

# Comparative oncological outcomes and survival following surgery for low rectal cancer – a single center experience

CĂLIN MOLNAR<sup>1)</sup>, COSMIN NICOLESCU<sup>2)</sup>, BIANCA LIANA GRIGORESCU<sup>3)</sup>, MARIAN BOTONCEA<sup>1)</sup>, VLAD-OLIMPIU BUTIURCA<sup>1)</sup>, MARIUS DANIEL PETRIȘOR<sup>4)</sup>, SIMONA GURZU<sup>5)</sup>

<sup>1)</sup>Department of Surgery, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Romania

<sup>2)</sup>Department of Anatomy and Embryology, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Romania

<sup>3)</sup>Department of Pathophysiology, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Romania

<sup>4)</sup>Department of Simulation Applied to Medicine, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Romania

<sup>5)</sup>Department of Pathology, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Romania

## Abstract

In patients with low rectal cancer, intersphincteric resection (ISR) technique is a better alternative of abdominoperineal resection (APR), but is recommended to be done in non-locally advanced stages ( $\leq T_2$ ) only. The aim of this study was to evaluate the long-term oncological outcome and survival rate in patients with early and locally advanced stages that underwent ISR, as compared to APR. In order to assess the quality of life and prognosis of patients with low rectal cancer, the 5-year follow-up was done in 72 consecutive cases diagnosed in pT1–T4 stage that underwent ISR or APR. Histopathological and clinical parameters were compared between the two included groups. Although the quality of life was better in patients which underwent ISR, the 5-year overall survival rate was not found to be influenced by the used surgical technique (71% for ISR and 58% for APR) either by the histological grade of differentiation ( $p=0.62$ ), independently from the T stage ( $p=0.61$ ). Regardless of the type of surgery, the independent prognostic factors proved to be lymph node status ( $p=0.001$ ), lymph node ratio ( $p=0.001$ ), and clinical stage ( $p=0.0001$ ). Lymph node status remains the most important prognostic factor of patients with low rectal cancer. Independently from the histological subtype and depth of tumor infiltration, good oncological results can be obtained when performing ISR in selected cases.

**Keywords:** rectal cancer, stage, histology, prognosis, intersphincteric resection, long-term survival.

## Introduction

Cancer is the leading cause of death in 91 of 172 countries globally. Despite screening programmes, colorectal cancer (CRC) remains an important cause of cancer-related deaths, being estimated that 1 in 10 annual deaths is caused by it [1]. The highest incidence of CRC is found in European eastern countries, such Hungary and Slovenia, followed by Australia, New Zealand and North America [1]. In Romania, CRC represents the fourth cause of cancer-related death after breast, prostate and lung cancer [1]. Despite the fact that specific guidelines, such as diagnostic, treatment, radiotherapy and postoperative care are available, a consensus on an ideal scheme is lacking [2–4].

Diagnostic and surgical management of low rectal cancer is even more difficult, because limited surgical options are available. Abdominoperineal resection (APR), which was described by William Ernest Miles, in 1908, remains the gold standard technique [4]. Perineal wound healing difficulties and wound infection are the commonest complications but quality of life is negatively influenced by the presence of permanent colostomy bag [5, 6]. In highly selected cases, the intersphincteric resection (ISR) is the therapy of choice [7]. As the patient is exempt from a permanent colostomy bag, this technique is preferred by

most of them but experienced surgeons and well-defined selection criteria are the two contributing factors in patients that can underwent this type of surgery [4, 8, 9]. Before choosing the operative technique, preoperative magnetic resonance imaging (MRI) is mandatory to be done for evaluation of the internal or external sphincter infiltration [10, 11].

Independently from the surgical technique, the patient's follow-up strongly depends on the information included in the histopathological (HP) report [11]. For this reason, although the previously studies mostly compared the patients' oncological outcome, reported to the used surgical technique [12–16], in the present report we tried to find the prognostic value of the histological and clinical parameters in patients with low rectal cancer, which underwent ISR vs. APR.

