regardless of the completion of preoperative radiotherapy, is reported to be in the range of 3.7–13 %, with an average of 5.9 % (21, 22, 23). In our study, all patients with local recurrence underwent surgery according to Dixon despite previous knowledge that the incidence of local recurrence is higher with abdominoperineal amputation according to Miles than that after sphincter-preserving surgeries.

All patients underwent an MR examination at one workplace. During the implementation of the study, we could observe how the “learning curve” of the describing radiologists gradually increased and the rate of consistency between the results of preoperative T staging and histological examination gradually increased. Nowadays, the dominant examination for tumors of the lower and middle parts of the rectum is MR, which allows us to ideally visualize the anatomical conditions in the small pelvis. It is necessary to judge the interpretation of lymph nodes critically, as it is not possible to assess whether they are affected by a tumor process or whether it is a case of reactive lymphadenopathy being involved. Also, in many cases, the results of T staging are overestimated, which is mainly caused by the desmoplastic reaction of the surrounding tissue. Therefore, it is necessary for the examination to be carried out at high-volume workplaces, which reduces the risk of misinterpretation of magnetic resonance imaging results. Due to the limitations of the TNM classification, the trend today is to determine the circumferential margin according to MR, distance of tumor from the mesorectal fascia, and determination of EMVI. However, we should not forget the classical physical examination of the anus per rectum and the old well-known Mason's criteria, with the help of which we can assess the character, distance, and mobility of the tumor and thereby evaluate the operability of the tumor and possible surgical performance.

Our results, as well as those of other studies, confirmed a significant discrepancy in preoperative MR staging of N-status with definitive histology. Also, no greater occurrence of local recurrences was confirmed when N-status was not assessed for neoadjuvant therapy. Nowadays, there is no diagnostic method that can recognize the involvement of lymph nodes by a tumor process, and therefore one must adopt a critical view of the patient's indications for neoadjuvant therapy based only on the N status.

References

1. Danihel L et al. Súčasně terapeutické možnosti diagnostiky kolorektálního karcinomu. *Onkológia* 2016; 11 (1): 50–53. <https://www.solen.sk/casopisy/onkologia/sucasne-moznosti-diagnostiky-kolorektalneho-karcinomu>.

