ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Factors influencing the pathological quality of the surgical specimen in rectal cancer – a retrospective single-centre study

DRAGOŞ-VIOREL SCRIPCARIU[1,2], CRISTIAN DUMITRU LUPAŞCU[1,3], IONUŢ HUŢANU[1,2], BOGDAN FILIP[1,2], MARIA-GABRIELA ANIŢEI[1,2], DAN FERARIU[4], MIHAELA MOSCALU[5], VIOREL SCRIPCARIU[1,2]

[1] *Department of Surgery, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*
[2] *1st Surgical Oncology Unit, Regional Institute of Oncology, Iaşi, Romania*
[3] *2nd General Surgery Unit, "St. Spiridon" Emergency County Hospital, Iaşi, Romania*
[4] *Department of Pathology, Regional Institute of Oncology, Iaşi, Romania*
[5] *Department of Preventive Medicine and Interdisciplinarity, Medical Informatics and Biostatistics, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

Abstract

Aim: The pathologist's role in the multidisciplinary treatment of rectal cancer is to evaluate and stage the tumor according to the latest standards, as well as indicate the quality of the surgical act. This study aims to evaluate circumferential and distal resection margins as well as quality of mesorectal resection and correlate them with different clinical, pathological and therapeutic factors. *Patients, Materials and Methods*: Four hundred ninety-eight patients treated radically for mid and low rectal cancer within one Clinic of Oncological Surgery in Iaşi, Romania, were included in this study. *Results*: The distal resection margin showed significant correlations with the type of surgical intervention, chemotherapy in the neoadjuvant treatment plan and pathological node staging. The circumferential resection margin depended mostly on pathological node staging and the length of the interval between neoadjuvant treatment and surgery. Finally, the aspect of the mesorectum varied according to neoadjuvant treatment and the type of surgical intervention performed. *Conclusions*: The study reached its aim in providing important data for the expected outcome of the specimen after curative treatment for rectal cancer.

Keywords: rectal cancer, pathological specimen, distal margin, circumferential margin, mesorectal aspect.

Introduction

Colorectal cancer is a major healthcare issue, being the third most common cancer in men and second in women worldwide [1]. Rectal cancer is especially aggressive due to its anatomic position and biology that result in a tumor more prone to rapid local invasion and high rates of local recurrence in lack of an adequate treatment scheme. Calman & Hine first postulated multidisciplinary approach in 1995 [2] and since, rectal cancer treatment has seen great improvement due to the concept of multidisciplinary treatment. This approach means accurate staging by pelvic magnetic resonance imaging (MRI) and ultrasound, appreciation of the opportunity of neoadjuvant radio-chemotherapy, as well as pathological evaluation of the surgical specimen that dictates the adequacy of the technique and guides the decision upon adjuvant treatment [3].

Surgical treatment options in rectal cancer comprise of low anterior resection (LAR) of the rectum with colo-rectal anastomosis, in cases where tumor localization permits obtaining an adequate distal margin, without affecting the sphincter (so-called sphincter-saving procedures), or an abdominoperineal excision (APE) of the rectum (so-called amputations of the rectum), in cases where the anal sphincter or anal canal are involved in the tumor [4, 5]. In addition, there is the option for Hartmann's procedure with a total excision of the meso-rectum, consisting of resection of the rectum with total mesorectal excision, followed by closure of the rectal stump and terminal colostomy.

In the past decades, the LAR level has been lowered, through a decrease in the distal resection margin down to 1 cm [6] and due to the increase in availability of mechanical suture devices, aiming to obtain a better quality of life for the patients.

The pathologist plays a crucial role in the multi-disciplinary team in rectal cancer: it can provide feedback to radiologists regarding staging; it can evaluate the effectiveness of the neoadjuvant treatment scheme. Moreover, and most importantly, it offers feedback to the surgeon regarding the quality of the surgical dissection and, consequently, of the pathological specimen, and gives the primary staging of the tumor. The pathologist must assess the quality of the mesorectal dissection, the circumferential resection margin (CRM) and the distal resection margin (DRM) of the specimen [7].

The aim of this study is to evaluate the correlations between the DRM, CRM and overall aspect of the mesorectum, on the one side, and the type of surgical procedure, clinical and pathological staging and options related to neoadjuvant therapy, on the other side.

Patients, Materials and Methods

Patients

The study took into consideration patients treated for

mid and low rectal cancer in the First Surgical Unit of the Regional Institute of Oncology, Iaşi, Romania, over a period of five years, between May 2012 and April 2017 (Figure 1). The study was approved by the Ethics Board of the Regional Institute of Oncology RN78/27.02.2018.

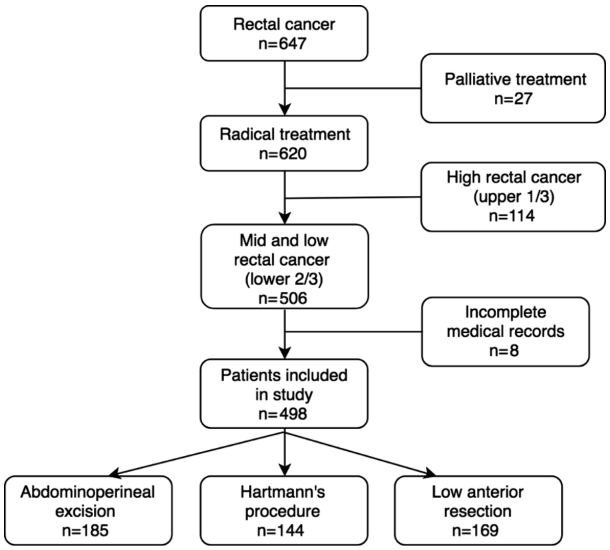


Figure 1 – ***Patient flowchart.***

Inclusion criteria were: patients with rectal adenocarcinoma located in the mid or lower thirds, receiving curative treatment, with complete medical records, who had given their consent for clinical data to be used for scientific purposes. Exclusion criteria consisted of localization of the tumor at the level (or higher than) the upper rectum, patients that had incomplete medical records within the First Surgical Unit of the Regional Institute of Oncology, Iaşi.

Medical records were reviewed to obtain the following information: patient age, gender, type and localization of rectal neoplasia, clinical and pathological tumor staging using the *American Joint Committee on Cancer* (AJCC) [8], existence of neoadjuvant treatment (including type of neoadjuvant treatment), time between neoadjuvant treatment and surgical sequence, type of surgery, DRM, CRM and aspect of the mesorectum, using Quirke's grading system [9].

Neoadjuvant treatment

The indication for neoadjuvant treatment was set within the multidisciplinary team and took into account the *National Comprehensive Cancer Network* (NCCN) and the *European Society of Medical Oncology* (ESMO) guidelines for treatment in rectal cancer; thus, rectal cancers with imagistic criteria for positive CRMs (cT3/4 and cN+) and no distant metastases (cM0) were directed towards neoadjuvant treatment [10, 11].

The cases that were subjected to neoadjuvant treatment underwent a long-course plan, with 50.4 Gray in 28 fractions, during a five weeks and a half treatment programme. Two patients underwent short course neoadjuvant treatment – 25 Gray administered in five days. Capecitabine was associated as chemotherapy to radiation treatment with the purpose of increasing susceptibility of tumor cells to radiation. There were four cases with standalone chemotherapy (*i.e.*, without radiotherapy).

Surgical procedure

After neoadjuvant treatment, the surgical sequence was applied after a mean of 73.5 days (minimum five days; maximum 360 days).