## Patients, Materials and Methods

### Selection of cases

This observational study was performed in the Department of Pathology and No. 1 Surgical Clinic of the Emergency County Hospital, Târgu Mureș, Romania. All consecutive patients diagnosed with low rectal cancer,

which underwent surgery between January 2011 and December 2013, were included. Written informed consent was obtained from any patient, before surgery, for surgical intervention and publishing of medical data. The Ethics Committee of the Emergency County Hospital, Târgu Mureș, approved this study.

All of the 72 patients underwent MRI or computed tomography (CT) investigation prior to surgery had a preoperative positive malignancy report. Before surgery, based on specific inclusion and exclusion criteria, patients were divided in two groups: Group I, with patients that underwent ISR and Group II, with patients that underwent APR.

### Inclusion and exclusion criteria

We have included 72 consecutive patients with tumors located at 10–40 mm from the anal verge, 15 mm from the dentate line or 10 mm from the anorectal ring. Patients with tumors located above the upper rectum and those with incomplete medical records were excluded from the present study.

In the first group, we included patients with low rectal cancer that showed a Wexner score lower than 10, without MRI-detected invasion of the *levator ani* and/or *puborectalis* muscles, without invasion of external anal sphincter fascia and/or external sphincter muscle involvement. First group also included those patients which refuse a post-operative colostomy bag. All the other patients, which did not accomplish criteria of inclusion in the first group, were included in the second group.

### HP assessment

In all cases, the surgical specimens were sent for HP assessment. Histological parameters taken into account were the macro- and microscopic aspect, quality of resection margins and fascia integrity. For prognostic and predictive purposes, the grade of differentiation, tumor stage (pT, pN) and lymph node ratio (LNR) were also evaluated. All cases were restaged, based on *American Joint Committee on Cancer (AJCC)* 8<sup>th</sup> edition Staging System criteria. Operative time and estimated blood loss were also taken into account.

### Follow-up

All patients were followed for a period of 62 months. Patient follow-up included general examination every three months, pulmonary X-ray, abdominal ultrasound, colonoscopy and pelvic MRI or CT scans every six months. Local recurrence was defined as the presence of any pelvic, perineal or anastomotic recurrence or positive regional lymph nodes found on postoperative examination.

### Statistical data

To perform statistical assessment, we used the *log-rank* (Mantel–Cox) and  $\chi^2$  (chi-square) tests. A *p*-value less than 0.05 was considered statistically significant. We defined LNR as the ratio of the number of positive lymph nodes to the total of all resected nodes [17]. For statistical analysis, a cutoff value of 0.2 was used. The overall survival (OS) rate was estimated based on Kaplan–Meier survival curves.

## Results

### Demographic data

After applying inclusion and exclusion criteria, 37 (51.39%) patients were assigned to Group I and 35 (48.61%) to Group II. Group I mostly consisted of male patients (65%), while a predominance of females (63%) was seen in Group II ( $p=0.0001$ ). The median age of the included patients was  $65.45 \pm 10.4$  years (range between 40–88 years), without significant differences between the two groups (Table 1).

**Table 1 – Demographic characteristics of patients with low rectal cancer in the two examined groups**

	Group I (ISR, n=37)	Group II (APR, n=35)
Gender		
Males	24 (65%)	13 (37%)
Females	13 (35%)	22 (63%)
Age [years]	66±11.1 (range 40–88)	65±9.8 (range 47–84)

ISR: Intersphincteric resection; APR: Abdominoperineal resection; n: No. of cases.

### HP parameters

Negative circular resection margins (CRM) were achieved in 32 of the 37 (87%) cases from Group I, respectively 33 of the 35 (94%) patients from Group II. Independently from the inclusion group, predominance of cases diagnosed in locally advanced stages (pT3, pT4) was seen. It is important mentioning that about half of the patients were diagnosed with a low rectal cancer before occurring of lymph node metastases (Table 2).