2. **Danihel L et al.** Significance of MRI in rectal carcinoma therapy optimization – correlation of preoperative T- and N-staging with definitive histopathological findings. *Neoplasma* 2019; 66 (3): 494–498. https://doi.org/10.4149/neo_2018_180522N334.
3. **Kreis ME, Strassburg J (Eds).** *Moderne Chirurgie des Rektumkarzinoms*. Springer-Verlag Berlin, 2015.
4. **Van De Velde CJ, Boelens PG, Borras JM, Coebergh JW, Cervantes A et al.** EURECCA colorectal: multidisciplinary management: European consensus conference colon & amp; rectum. *Eur J Cancer* 2014; 50: 1.e1–1.e34. <https://doi.org/10.1016/j.ejca.2013.06.048>.
5. **Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y et al.** Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. *Int J Clin Oncol* 2015; 20: 207–239. <https://doi.org/10.1007/s10147-015-0801-z>.
6. **Wang R, Zhao D, Liu YJ, Ye C, Qian JR, Dai JN, Liu SY, Liu JY, Li B, Wang MJ, Ping J.** Prognostic significance of preoperative radiotherapy in stage II and III rectal cancer patients: A Strobe-compliant study of SEER 18 registries database (1988–2011) *Neoplasma* 2019; 66 (6): 995–1001 https://doi.org/10.4149/neo_2019_190112N36.
7. **Uehara K, Nagino M.** Neoadjuvant treatment for locally advanced rectal cancer: a systematic review. *Surg Today* 2016; 46: 161–168. <https://doi.org/10.1007/s00595-015-1218-z>.
8. **Yun JA, Huh JW, Kim HC et al.** Local recurrence after curative resection for rectal carcinoma: The role of surgical resection. *Medicine (Baltimore)*. 2016;95(27):e3942. <https://doi.org/10.1097/MD.0000000000003942>.
9. **National Comprehensive Cancer Network .** NCCN Guidelines for Rectal Cancer Version 3; 2017. https://http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
10. **Rectal Cancer: ESMO Clinical Practice Guidelines.** *Gastrointestinal Cancers*. Published in 2017 – *Ann Oncol* (2017) 28 (suppl 4): iv22–iv40 <https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/rectal-cancer>.
11. **Ling CR, Wang R, Wang MJ, Ping J, Zhuang W.** Prognosis and value of preoperative radiotherapy in locally advanced rectal signet-ring cell carcinoma. *Sci Rep* 2017; 7: 45334. <https://doi.org/10.1038/srep45334>.
12. **Ruppert R, Junginger T, Ptok H, Strassburg J, Maurer CA, Brosi P, Sauer J, Baral J, Kreis M, Wollschlaeger D, Hermanek P, Merkel S; OCUM group.** Oncological outcome after MRI-based selection for neoadjuvant chemoradiotherapy in the OCUM Rectal Cancer Trial. *Br J Surg* 2018; 105 (11): 1519–1529. <https://doi.org/10.1002/bjs.10879>.
13. **Taylor FG, Quirke P, Heald RJ, Moran BJ, Blomqvist L et al.** Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol* 2014; 32: 34–43. <https://doi.org/10.1200/JCO.2012.45.3258>.
14. **AL-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC et al.** Diagnostic accuracy of MRI for assessment of T category, lymph node metastases and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2012; 19: 2212–2223. <https://doi.org/10.1245/s10434-011-2210-5>.
15. **Iafrate F, Laghi A, Paolantonio P, Rengo M, Mercantini P et al.** Preoperative staging of rectal cancer with MR Imaging: correlation with surgical and histopathologic findings. *Radiographics* 2006; 26: 701–714. <https://doi.org/10.1148/rg.263055086>.
16. **Al-Sukhni E, Milot L, Fruitman M et al.** Diagnostic accuracy of MRI for assessment of T category, lymph node metastases and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2012; 19 (7): 2212–2223. <https://doi.org/10.1245/s10434-011-2210-5>.
17. **Huh JW, Kim YJ, Kim HR.** Distribution of lymph node metastases is an independent predictor of survival for sigmoid colon and rectal cancer. *Ann Surg* 2012; 255: 70–78. <https://doi.org/10.1097/SLA.0b013e31823785f6>.
18. **Liu Qi et al.** Circumferential resection margin as a prognostic factor after rectal cancer surgery: A large population-based retrospective study. *Cancer Med* 2018; 7–8: 3673–3681. <https://doi.org/10.1002/cam4.1662>.
19. **Jugra L.** Radiobiologické predpoklady liečby žiarením in Jurga a kol. In: *Klinická onkológia a radioterapia*. Slovak Academic Press Bratislava, 2000: 236–307.
20. **Chi P, Huang S.** (Anastomotic leakage after rectal cancer surgery: classification and management). *Zhonghua Wei Chang Wai Ke Za Zhi* 2018; 21 (4): 365–371. <https://pubmed.ncbi.nlm.nih.gov/29682704/>.
21. **Yun JA, Huh JW, Kim HC et al.** Local recurrence after curative resection for rectal carcinoma: The role of surgical resection. *Medicine (Baltimore)* 2016; 95 (27): e3942. DOI: 10.1097/MD.0000000000003942.
22. **Ganeshan D, Nougaret S, Korngold E, Rauch GM, Moreno CC.** Locally recurrent rectal cancer: what the radiologist should know. *Abdom Radiol (NY)* 2019; 44 (11): 3709–3725. <https://doi.org/10.1007/s00261-019-02003-5>.

Received January 26, 2023.

Accepted March 7, 2023.