A total of 169 patients underwent a low or very low anterior resection of the rectum with a total excision of the mesorectum (Figure 2), 185 patients suffered an abdominoperineal excision of the rectum, that was performed in an extralevator plane in the majority of cases (Figure 3), and 144 cases had Hartmann's procedure with a total excision of the mesorectum (Figure 4). Dissection was performed in all cases respecting the mesorectal fascia that was set by Heald *et al.* as a landmark for a correct oncological procedure [12].

Pathological evaluation

The pathological evaluation was performed by the Hospital's Pathology Unit. Standardized examination was performed, using the same protocol, as described by Quirke *et al.* [9]. The completeness of the surgical specimen was evaluated macroscopically (Figures 5 and 6) and reported in accordance in a descriptive manner, which was used to classify specimens in accordance with the three-point grading system [3] (Table 1). Careful examination of the specimen's distal margin and circumferential margin were performed after fixation. Moreover, investigation of the tumor invasion and lymph node yield and positivity was performed and reported.

Table 1 – ***Specimen grading in (a) LAR and (b) APE [9]***

(a)	Grade	Short description	Long description
	Mesorectal plane	Good surgery	▪ Intact smooth mesorectal surface with only minor irregularities. ▪ Any defects must not be deeper than 5 mm. ▪ No coning of the specimen distally. ▪ Smooth CRM on slicing.
	Intramesorectal plane	Moderate surgery	▪ Moderate bulk to mesorectum but irregularity of the mesorectal surface. ▪ Moderate distal coning. ▪ Muscularis propria not visible with the exception of levator insertion. ▪ Moderate irregularity of CRM.
	Muscularis propria plane	Poor surgery	▪ Little bulk to mesorectum with defects down onto the muscularis propria and/or very irregular CRM. ▪ It includes infraperitoneal perforations.
(b)	**Grade**	**Short description**	**Long description**
	Extra-levator plane	Good surgery	▪ The specimen has a cylindrical shape due to the presence of levator ani removed en bloc with the mesorectum and sphincters (it forms a "collarette" around the distal aspect of the specimen). ▪ Any defects must be no deeper than 5 mm. ▪ No waisting of the specimen. ▪ Smooth CRM on slicing.
	Sphincteric plane	Moderate surgery	▪ The specimen is waisted. ▪ The CRM in this region is formed by the surface of the sphincter muscles which have been removed intact.

(b)	Grade	Short description	Long description
	Intrasphincteric plane	Poor surgery	▪ The specimen is waisted and includes deviations into the sphincter muscles, submucosa and complete perforations.

LAR: Low anterior resection; APE: Abdominoperineal excision; CRM: Circumferential resection margin.

Statistical analysis

All statistical data analysis was performed using *Statistical Package for Social Sciences* (SPSS) *v*.24. Quantitative variables were reported as mean with standard deviation. Comparisons between analyzed study groups were dine using Student's *t*-test or Wilcoxon rank-sum tests. Qualitative variables were presented as absolute and relative frequencies and comparisons between analyzed study groups was performed by McNemar χ^2 (chi-square) test or Fisher's exact test. Univariate and multivariate analysis were performed using the logistic and nominal regression model. The level of significance in the used tests (*p*-value) was considered for values <0.05; this value represented the maximum accepted probability of error.

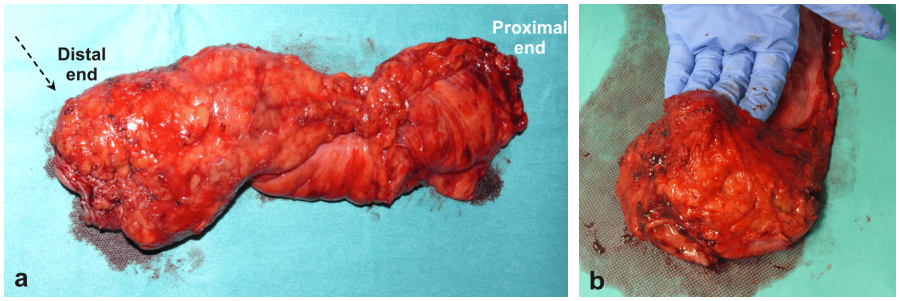


Figure 2 – ***Low anterior resection of the rectum specimen comprised of rectum, mesorectum and sigmoid colon and mesocolon: (a) Posterior aspect with intact mesorectal fascia and no defects (dotted arrow); (b) Anterior aspect with complete mesorectal excision including Douglas's pouch as shown by presenting hand.***

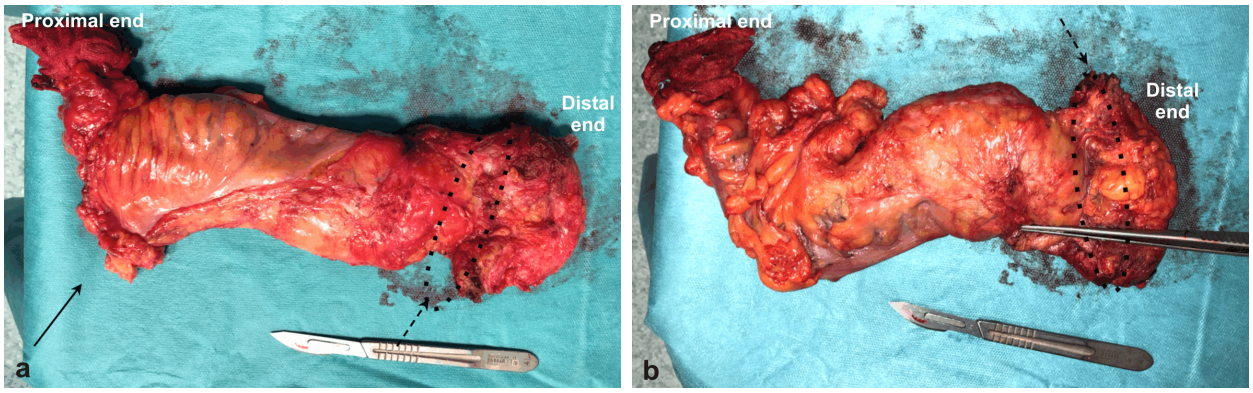
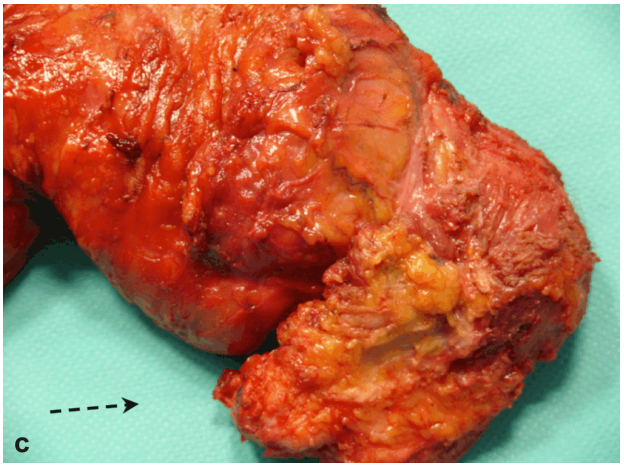


Figure 3 – ***Extralevator abdominoperineal excision of the rectum specimen comprised of anal canal, levator ani (dotted circle) and coccyx (dotted arrow), rectum, mesorectum and sigmoid colon and mesocolon: (a) Right lateral aspect with intact mesorectal fascia, high vascular ligation (full arrow), coccyx (dotted arrow) and levator ani muscle attached to the specimen (dotted circle); (b) Anterior – left lateral aspect depicting retracted mesorectal fascia shown by DeBakey forceps; (c) Detail on levator ani plane with coccyx attached (dotted arrow).***