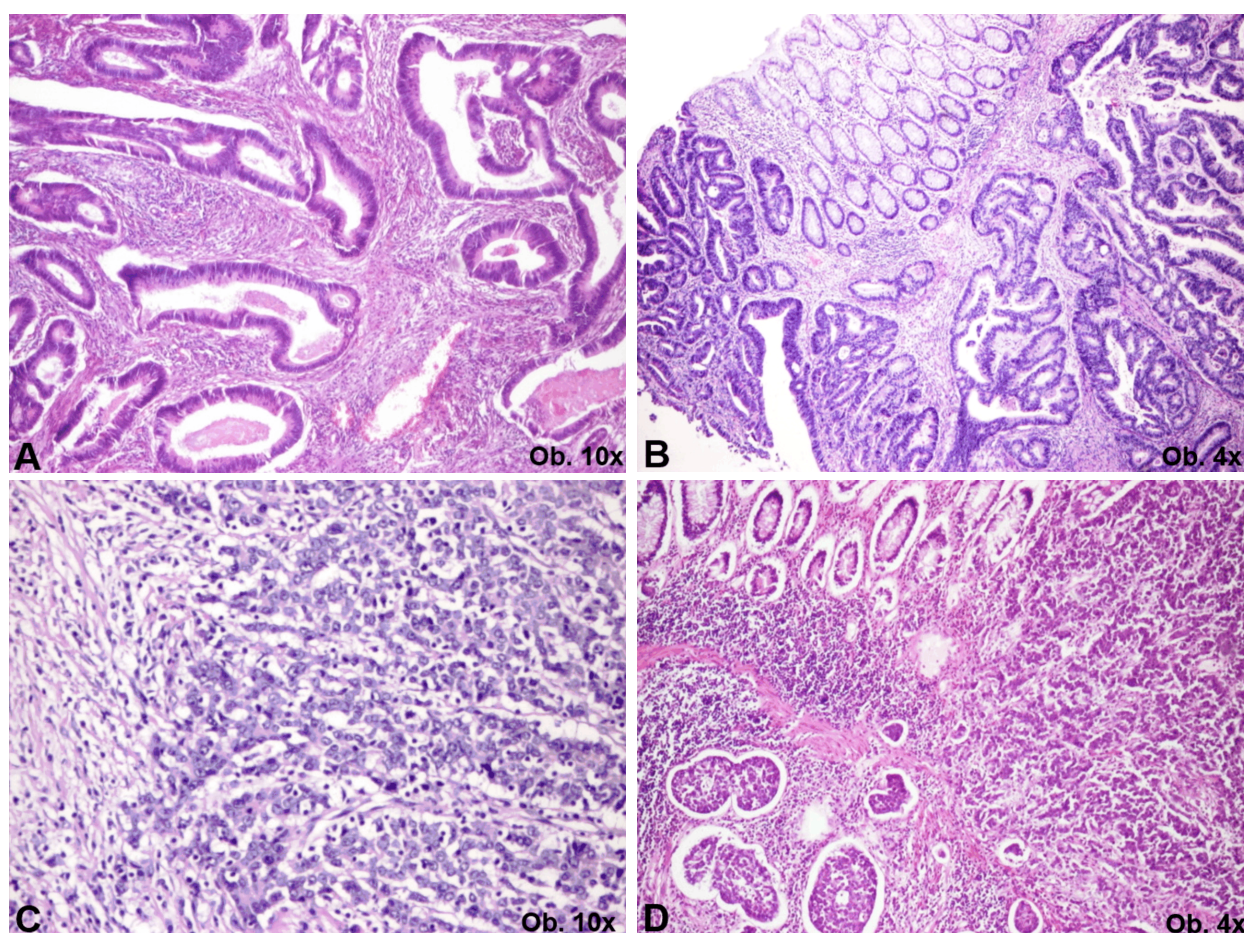
**Table 2 – Staging of low rectal carcinoma cases in the two examined groups**

	Group I (ISR, n=37)	Group II (APR, n=35)
T staging		
T1	4 (10.8%)	4 (11%)
T2	5 (13.5%)	11 (31%)
T3	26 (70.3%)	18 (51%)
T4a	1 (2.7%)	0 (0%)
T4b	1 (2.7%)	2 (6%)
N staging		
N0	19 (51%)	18 (48%)
N1+2	22 (59%)	13 (35%)
TNM staging		
I	7 (19%)	14 (40%)
IIA	11 (30%)	7 (20%)
IIB	1 (2.7%)	0 (0%)
IIC	1 (2.7%)	1 (2.8%)
IIIA	2 (5.4%)	1 (2.8%)
IIIB	13 (35%)	8 (23%)
IIIC	1 (2.7%)	0 (0%)
IVA	1 (2.7%)	3 (8.6%)
IVB	0 (0%)	1 (3%)

ISR: Intersphincteric resection; APR: Abdominoperineal resection; n: No. of cases; TNM: Tumor, node, metastasis.

In the examined database, few cases of mucinous adenocarcinomas ( $n=6$ ) were included and only one case of squamous cell carcinoma was identified in the Group II. All the other cases ( $n=65$ ; 90.28%) were adenocarcinomas, which proved to be well (G1), moderate (G2), poorly (G3) differentiated or undifferentiated (G4) cases (Figure 1). No differences regarding the HP type was seen between the two groups ( $p=0.61$ ) (Table 3).





**Figure 1** – Based on the histological grading system used for rectal adenocarcinomas, which is evaluated in Hematoxylin–Eosin staining, cases are classified as G1 (A), G2 (B), G3 (C) and G4 (D).

**Table 3** – Histological type of tumors in the two examined groups

Microscopic type	Group I (ISR, n=37)	Group II (APR, n=35)
G1+G2 adenocarcinomas	23 (62%)	23 (66%)
G3+G4 adenocarcinomas	11 (30%)	8 (23%)
Mucinos adenocarcinoma	3 (8%)	3 (8%)
Squamous cell carcinoma	0 (0%)	1 (3%)

ISR: Intersphincteric resection; APR: Abdominoperineal resection; n: No. of cases; G: Histological grade.

### Morbidity rate and recurrences

The surgical parameters, which were intraoperatively monitored, showed a longer operative time for Group II, compared with Group I (180 minutes, ranging 155–230 minutes, vs. 160 minutes, ranging 130–180 minutes). Increased estimated blood loss was counted in patients from Group II, compared with Group I (150 mL, ranging between 90–180 mL, vs. 100 mL, ranging between 70–160 mL).

In Group I, the overall postoperative morbidity was 16%. The most common complication was necrosis of the pulled-through mucosa/submucosa. This complication was encountered in three (8%) cases and occurred on an average of 10 days after surgery. No reintervention was necessary; removal of the necrotic tissue was sufficient, without the appearance of an anastomotic fistulae (Clavien–Dindo grade I). One patient (3%) developed a transmural necrosis of the colon, requiring second surgery, with

transformation of ISR in APR (Clavien–Dindo grade IIIb). Stenosis of coloanal anastomosis was found in two (5%) of cases and was successfully managed with dilatation (Clavien–Dindo grade IIIa). Anastomotic leakage was not identified as a postoperative complication.

The 3-month medium value of Wexner score was of  $10.12 \pm 2.34$ , decreasing until  $9.02 \pm 3.14$  at five months. Patients reported satisfactory continence taking into account the absence of a colostomy/temporary ileostomy bag. In Group I, we found two (5.4%) local recurrences: one cutaneous sacral metastasis and one anastomotic relapse. In two of the 37 (5.4%) cases, distant metastases were diagnosed in the liver.

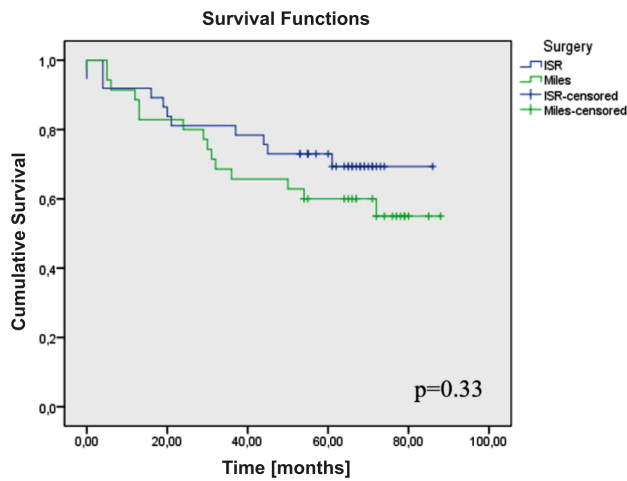
In Group II, the overall postoperative morbidity rate was 26% ( $n=9$ ). The commonest complications consisting of abdominal site infection ( $n=4$ ), perineal wound infection ( $n=3$ ), colostomy stenosis ( $n=1$ ), and colostomy necrosis ( $n=1$ ). Five of the 35 (14%) patients showed local recurrence and nine (25%) patients developed metastatic disease.