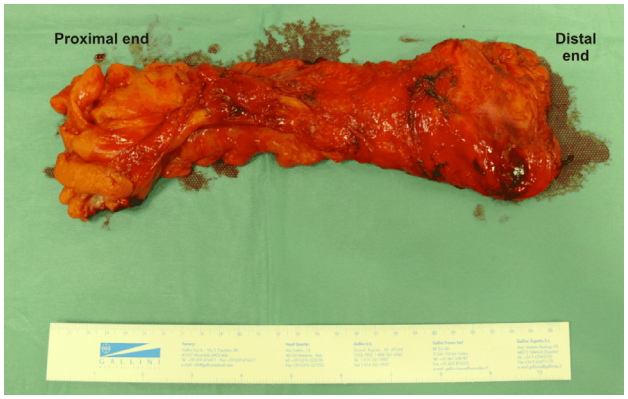


Figure 4 – ***Hartmann's operation with total mesorectal excision specimen comprised of rectum, mesorectum and sigmoid colon and mesocolon, similar to the low anterior resection specimen.***

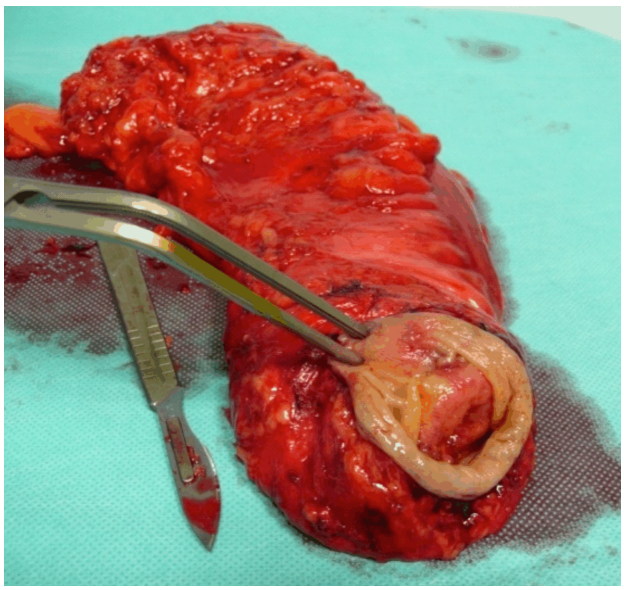


Figure 5 – ***Postoperative aspect of an adequate distal resection margin greater than 1 cm. Specimen has not yet been transferred to the pathology unit, thus fixation has not yet taken place.***

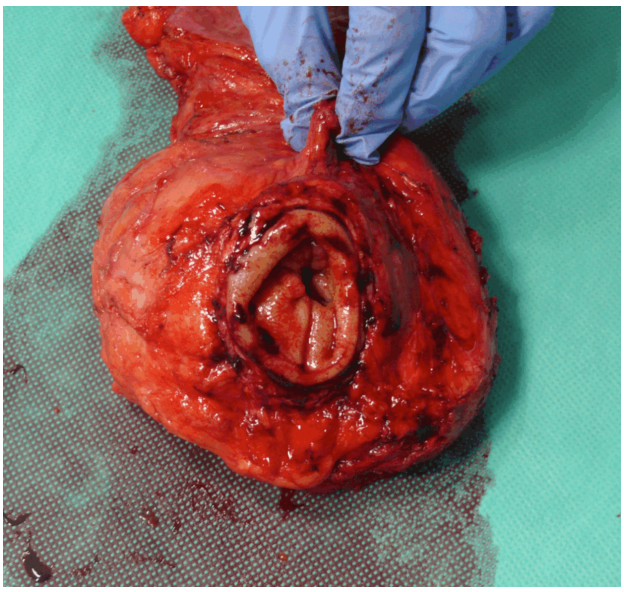


Figure 6 – ***Postoperative aspect of a low anterior resection specimen depicting a smooth, symmetrical circumferential margin that will subsequently be evaluated by the pathologist, after slices through the specimen will have been performed.***

Results

Clinico-pathological characteristics of the study group

There were a total of 498 patients treated radically or low and mid rectal cancer, of which the majority were males, mostly in the 7th decade of life. The initial, clinical staging showed a wide majority of cases with advanced rectal cancer – 72.3% stage III and 14.5% stage IV. Thus, over half of the patients (58%) underwent neoadjuvant radiotherapy and obtained good results, with a drop in stage III and IV rectal cancers to 46.2%. Seventy-four percent of the patients who had neoadjuvant radiotherapy had associated chemotherapy. There were four patients who had neoadjuvant chemotherapy alone; in these cases, all of which had liver metastases, it was the decision taken within the multidisciplinary team.

The main clinico-pathological features of the patients were summarized in Table 2.

Table 2 – ***Baseline patients characteristics***

Baseline data	Surgical procedure			Total (*n*=498)
	APE (n=185)	*Hartmann's procedure (n=144)*	*LAR (n=169)*	
Age [years]†	63.5±12.3	64.6±12.2	61.8±12.5	63.2±12.4
Gender (male : female) ratio	123 (66.5) : 62 (33.5)	98 (68.1) : 46 (31.9)	106 (62.7) : 63 (37.3)	327 : 171 (65.7 : 34.3)
Clinical T stage				
cT1	1 (0.5)	4 (2.8)	4 (2.4)	9 (1.8)
cT2	19 (10.3)	5 (3.5)	28 (16.6)	52 (10.4)
cT3	122 (65.9)	97 (67.4)	123 (72.8)	342 (68.7)
cT4	43 (23.2)	38 (26.4)	14 (8.3)	95 (19.1)
Clinical N stage				
cN0	21 (11.4)	21 (14.6)	28 (16.6)	70 (14.1)
cN1	71 (38.4)	44 (30.6)	66 (39.1)	181 (36.3)
cN2	93 (50.3)	78 (54.2)	75 (44.4)	246 (49.4)
cN+	0 (0)	1 (0.7)	0 (0)	1 (0.2)
Initial clinical M stage				
cM0	166 (89.7)	101 (70.1)	159 (94.1)	426 (85.5)
cM1	19 (10.3)	43 (29.9)	10 (5.9)	72 (14.5)
Clinical TNM stage				
I	9 (4.9)	6 (4.2)	14 (8.3)	29 (5.8)
II	11 (5.9)	13 (9)	13 (7.7)	37 (7.4)
III	146 (78.9)	82 (56.9)	132 (78.1)	360 (72.3)
IV	19 (10.3)	43 (29.9)	10 (5.9)	72 (14.5)