### Overall survival rate

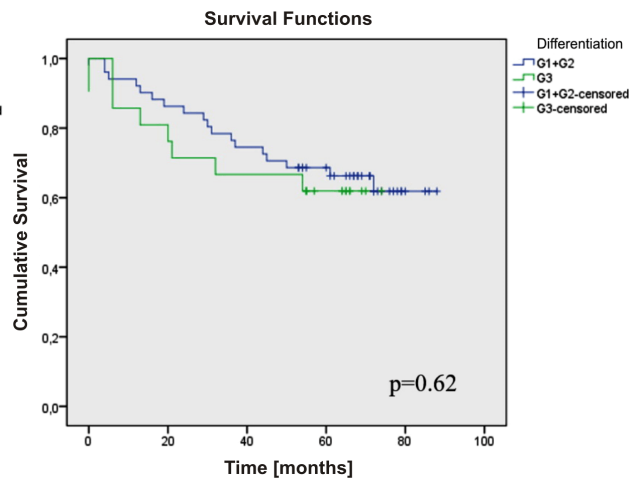
The median follow-up period was of 62 months (range 55–80 months). We recorded a total of 11 (29%) deaths in Group I, respectively 15 (42%) deaths in Group II. The 5-year survival rate was 71% for patients included in Group I and 58% for those belonging to Group II, without statistically difference among the groups.

Kaplan–Meier curves did not show independent prognostic value for the type of surgery (Figure 2) even for grade of differentiation (Figure 3). Lymph node status (Figure 4), along with LNR (Figure 5) and clinical stage

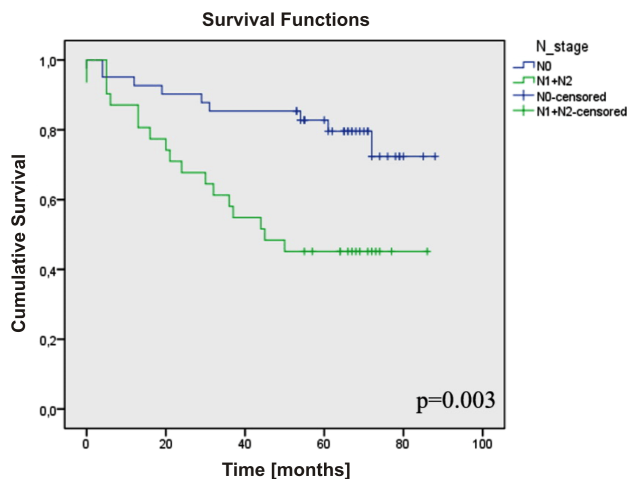
(Figure 6) proved to be the most important independent prognostic parameters, independently from the type of surgery. The tumor depth of infiltration was proved to not be independent prognostic parameter (Figure 7).



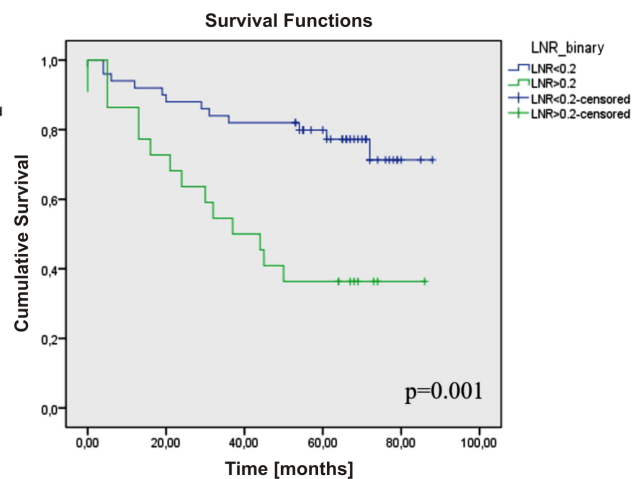
**Figure 2** – In patients with low rectal cancer, the type of surgery does not influence the long-term survival rate. ISR: Intersphincteric resection.