Baseline data	Surgical procedure			Total (*n*=498)
	APE (n=185)	*Hartmann's procedure (n=144)*	*LAR (n=169)*	
Neoadjuvant radiotherapy				
Yes	127 (68.6)	59 (41)	103 (60.9)	289 (58)
No	58 (31.4)	85 (59)	66 (39.1)	209 (42)
Neoadjuvant chemotherapy				
Yes	98 (53)	42 (29.2)	78 (46.2)	218 (43.8)
No	87 (47)	102 (70.8)	91 (53.8)	280 (56.2)
Pathological T stage				
pT0	6 (3.2)	1 (0.7)	11 (6.5)	18 (3.6)
pTis	3 (1.6)	2 (1.4)	3 (1.8)	8 (1.6)
pT1	5 (2.7)	3 (2.1)	8 (4.7)	16 (3.2)
pT2	53 (28.6)	13 (9)	47 (27.8)	113 (22.7)
pT3	101 (54.6)	98 (68.1)	91 (53.8)	290 (58.2)
pT4	17 (9.2)	27 (18.8)	9 (5.3)	53 (10.6)
Pathological N stage				
pN0	102 (55.1)	56 (38.9)	120 (71)	278 (55.8)
pN1	54 (29.2)	47 (32.6)	33 (19.5)	134 (26.9)
pN2	29 (15.7)	41 (28.5)	16 (9.5)	86 (17.3)
Postoperative cM stage				
cM0	165 (89.2)	98 (68.1)	158 (93.5)	421 (84.5)
cM1	20 (10.8)	46 (31.9)	11 (6.5)	77 (15.5)
Pathological TNM stage (extended)				
pCR	5 (2.7)	1 (0.7)	11 (6.5)	17 (3.4)
0	3 (1.6)	2 (1.4)	3 (1.8)	8 (1.6)
I	50 (27)	15 (10.4)	48 (28.4)	113 (22.7)
IIA	35 (18.9)	33 (22.9)	54 (32)	122 (24.5)
IIB	3 (1.6)	1 (0.7)	1 (0.6)	5 (1)
IIC	2 (1.1)	0 (0)	1 (0.6)	3 (0.6)
IIIA	6 (3.2)	0 (0)	7 (4.1)	13 (2.6)
IIIB	45 (24.3)	34 (23.6)	24 (14.2)	103 (20.7)
IIIC	17 (9.2)	12 (8.3)	9 (5.3)	38 (7.6)
IV	19 (10.3)	46 (31.9)	11 (6.5)	76 (15.3)
Pathological TNM stage				
pCR	5 (2.7)	1 (0.7)	11 (6.5)	17 (3.4)
0	3 (1.6)	2 (1.4)	3 (1.8)	8 (1.6)
I	50 (27)	15 (10.4)	48 (28.4)	113 (22.7)
II	40 (21.6)	34 (23.6)	56 (33.1)	130 (26.1)
III	68 (36.8)	46 (31.9)	40 (23.7)	154 (30.9)
IV	19 (10.3)	46 (31.9)	11 (6.5)	76 (15.3)
Interval [days]† neoadjuvant therapy – surgical sequence	81.4±27	85.1±47.1	77.4±17.7	80.7±29.9

† Continuous variables were expressed as: mean ± standard deviation, categorical variables: number (%); Kruskal–Wallis for continuous variables; (*) Marked effects are significant at $p<0.05$; ‡ *Chi*-square test (McNemar or Yates *chi*-square) or Fisher's exact test; APE: Abdomino-perineal excision; LAR: Low anterior resection; pTis: Pathological tumor *in situ*; pCR: Pathological complete response.

Assessment of the distal margin

There was a significant association between the adequacy of the DRM, type of surgical intervention and multiple clinico-pathological characteristics, *i.e.*, clinical and pathological tumor and lymph node staging, neo-adjuvant treatment in different schemes (radiotherapy with or without chemotherapy) (Table 3). Between patients with Hartmann's procedure, the lymph node status showed significant differences in matter of DRM involvement: more frequent inadequate DRM (<1 cm) in cases with more advanced lymph node staging compared to appropriate DRM (≥1 cm). Moreover, high tumor and lymph node stages (both clinical and pathological) showed significant association with DRM <1 cm.

Univariate logistic regression was used to determine the risk of DRM involvement (Table 4). The results showed that the type of procedure, cN2, pN2 and the use of chemotherapy within the neoadjuvant treatment are predictive factors for a positive DRM.

The results of multiple logistic regression (Table 5) identified the type of procedure, neoadjuvant chemo-therapy and pN staging as the elements with high predictive potential for DRM. An important finding is that the interval between neoadjuvant treatment and surgery showed no statistical significance in relation to the DRM.

Table 3 – ***Clinical, pathological and therapeutic characteristics related to distal resection margin***

Variable	Hartmann's procedure (*n*=144)		LAR (*n*=169)		*p*-value
	DRM ≥1 cm 131 (91.97)	***DRM <1 cm 13 (9.03)***	***DRM ≥1 cm 165 (97.63)***	***DRM <1 cm 4 (2.37)***	***0.01922****
Clinical T stage	*p*=0.61286		*p*=0.01955*		0.0344*
cT1	4 (2.8)	–	3 (1.8)	1 (0.6)	0.9987
cT2	5 (3.5)	–	28 (16.6)	–	0.9971
cT3	88 (61.1)	9 (6.3)	120 (71)	3 (1.8)	0.0253*
cT4	34 (23.6)	4 (2.8)	14 (8.3)	–	0.4984
Clinical N stage	*p*=0.00246*		*p*=0.62552		0.00118*
cN0	20 (13.9)	1 (0.7)	28 (16.6)	–	0.8840
cN1	43 (29.9)	1 (0.7)	65 (38.5)	1 (0.6)	0.7730
cN2	68 (47.2)	10 (6.9)	72 (42.6)	3 (1.8)	0.04465*
cN+	–	1 (0.7)	–	–	
Neoadjuvant treatment	*p*=0.4877		*p*=0.2706		0.00871*
No	79 (54.9)	6 (4.2)	66 (39.1)	–	0.02762*
Yes	52 (36.1)	7 (4.9)	99 (58.6)	4 (2.4)	0.05773
Neoadjuvant chemotherapy	*p*=0.27444		*p*=0.0288*		0.00248*
No	95 (66)	7 (4.9)	91 (53.8)	–	0.03078
Yes	36 (25)	6 (4.2)	74 (43.8)	4 (2.4)	0.16607
Pathological T stage	*p*=0.5481		*p*=0.0874		0.0315*
pT0	1 (0.7)	–	11 (6.5)	–	0.0991
pTis	2 (1.4)	–	3 (1.8)	–	0.9987
pT1	3 (2.1)	–	7 (4.1)	1 (0.6)	0.5925
pT2	12 (8.3)	1 (0.7)	44 (26)	3 (1.8)	0.6450
pT3	91 (63.2)	7 (4.9)	91 (53.8)	–	0.02692*
pT4	22 (15.3)	5 (3.5)	9 (5.3)	–	0.4038
Pathological N stage	*p*=0.02634*		*p*=0.6592		0.00219*
pN0	54 (37.5)	2 (1.4)	117 (69.2)	3 (1.8)	0.69027
pN1	44 (30.6)	3 (2.1)	32 (18.9)	1 (0.6)	0.4854
pN2	33 (22.9)	8 (5.6)	16 (9.5)	–	0.01634*
Interval [days]†	*p*=0.3167		*p*=0.3178		
neoadjuvant therapy – surgical sequence	83.8±47.5	95.3±45.9	77.2±17.9	82±7.5	0.3784

† Continuous variables were expressed as: mean ± standard deviation, categorical variables: number (%); Kruskal–Wallis for continuous variables; (*) Marked effects are significant at $p<0.05$; ‡ *Chi*-square test (McNemar or Yates *chi*-square) or Fisher's exact test; LAR: Low anterior resection; DRM: Distal resection margin; pTis: Pathological tumor *in situ*.

Table 4 – ***Univariate analysis of the predictive factors for distal resection margin. Logistic regression***

Logistic regression Distal resection margin *vs.*	*p*-value	Exp (B) OR	95% CI for Exp (B)	
			Lower	*Upper*
Procedure (Hartmann *vs.* LAR)	.016*	4.094	1.304	7.849
cT2 *vs.* cT1	.998	.002	.001	1.008
cT3 *vs.* cT1	.414	.404	.046	3.553
cT4 *vs.* cT1	.65	.583	.057	5.998
cN1 *vs.* cN0	.924	.889	.079	10.041
cN2 *vs.* cN0	.015*	3.457	2.568	8.978
cN+ *vs.* cN0	.978	.754	.003	9.863
Neoadjuvant treatment (No *vs.* Yes)	.277	1.76	.635	4.885
Neoadjuvant chemotherapy (No *vs.* Yes)	.024*	3.279	1.173	9.169
pTis *vs.* pT0	.991	1.004	.574	6.812
pT1 *vs.* pT0	.989	1.161	.473	5.669
pT2 *vs.* pT0	.988	1.109	.139	4.112
pT3 *vs.* pT0	.977	1.628	.133	3.527
pT4 *vs.* pT0	.982	1.795	.605	2.26
pN1 *vs.* pN0	.659	1.363	.344	5.403
pN2 *vs.* pN0	.032*	3.817	1.125	6.951
Interval: neoadjuvant therapy – surgical sequence	.301	1.007	.994	1.02

OR: Odds ratio; CI: Confidence interval; LAR: Low anterior resection; pTis: Pathological tumor *in situ*; (*) Marked effects are significant at $p<0.05$.

Table 5 – ***Multivariate analysis of the predictive factors for distal resection margin. Logistic regression***

Logistic regression Distal resection margin *vs.*	*p*-value	Exp (B) OR	95% CI for Exp (B)	
			Lower	*Upper*
Procedure (Hartmann *vs.* LAR)	.026*	3.258	1.925	9.473
cN1 *vs.* cN0	.522	.436	.034	5.535
cN2 *vs.* cN0	.721	1.497	.163	13.755
cN+ *vs.* cN0	.982	.189	0	5.024
Neoadjuvant chemotherapy (No *vs.* Yes)	.012*	4.593	1.398	7.097
pN1 *vs.* pN0	.448	1.737	.417	7.237
pN2 *vs.* pN0	.036*	3.873	1.196	5.545

OR: Odds ratio; CI: Confidence interval; LAR: Low anterior resection; (*) Marked effects are significant at $p<0.05$.

Assessment of the circumferential resection margin

The CRM had significant association with the type of surgery, clinical and pathological tumor and lymph node staging, presence of neoadjuvant treatment and its association with chemotherapy. Moreover, the interval between the end of neoadjuvant treatment and the surgical

sequence showed significant differences in relationship with CRM (<1 mm *versus* ≥1 mm) (Table 6).

In univariate analysis, Hartmann procedure and APE had significantly higher risks of positive CRM as compared to LAR, as well as advanced cN and pN staging, and the interval between neoadjuvant therapy and surgery (Table 7).

The multiple regression analysis demonstrated that the clinico-pathological characteristics with a high predictive potential for CRM are pN staging and the neoadjuvant therapy – surgical treatment interval (Table 8).

Table 6 – ***Clinical, pathological and therapeutic characteristics related to circumferential resection margin***

Variable	APE (*n*=185)		Hartmann's procedure (*n*=144)		LAR (*n*=169)		*p*-value
	CRM ≥1 mm 148 (80)	*CRM <1 mm 37 (20)*	*CRM ≥1 mm 118 (81.9)*	*CRM <1 mm 26 (18.1)*	*CRM ≥1 mm 168 (99.4)*	*CRM <1 mm 1 (0.6)*	*<<0.001**
Clinical T stage	*p*=0.02191*		*p*=0.149		*p*=0.8877		0.0001*
cT1	1 (0.5)	–	4 (2.8)	–	4 (2.4)	–	0.9981
cT2	18 (9.7)	1 (0.5)	5 (3.5)	–	28 (16.6)	–	0.3591
cT3	101 (54.6)	21 (11.4)	81 (56.3)	16 (11.1)	122 (72.2)	1 (0.6)	0.00003*
cT4	28 (15.1)	15 (8.1)	28 (19.4)	10 (6.9)	14 (8.3)	–	0.0064*
Clinical N stage	*p*=0.0943		*p*=0.0058*		*p*=0.0297*		0.00041*
cN0	20 (10.8)	1 (0.5)	21 (14.6)	–	28 (16.6)	–	0.2949
cN1	59 (31.9)	12 (6.5)	36 (25)	8 (5.6)	66 (39.1)	–	0.00154*
cN2	69 (37.3)	24 (13)	61 (42.4)	17 (11.8)	74 (43.8)	1 (0.6)	0.00006*
cN+	–	–	–	1 (0.7)	–	–	–
Radiotherapy	*p*=0.5218		*p*=0.5528		*p*=0.1692		<<0.001*
No	48 (25.9)	10 (5.4)	71 (49.3)	14 (9.7)	65 (38.5)	1 (0.6)	0.00129*
Yes	100 (54.1)	27 (14.6)	47 (32.6)	12 (8.3)	103 (60.9)	–	<<0.001*
Chemotherapy	*p*=0.8828		*p*=0.1034		*p*=0.2648		<<0.001*
No	70 (37.8)	17 (9.2)	87 (60.4)	15 (10.4)	90 (53.3)	1 (0.6)	0.00036*
Yes	78 (42.2)	20 (10.8)	31 (21.5)	11 (7.6)	78 (46.2)	–	0.00003*
Pathological T stage	*p*=0.00106*		*p*=0.00348*		*p*=0.0703		0.0319*
pT0	6 (3.2)	–	1 (0.7)	–	11 (6.5)	–	0.9897
pTis	3 (1.6)	–	2 (1.4)	–	3 (1.8)	–	0.9981
pT1	5 (2.7)	–	3 (2.1)	–	8 (4.7)	–	0.9982
pT2	50 (27)	3 (1.6)	13 (9)	–	47 (27.8)	–	0.0763
pT3	72 (38.9)	29 (15.7)	81 (56.3)	17 (11.8)	91 (53.8)	–	<<0.001*
pT4	12 (6.5)	5 (2.7)	18 (12.5)	9 (6.3)	8 (4.7)	1 (0.6)	0.3857
Pathological N stage	*p*=0.00013*		*p*=0.1682		*p*=0.1258		<<0.001*
pN0	93 (50.3)	9 (4.9)	50 (34.7)	6 (4.2)	120 (71)	–	0.00014*
pN1	35 (18.9)	19 (10.3)	36 (25)	11 (7.6)	32 (18.9)	1 (0.6)	0.00259*
pN2	20 (10.8)	9 (4.9)	32 (22.2)	9 (6.3)	16 (9.5)	–	0.01025*
Interval [days]† neoadjuvant therapy – surgical sequence	*p*=0.0093*		*p*=0.041*		*p*=0.0874		
	77.5±20.1	95.9±41.5	79.5±33.3	108.2±81.3	77.3±17.6	79.2±19.5	0.0004*

† Continuous variables were expressed as: mean ± standard deviation, categorical variables: number (%); Student's *t*-test or Wilcoxon rank-sum tests for continuous variables; (*) Marked effects are significant at $p<0.05$; ‡ *Chi*-square test (McNemar *chi*-square) or Fisher's exact test; APE: Abdominoperineal excision; LAR: Low anterior resection; CRM: Circumferential resection margin; pTis: Pathological tumor *in situ*.