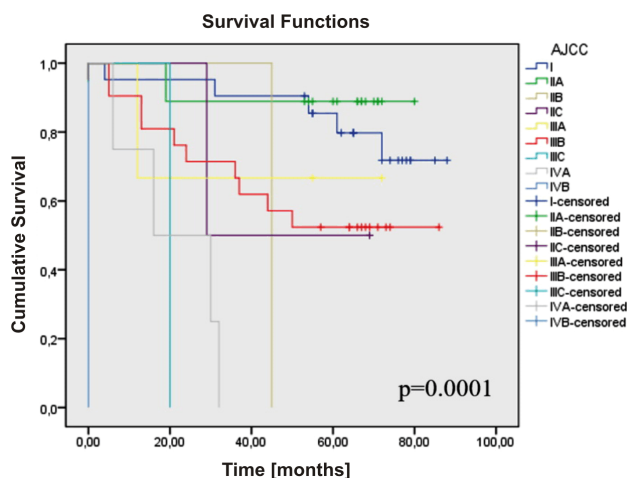
**Figure 3** – In patients with adenocarcinomas of the inferior rectum, the histological grade (G) is not an independent prognostic parameter.



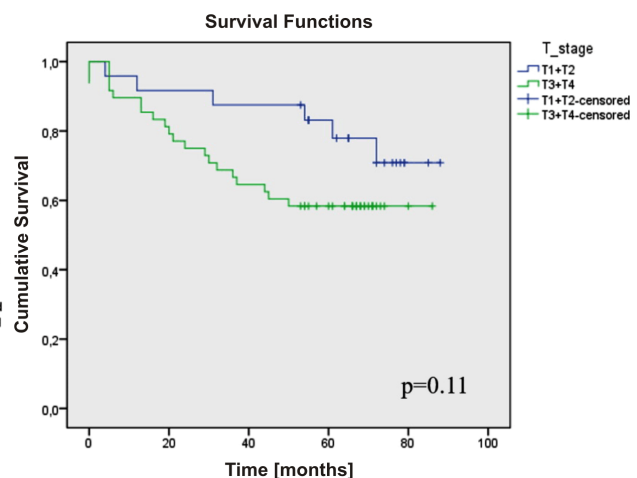
**Figure 4** – In patients with adenocarcinomas of the inferior rectum, a better overall survival can be seen in cases with a lower value of lymph node (N) ratio.



**Figure 5** – In patients with adenocarcinomas of the inferior rectum, absence of lymph node metastases is a strong indicator of a significant longer survival. LNR: Lymph node ratio.



**Figure 6** – In patients with adenocarcinomas of the inferior rectum, the clinical stage is a strong prognostic parameter. AJCC: American Joint Committee on Cancer.



**Figure 7** – In patients with adenocarcinomas of the inferior rectum, the depth of infiltration, evaluated under microscope, is not an independent prognostic parameter. T: Tumor.

## Discussions

The incidence of rectal cancer is steadily decreasing worldwide probably due to better screening methods but still remains high in low developed countries where access to medical service is difficult. Nevertheless, it remains a dreadful disease with its peak incidence in the late 5<sup>th</sup> decade and showing a steady increase afterwards, findings similar to those in our study [1, 18]. A recent study analyzing CRC trends in Canada shows an incidence increase in younger patients, an observation that we also noticed in our study groups [19].

Disease staging is dependent on patient's first presentation and, although in our database the advanced localized stages were observed, half of the patients did not show lymph node metastases and the 5-year survival rate was optimistically. The majority of patients presented with tumor stage T3, respectively clinical stage IIIB and IIA, a fact that is probably due the lack of screening programs and various social aspects, but a fact noted by other authors as well [13, 15]. One drawback of our study is the inability to quantify patients that following chemoradiation therapy (CRT) showed downstaging and downsizing. This is due to the lack of a *National Cancer Registry* and hospital dependent follow-up.

From a surgical point of view, our study showed a longer operative time for patients that underwent APR and also a larger amount of blood loss for these patients. Taking into consideration the procedural steps of APR, it is understandable why the operative time is higher in the APR group, a finding also consistent with other studies [16, 20, 21]. Slightly lower intraoperative blood loss associated with ISR can be attributed to current use of sealing devices, on one hand, and the to relatively straightforward dissection plane at the level of the perineum when performing ISR.

Local anatomy also has to be taken into account when analyzing negative CRM in our two groups. It is easier to achieve a negative CRM when performing APR as the entire perineal time consists of local excision. When performing ISR and aiming for a R0 resection, the value of preoperative MRI comes into play. This investigation can predict if the CRM is going to be negative with an accuracy of 88% [10]. We found negative CRM in 87% of patients that underwent ISR and 94% of patients that underwent APR, findings that are similar to those reported by others [5, 8, 12, 15].

Oncological outcomes measured in other studies show that there is no difference between APR and ISR a finding that overall, we agree with [9, 12–16]. However, the emotional impact of a stoma, which is absent after ISR, should also be taken into account [13, 22, 23]. As a good Wexner score was obtained at three and six months of follow-up and patients reported satisfactory continence following ISR, the examined material proved the superiority of ISR to APR, as regarding the postoperative quality of life.

Morbidity following ISR seems to be slightly lower as compared to APR especially taking into account the complications associated with the presence of a stoma, be it a temporary one, but this was not the focus point of the present study [5, 7, 15, 20]. Most postoperative

complications following ISR in our study proved to be simple in nature (necrosis of the submucosa/mucosa) and did not required another surgery to treat them although we were forced to turn an ISR into APR due to colon necrosis (one from 72 cases). The lower complication rate following ISR, as compared to APR, prove that the ISR should be used in those patients that accomplish the inclusion criteria [15, 16].

Although the 5-year mortality appears to be better in the case of ISR, compared with ASR (71% vs. 58%), this aspect is rather stage-dependent [9, 14–16]. As no survival differences were seen between patients diagnosed in T2 vs. T3 or T4, when the parameter was analyzed as independent prognostic factor, the present study proved that, in highly selected cases, good results might be obtained with ISR, independently from the pT stage.

As regarding the parameters which have independent prognostic value, the present material proved that, although the histological subtype of the tumor, including grade of differentiation, are still used for choosing the best therapeutically regimen of patients with CRC, in carcinomas of the lower rectum, this parameter does not have prognostic involvement. The clinical stage assessment is mandatory to be determined, based on imagistic methods, especially for identification and surgical removal of suspected lymph nodes. It is not enough to estimate the pN stage, although it still have great oncological importance. In line to our studies [17], a more significant importance is the LNR, which proper value is still under debate. Although new molecular groups of CRCs are proposed [24], the pTNM stage remains the gold standard parameter of survival rate.

## Conclusions

In patients with low rectal cancer, good oncological results are obtained when performing ISR but the trans-disciplinary team should respect highly selection criteria. Independently by the type of surgery, lymph node status and LNR remains the most important prognostic value.

## Conflict of interests

The authors declare that they have no conflict of interests.

## Acknowledgments

This paper was supported by a grant of the Romanian National Authority for Scientific Research, CNCS – UEFISCDI, project number 20 PCCF/2018, code: PN-III-P4-ID-PCCF-2016-0006.

## References

- [1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 2018, 68(6):394–424.
- [2] Haq AI, Schneeweiss J, Kalsi V, Arya M. The Dukes staging system: a cornerstone in the clinical management of colorectal cancer. *Lancet Oncol*, 2009, 10(11):1128.
- [3] Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D; ESMO Guidelines. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2017, 28(Suppl\_4):iv22–iv40.
- [4] Rullier E, Denost Q, Vendrely V, Rullier A, Laurent C. Low rectal cancer: classification and standardization of surgery. *Dis Colon Rectum*, 2013, 56(5):560–567.