Table 7 – ***Univariate analysis of the predictive factors for circumferential resection margin. Logistic regression***

Logistic regression Circumferential resection margin *vs.*	*p*-value	Exp (B) OR	95% CI for Exp (B)	
			Lower	*Upper*
Procedure (Hartmann *vs.* LAR)	0*	4	3.692	9.883
Procedure (APE *vs.* LAR)	0*	7.017	4.954	11.58
cT2 *vs.* cT1	.979	4.13	.675	11.165
cT3 *vs.* cT1	.989	5.1	.193	10.229
cT4 *vs.* cT1	.987	7.4	.694	12.414
cN1 *vs.* cN0	.04*	8.454	3.098	12.099
cN2 *vs.* cN0	.012*	13.254	4.77	19.257
cN+ *vs.* cN0	.988	.738	0.51	8.289
Neoadjuvant treatment (No *vs.* Yes)	.614	1.148	.671	1.964
Neoadjuvant chemotherapy (No *vs.* Yes)	.421	1.241	.733	2.099
pTis *vs.* pT0	.987	.006	.001	1.009
pT1 *vs.* pT0	.991	.002	.001	1.024
pT2 *vs.* pT0	.986	.025	.008	2.09
pT3 *vs.* pT0	.998	.329	.155	1.063
pT4 *vs.* pT0	.998	.315	.287	2.637
pN1 *vs.* pN0	0*	4.433	2.24	7.774
pN2 *vs.* pN0	.001*	3.631	1.684	6.832
Interval: neoadjuvant therapy – surgical sequence	.001*	2.019	1.208	3.03

OR: Odds ratio; CI: Confidence interval; LAR: Low anterior resection; APE: Abdominoperineal excision; pTis: Pathological tumor *in situ*; (*) Marked effects are significant at $p<0.05$.

Table 8 – ***Multivariate analysis of the predictive factors for circumferential resection margin. Logistic regression***

Logistic regression Circumferential resection margin *vs.*	*p*-value	Exp (B) OR	95% CI for Exp (B)	
			Lower	*Upper*
Procedure (Hartmann *vs.* LAR)	.996	.217	.020	8.780
Procedure (APE *vs.* LAR)	.996	.257	.041	5.961
cN1 *vs.* cN0	.998	.796	.053	2.903
cN2 *vs.* cN0	.998	.289	.002	2.988
pN1 *vs.* pN0	.002*	4.091	1.697	9.861
pN2 *vs.* pN0	.032*	2.871	1.99	8.327
Interval: neoadjuvant therapy – surgical sequence	.004*	1.918	1.006	2.031

OR: Odds ratio; CI: Confidence interval; LAR: Low anterior resection; APE: Abdominoperineal excision; (*) Marked effects are significant at $p<0.05$.

Assessment of the mesorectal dissection

The quality of the mesorectal dissection had a significant link to the type of surgical intervention and the clinical and pathological staging (Table 9). This is based on the large number of cases with Hartmann's operation (compared to APR and LAR) or cases staged cT3 as well as cN2 and pT3, with an inadequate mesorectum on macroscopic evaluation (namely more frequent grade 1 and grade 2 specimens). In cases with Hartmann's operation and neoadjuvant treatment, there were significantly more G1 type specimens (10.2%), in comparison with APE (3.9%) and LAR (1%). Regarding the quality of mesorectal dissection, we noted a significant correlation with pT stage, pN stage and the type of surgical procedure. Thus, pT3/pT4, and pN1/pN2 were more frequently identified in patients with APE or Hartmann's operation (Table 9). The time interval between the two therapeutic sequences had an impact on the quality of the mesorectum.

In multivariate analysis (Table 10), the study results showed that in patients with neoadjuvant therapy, the type of surgery, cT and pT staging are predictive factors for the outcome of the mesorectum. On the other hand, patients without neoadjuvant treatment had the type of surgery as single predictive factor for the mesorectum (odds ratio – OR=2.54, p=0.021).

Table 9 – ***Clinical, pathological and therapeutic characteristics related to the quality of the mesorectal dissection***

Variable	APE (*n*=185)			Hartmann's procedure (*n*=144)			LAR (*n*=169)			*p*-value
	G1	*G2*	*G3*	*G1*	*G2*	*G3*	*G1*	*G2*	*G3*	
	6 (3.2)	*40 (21.6)*	*139 (75.1)*	*7 (4.9)*	*27 (18.8)*	*110 (76.4)*	*1 (0.6)*	*9 (5.3)*	*159 (94.1)*	*<<0.01**
Clinical T stage		*p*=0.2537			*p*=0.1009			*p*=0.5177		0.0083*
cT1	–	–	1 (0.5)	–	1 (0.7)	3 (2.1)	–	–	4 (2.4)	0.5605
cT2	1 (0.5)	1 (0.5)	17 (9.7)	–	–	5 (3.5)	–	2 (1.2)	26 (15.4)	0.6034
cT3	2 (1.1)	30 (16.2)	90 (48.6)	3 (2.1)	18 (12.5)	76 (52.8)	1 (0.6)	5 (3)	117 (69.2)	0.0001
cT4	3 (1.6)	9 (4.8)	31 (16.7)	4 (2.8)	8 (5.6)	26 (18.1)	–	2 (1.2)	12 (7.1)	0.5206
Clinical N stage		*p*=0.087			*p*=0.2362			*p*=0.3026		0.0328*
cN0	–	3 (1.6)	18 (9.7)	–	2 (1.4)	19 (13.2)	–	1 (0.6)	27 (16)	0.1858
cN1	–	20 (10.8)	51 (27.6)	3 (2.1)	8 (12.5)	33 (22.9)	–	3 (1.8)	63 (37.3)	0.0005*
cN2	6 (3.2)	17 (9.1)	70 (37.8)	4 (2.8)	17 (11.8)	57 (39.6)	1 (0.6)	5 (3)	69 (40.8)	0.0165*
cN+	–	–	–	–	–	1 (0.7)	–	–	–	–
Neoadjuvant treatment		*p*=0.7029			*p*=0.0273*			*p*=0.3641		0.00002*
No	1 (0.5)	13 (7)	44 (23.8)	1 (0.7)	14 (9.7)	70 (48.6)	–	5 (3)	61 (36.1)	0.0112*
Yes	5 (2.7)	27 (14.6)	95 (51.4)	6 (4.2)	13 (9)	40 (27.8)	1 (0.6)	4 (2.4)	98 (58)	0.0003*
Neoadjuvant chemotherapy		*p*=0.7377			*p*=0.04286			*p*=0.2883		0.00002*
No	2 (1.1)	20 (10.8)	65 (35.1)	2 (1.4)	18 (12.5)	82 (56.9)	1 (0.6)	6 (3.6)	84 (49.7)	0.0252*
Yes	4 (2.2)	20 (10.8)	74 (40)	5 (3.4)	9 (6.3)	75 (52.1)	–	3 (1.8)	75 (44.4)	0.00126*
pT stage		*p*=0.2397			*p*=0.00317*			*p*=0.8584		0.00002*
pT0	–	1 (0.5)	5 (2.7)	1 (0.7)	–	–	–	–	11 (6.5)	0.00049*
pTis	–	–	3 (1.6)	–	–	2 (1.4)	–	–	3 (1.8)	0.9981
pT1	–	2 (1.1)	3 (1.6)	–	–	3 (2.1)	–	1 (0.6)	7 (4.1)	0.321
pT2	1 (0.5)	7 (3.8)	45 (24.3)	–	–	13 (9)	–	4 (2.4)	43 (25.4)	0.286
pT3	5 (2.7)	28 (15.1)	68 (36.8)	4 (2.8)	22 (15.3)	72 (50)	1 (0.6)	3 (1.8)	87 (51.5)	0.00006*
pT4	–	2 (1.1)	15 (8.1)	2 (1.4)	5 (3.4)	20 (13.9)	–	1 (0.6)	8 (4.7)	0.4823
pN stage		*p*=0.0199*			*p*=0.7681			*p*=0.8799		0.00003
pN0	4 (2.2)	16 (8.6)	82 (44.3)	3 (2.1)	9 (6.3)	44 (30.6)	1 (0.6)	7 (4.1)	112 (66.3)	0.0043*
pN1	–	19 (10.3)	35 (19)	3 (2.1)	9 (6.3)	35 (24.3)	–	1 (0.6)	32 (18.9)	0.0015*
pN2	2 (1.1)	5 (2.7)	22 (11.9)	1 (0.7)	9 (6.3)	31 (21.5)	–	1 (0.6)	15 (8.9)	0.3432
Interval [days]† neoadjuvant therapy – surgical sequence		*p*=0.4649			*p*=0.0058*			*p*=0.0023*		0.0067*
	74.4±9.4	85±36.1	80.7±24.6	115.5±21.2	87±33.2	80.1±31.3	102±11.2	79±16.4	77.1±17.7	0.0238*