- [5] Hawkins AT, Albutt K, Wise PE, Alavi K, Sudan R, Kaiser AM, Bordeianou L; Continuing Education Committee of the SSAT. Abdominoperineal resection for rectal cancer in the twenty-first century: indications, techniques, and outcomes. *J Gastrointest Surg*, 2018, 22(8):1477–1487.
- [6] Wiatrek RL, Thomas JS, Papaconstantinou HT. Perineal wound complications after abdominoperineal resection. *Clin Colon Rect Surg*, 2008, 21(1):76–85.
- [7] Schiessel R, Karner-Hanusch J, Herbst F, Teleky B, Wunderlich M. Intersphincteric resection for low rectal tumours. *Br J Surg*, 1994, 81(9):1376–1378.
- [8] Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg*, 1998, 133(8):894–898.
- [9] Schiessel R, Novi G, Holzer B, Rosen HR, Renner K, Hölbling N, Feil W, Urban M. Technique and long-term results of intersphincteric resection for low rectal cancer. *Dis Colon Rectum*, 2005, 48(10):1858–1865; discussion 1865–1867.
- [10] MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ*, 2006, 333(7572):779.
- [11] Tsukada Y, Ito M, Watanabe K, Yamaguchi K, Kojima M, Hayashi R, Akita K, Saito N. Topographic anatomy of the anal sphincter complex and *levator ani* muscle as it relates to intersphincteric resection for very low rectal disease. *Dis Colon Rectum*, 2016, 59(5):426–433.
- [12] Saito N, Sugito M, Ito M, Kobayashi A, Nishizawa Y, Yoneyama Y, Minagawa N. Oncologic outcome of intersphincteric resection for very low rectal cancer. *World J Surg*, 2009, 33(8):1750–1756.
- [13] Kim HS, Ko S, Oh NG. Long-term results of extended intersphincteric resection for very low rectal cancer: a retrospective study. *BMC Surg*, 2016, 16:21.
- [14] Kuo LJ, Hung CS, Wu CH, Wang W, Tam KW, Liang HH, Chang YJ, Wei PL. Oncological and functional outcomes of intersphincteric resection for low rectal cancer. *J Surg Res*, 2011, 170(1):e93–e98.
- [15] Saito N, Moriya Y, Shirouzu K, Maeda K, Mochizuki H, Koda K, Hirai T, Sugito M, Ito M, Kobayashi A. Intersphincteric resection in patients with very low rectal cancer: a review of the Japanese experience. *Dis Colon Rectum*, 2006, 49(10 Suppl):S13–S22.
- [16] Martin ST, Heneghan HM, Winter DC. Systematic review of outcomes after intersphincteric resection for low rectal cancer. *Br J Surg*, 2012, 99(5):603–612.
- [17] Fulop ZZ, Gurzu S, Bara T, Dragus E, Bara T Jr, Voidazan S, Banias L, Jung I. Lymph node ratio, an independent prognostic factor for patients with stage II–III rectal carcinoma. *Pathol Res Pract*, 2019, 215(6):152384.
- [18] Triantafyllidis JK, Nasioulas G, Kosmidis PA. Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. *Anticancer Res*, 2009, 29(7):2727–2737.
- [19] Brenner DR, Heer E, Sutherland RL, Ruan Y, Tinmouth J, Heitman SJ, Hilsden RJ. National trends in colorectal cancer incidence among older and younger adults in Canada. *JAMA Netw Open*, 2019, 2(7):e198090.
- [20] Perry WB, Connaughton JC. Abdominoperineal resection: how is it done and what are the results? *Clin Colon Rectal Surg*, 2007, 20(3):213–220.
- [21] Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Teoh AY, Leung WW. Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. *Ann Surg Oncol*, 2008, 15(9):2418–2425.
- [22] Russu PC, Molnar C, Gurzu S, Jung I, Voidăzan TS, Copotoiu C. The role of clinical and pathological assessment in choosing the best therapeutic management to improve survival in rectal cancer. *Rom J Morphol Embryol*, 2016, 57(4):1253–1259.
- [23] Koyama M, Murata A, Sakamoto Y, Morohashi H, Takahashi S, Yoshida E, Hakamada K. Long-term clinical and functional results of intersphincteric resection for lower rectal cancer. *Ann Surg Oncol*, 2014, 21(Suppl 3):S422–S428.
- [24] Gurzu S, Szentirmay Z, Jung I. Molecular classification of colorectal cancer: a dream that can become a reality. *Rom J Morphol Embryol*, 2013, 54(2):241–245.

### Corresponding author

Vlad-Olimpiu Butiurca, MD, Department of Surgery, “George Emil Palade” University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, 38 Gheorghe Marinescu Street, 540139 Târgu Mureș, Romania; Phone +40722–241 281, e-mail: vladbutiurca@yahoo.com

*Received: April 10, 2019*

*Accepted: December 8, 2019*