† Continuous variables were expressed as: mean ± standard deviation, categorical variables: number (%); Student's t-test or Wilcoxon rank-sum tests for continuous variables; (*) Marked effects are significant at $p<0.05$; ‡ *Chi*-square test (McNemar *chi*-square) or Fisher's exact test; APE: Abdominoperineal excision; LAR: Low anterior resection; pT: Pathological T stage; pTis: Pathological tumor *in situ*; pN: Pathological N stage; G1: Muscularis propria/intrasphincteric plane; G2: Intramesorectal/sphincteric plane; G3: Mesorectal/extra-levator plane.

Table 10 – ***Multivariate analysis of the predictive factors for quality of the mesorectal dissection. Nominal regression***

Radiotherapy (Yes) Nominal regression Quality of the mesorectal dissection *vs.*	*p*-value	Exp (B) OR	95% CI for Exp (B)	
			Lower	*Upper*
Procedure (Hartmann *vs.* LAR)	0*	2.468	1.306	4.716
Procedure (APE *vs.* LAR)	.197	1.633	0.316	2.269
cT	.043*	1.87	1.021	3.424
cN	.851	.984	.832	1.164
pT	.429	1.12	.846	1.482
pN	.039*	2.928	1.861	4.08
Interval: neoadjuvant therapy – surgical sequence	.052	1.012	1	1.025
Radiotherapy (No) Nominal regression Quality of the mesorectal dissection *vs.*	***p*-value**	**Exp (B) OR**	**95% CI for Exp (B)**	
			Lower	***Upper***
Procedure (Hartmann *vs.* LAR)	.021*	2.547	1.328	4.913
Procedure (APE *vs.* LAR)	.306	0.329	0.039	2.773
cT	.644	1.056	.837	1.333
cN	.049	.876	.769	.999
pT	.396	1.222	.769	1.943
pN	.065	.915	.833	1.005
Interval: neoadjuvant therapy – surgical sequence	.996	.001	.002	5.304

OR: Odds ratio; CI: Confidence interval; LAR: Low anterior resection; APE: Abdominoperineal excision; (*) Marked effects are significant at $p<0.05$.

Discussions

The anatomy of the rectum dictates a particular clinical evolution of the rectal neoplasia. Thus, it is important to take note of the mesorectum as an important organ that not only hosts the vascular, lymphatic and nerve supply to the rectum, but it also has particular anatomic relations to surrounding organs. If we look at its superior limits, we see a layer of visceral peritoneum covering the anterior and partially the lateral mesorectum. The mesorectal fascia surrounds and fixes the conjunctive tissue that constitutes this organ; its fibers fuse with Denonvilliers' fascia anteriorly, as well as with elastic fibers beneath the peritoneum; it holds together a mass that is significantly larger posteriorly and reduces in size at the anterior aspect, making for a difficult dissection in this area especially [7].

The dissection of the surgical specimen should follow the so-called "holy plane", as described by Heald *et al.*, in 1982 [12]. The surgeon must rely on sharp circumferential dissection that will produce a high-quality specimen that respects the mesorectal fascia – it will remain on the specimen as a shiny layer and comprises the CRM. When talking about a "sphincter-saving" procedure, a DRM is documented. According to version 3.2017 of the NCCN guidelines, a positive CRM is when tumor residue (primary tumor or positive lymph nodes) is found at less than 1 mm from the CRM; moreover, a positive DRM is defined as involvement of the rectal wall at less than 1 cm from the tumor [11].

The findings in our study related to the DRM compared Hartmann's operation to LAR and identified a significantly higher risk of positive DRM when performing the former (OR=3.258, p=0.026). This may be because Hartmann's procedure is done more frequently in lower tumors than LAR. In addition, chemotherapy associated within the neoadjuvant treatment plan showed to be a beneficial factor, resulting in 4.593 times less DRM involvement in patients with neoadjuvant chemotherapy. Pathological lymph node involvement showed to be a risk factor for positive DRM (OR=3.873, p=0.036), which may be explained by the higher tumor aggressiveness and invasive potential in these stages. In contrast to CRM, DRM positivity is not influenced by the interval between neoadjuvant treatment and the surgical procedure.

Total mesorectal excision was a major improvement to the technique: the rates of local recurrence and survival have been substantially improved and this technique was validated initially by single-centre series [13, 14], followed by multicentre population studies and clinical trials [15–17]. The importance that the concept of total mesorectal excision has had in the treatment of rectal cancer is, thus, evident and is sustained by a drop in the CRM positivity rate from 30% to 8% [3, 18].

Bearing in mind that an adequate CRM is at a minimal distance of 1 mm from the tumor, in locally advanced rectal cancer, the surgeon is faced with the therapeutic decision that will guide the outcome of the patient: either an extensive resection, that involves en bloc removal of extra-fascial tissue or organs, or neoadjuvant chemoradiation therapy, aiming for a downstaging and downsizing of the tumor to an operable state. Thus, pretherapeutic staging is of crucial importance, as it will guide the decision; this is the domain in which radiologists play an important part, because staging is performed through endorectal ultrasound (for smaller tumors) and pelvic MRI (for large and advanced tumors), that will enable the radiologist to appreciate the CRM [19].

The surgical treatment is the main curative solution in rectal cancer treatment. Depending on the location of the tumor, there are different options that can be taken – the main difference is the preservation of the anal sphincter: LAR with total mesorectal excision *versus* APE; the former means the extraction of the rectum with the tumor, together with its mesorectum, followed by an anastomosis; the latter implies the extraction of the rectum and mesorectum, together with the anal sphincter and *levator ani* muscle (most frequently) [11, 20]. Decision upon the sphincter-preserving procedure will be taken in the cases when a DRM of at least 1 cm can be obtained without affecting the anal sphincter [11, 20].

There is wide variation in the frequency of the APE, which has been considered by some unacceptably high [21]. This is the reason why the rate of the APE may be considered by some a marker for the quality of surgery. However, the rates of APE *versus* LAR depend widely on the location of the tumor, the efficacy of the neoadjuvant treatment, as well as the stage in which the patient is diagnosed. This discussion is held not only for quality of life reasons, but also because of the recognized poorer outcomes for patients with APE as compared to LAR [22, 23]. However, the extra-levator APE as

compared to standard APE was demonstrated to remove more tissue around the tumor, with a reduction in CRM involvement from 50% to 20% and intraoperative perforations from 28% to 8%. Moreover, performing the perineal sequence in prone position, offers better visualization and lowers the risk of CRM involvement and perforation [24].

Our results confirmed the reported data – a rate of CRM positivity of 20% in APE, that is somewhat satisfactory, but is still very high compared to the rate of CRM positivity in LAR that is as low as 0.6%. Moreover, APE has a 7.017 times higher risk to yield positive CRM compared to LAR ($p<<0.001$). In addition, Hartmann's operation has similar results when compared to LAR. This aspect may be explained by the instance in which these interventions are selected, namely locally advanced mid and low rectal cancers that are more aggressive and have higher invasion rates compared to mid rectal neoplasia.

In our study, CRM is also highly dependent on the pathological lymph node staging, with OR of 4.091 and 2.871, respectively for pN1 and pN2. These results can be justified by the fact that lymph nodes and tumor deposits are the closest to the CRM and so the most susceptible to be reached by the plane of dissection.

In addition, time between the end of neoadjuvant treatment and the surgical sequence plays a major role in the CRM quality, because of the fibrosis that takes place after exceeding the optimal interval for surgery. Fibrosis makes surgical dissection more difficult and may lead to positive circular margins, on the one hand, or nerve damage on the other hand [12]. Thus, we can say that a longer interval is not a risk factor for DRM involvement, or even for switching from LAR to APE; however, dissection is more difficult and prone to error along the CRM in these patients.

If CRM and DRM are clearly quantifiable by measurement, the aspect of the mesorectum as a whole, which gives information on the quality of surgery, is more of a subjective feature. This is why Quirke *et al.* imagined a three-point grading system for LAR and APE in part, which was initially developed for the MRC CLASICC trial [9, 25] and has subsequently been demonstrated, both through small series [26, 27], as well as larger multicentre studies [3, 28], to predict local recurrence and patient survival.

We demonstrated that the quality of mesorectal excision is better in APE, depending mostly on the use of neoadjuvant treatment (p=0.00002). We have shown that the grading of the resection specimen based on the aspect of the mesorectum is firstly influenced by the type of surgical procedure that is applied, with significant differences between Hartmann's and LAR regarding the risk (OR of 2.468 and 2.547, respectively).

The role of pathologist is utmost important for offering information to surgeon about the quality of resection, thus giving crucial prognostic data in addition to staging ones. Therefore, an attentive dissection of the surgical specimen followed by a meticulous histopathology report plays a critical part in the outcome of the patient.

The main limits of our study consist of lack of follow up data regarding the patients taken into study, as well as lack of operator-oriented analysis regarding pathological results. We stressed the fact that rectal cancer treatment is standardized in our Clinic, so this bias may be overcome. However, examiner-dependant bias for the pathological specimen (however small, considering standardization in the Department of Pathology, as well) may have been possible, aspect that cannot be overcome.

Conclusions

Overall, this study has reached its aim and found significant correlations between DRM, CRM, macroscopic mesorectal aspect and surgical approach, clinical/pathological tumor staging and neoadjuvant treatment options in patients with mid and low rectal cancer with curative treatment. The surgical intervention, including its optimal timing, is an important factor that influences the pathological aspects of the surgical specimen.

Conflict of interest

The authors declare no conflict of interest.

References

[1] ***. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. World Health Organization (WHO), International Agency for Research on Cancer (IARC), Lyon, France, 2012, Available from: http://globocan.iarc.fr/Default.aspx.

[2] Whitehouse M. A policy framework for commissioning cancer services. BMJ, 1995, 310(6992):1425–1426.

[3] Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, O'Callaghan C, Myint AS, Bessell E, Thompson LC, Parmar M, Stephens RJ, Sebag-Montefiore D; MRC CR07/NCIC-CTG CO16 Trial Investigators; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet, 2009, 373(9666): 821–828.

[4] 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):894–899.

[5] Anugestad K, Crawshaw B, Delaney C. Cancer of the rectum: operative management. In: Fazio VW, Church JM, Delaney CP, Kiran RP (eds). Current therapy in colon and rectal surgery. 3rd edition, Elsevier, Philadelphia, 2017, 141–145.

[6] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR (eds). AJCC Cancer Staging Manual. 8th edition, American Joint Committee on Cancer (JCC), American College of Surgeons (ACS), Springer International Publishing, Switzerland, 2017.

[7] West NP, Quirke P. Quality of surgery. In: Baatrup G (ed). Multidisciplinary treatment of colorectal cancer. Springer International Publishing, Switzerland, 2015, 227–242.

[8] Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds). AJCC Cancer Staging Manual. 7th edition, Springer, New York, 2010, 143–159.

[9] Quirke P, Palmer T, Hutchins G, West NP. Pathology assessment. In: Moran B, Heald RJ (eds). Manual of total mesorectal excision. CRC Press, 2013, 191–202.

[10] National Comprehensive Cancer Network (NCCN). NCCN Guidelines version 1.2018 – Rectal cancer 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.

[11] Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D; ESMO Guidelines Committee. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2017, 28(Suppl_4):*iv*22–*iv*40.

[12] Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? Br J Surg, 1982, 69(10):613–616.
[13] Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet, 1986, 1(8496): 1479–1482.
[14] Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg, 1995, 181(4):335–346.
[15] Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet, 2000, 356(9224): 93–96.
[16] Kapiteijn E, Putter H, van de Velde CJ; Cooperative investigators of the Dutch ColoRectal Cancer Group. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. Br J Surg, 2002, 89(9):1142–1149.
[17] Wibe A, Møller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, Langmark F, Myrvold HE, Søreide O; Norwegian Rectal Cancer Group. A national strategic change in treatment policy for rectal cancer – implementation of total mesorectal excision as routine treatment in Norway. A national audit. Dis Colon Rectum, 2002, 45(7):857–866.
[18] Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet, 1986, 2(8514):996–999.
[19] Purkayastha S, Tekkis PP, Athanasiou T, Tilney HS, Darzi AW, Heriot AG. Diagnostic precision of magnetic resonance imaging for preoperative prediction of the circumferential margin involvement in patients with rectal cancer. Colorectal Dis, 2007, 9(5):402–411.
[20] Augestad K, Cranshaw B, Delaney C. Cancer of the rectum: operative management. In: Fazio VW, Church JM, Delaney CP, Kiran RP (eds). Current therapy in colon and rectal surgery. 3rd edition, Elsevier, Philadelphia, 2017, 146–151.
[21] Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? Gut, 2008, 57(12): 1690–1697.
[22] Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Søreide O; Norwegian Rectal Cancer Group. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior *vs.* abdominoperineal resection. Dis Colon Rectum, 2004, 47(1):48–58.
[23] Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P; Dutch Colorectal Cancer Group; Pathology Review Committee. Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol, 2005, 23(36): 9257–9264.
[24] West NP, Anderin C, Smith KJ, Holm T, Quirke P; European Extralevator Abdominoperineal Excision Study Group. Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. Br J Surg, 2010, 97(4):588–599.
[25] Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM; MRC CLASICC Trial Group. Short-term endpoints of conventional *versus* laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC Trial): multicentre, randomised controlled trial. Lancet, 2005, 365(9472):1718–1726.
[26] Maslekar S, Sharma A, Macdonald A, Gunn J, Monson JR, Hartley JE. Mesorectal grades predict recurrences after curative resection for rectal cancer. Dis Colon Rectum, 2007, 50(2): 168–175.
[27] García-Granero E, Faiz O, Muñoz E, Flor B, Navarro S, Faus C, García-Botello SA, Lledó S, Cervantes A. Macroscopic assessment of mesorectal excision in rectal cancer: a useful tool for improving quality control in a multidisciplinary team. Cancer, 2009, 115(15):3400–3411.
[28] Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH; Cooperative Clinical Investigators of the Dutch Colorectal Cancer Group. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol, 2002, 20(7): 1729–1734.

Corresponding author
Dragoş-Viorel Scripcariu, MD, 1st Surgical Oncology Unit, Regional Institute of Oncology, 2–4 General Henry Mathias Berthelot Street, 700483 Iaşi, Romania; Phone +40723–913 425, e-mail: dscripcariu@gmail.com

Received: March 30, 2018

Accepted: June 19, 2018