

## Histopathological findings regarding oncological feasibility of laparoscopic versus open approach for rectal cancer: a retrospective study

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### Abstract

Worldwide, colorectal cancer is one of the most prevalent malignancies. Due to oncological safety concerns, data regarding the laparoscopic surgical treatment of rectal cancer is scarce. Our study's main aim was investigate the oncological adequacy of laparoscopic surgery in the treatment of rectal cancer by comparing its oncological reliability with the oncological results obtained after open surgery for rectal cancer. In this retrospective study, 80 patients who underwent surgery for rectal cancer, admitted in our Clinic between January 1, 2014–November 31, 2015 were enrolled. The studied group was stratified according to the way of approach chosen: classic surgery (59 cases) and laparoscopic surgery (21 cases), respectively. Based on the histopathological examination, we analyzed the histological grading of rectal neoplasms, TNM staging, resection margins, lymphovascular and perineural invasion and the number of regional lymph nodes identified in the perirectal adipose tissue. The average number of isolated lymph nodes demonstrated non-significant differences between the two types of approaches: 20 lymph nodes in the classical approach versus 18 lymph nodes in the laparoscopic approach ( $p=0.109$ ). Lymph nodes affected by metastases were associated in the majority of cases with stage IIIB and stage IIIC rectal cancers (100% and 83.3%, respectively). The laparoscopic approach proved to be efficient in terms of reaching oncological resection limits. On the resection specimens extracted by laparoscopic surgery, the residual tumor (R1) was encountered in 5% of the cases versus in 6.7% of the cases after classic surgery. The laparoscopic approach is oncologically feasible in the rectal cancer surgical treatment.

**Keywords:** rectal cancer, laparoscopy, classic approach, lymph nodes, resection limits, tumor grade.

### Introduction

Colorectal cancer is one of the most prevalent malignancies worldwide, in the US being the third cause of death by cancer irrespectively of gender. Among colorectal cancers, rectal cancer counts approximately one third of these cases. In patients with colon cancer, laparoscopic surgery has proven its feasibility [1, 2]. In the past years, laparoscopic surgery has increased as a surgical choice of treatment for patients undergoing surgery for colonic cancer, thus slowly replacing open colonic surgery. The reason for this is attributed to a better perioperative evolution, considerably less blood loss, diminished postoperative pain, a faster recovery period and a shorter hospitalization.

The introduction of total mesorectal excision along with preoperative chemotherapy and radiotherapy demonstrated a positive impact on the survival rates in patients with rectal cancer. However, open surgery is associated with a longer recovery time, an increased surgical stress for the patient and may be associated with both short-term complications (such as surgical site infections) and long-term complications (e.g., postoperative hernias) [3].

Data regarding patients undergoing laparoscopic surgery

for rectal cancer is scarce. The main reason for this is the concern for oncological safety.

The equivalency regarding the oncological completion after laparoscopic surgery for rectal cancer is yet to be proven.

Through the present study, we aim to investigate the oncological feasibility of laparoscopy in the treatment of rectal cancer by comparing its oncological reliability with oncological result of classical approach treatment for rectal cancer.

### Patients, Materials and Methods

We enrolled 80 patients undergoing surgery for rectal cancer, admitted in our Clinic between January 1, 2014–November 31, 2015.

The studied cohort was divided according to the approach chosen [classic surgery (59 cases) laparoscopic surgery (21 cases), respectively] and analyzed accordingly. In 37.5% of cases, the type of operation was abdominal perineal rectal amputation, respectively in the rest of the cases (62.5%) anterior rectal resection.

The studied group baseline characteristics are presented in Table 1.

**Table 1 – Studied group baseline characteristics**

Male gender [%] <sup>a</sup>	54 (67.5%)
Age [years] <sup>b</sup>	65.7±9.7
Laparoscopic approach [%] <sup>a</sup>	21 (26.2%)
Classical approach [%] <sup>a</sup>	59 (73.8%)
Abdominal perineal rectal amputation [%] <sup>a</sup>	30 (37.5%)
Anterior rectal resection [%] <sup>a</sup>	50 (62.5%)

<sup>a</sup>Values are presented as number of individuals and (percentage from total); <sup>b</sup>Continuous variables with Gaussian distribution. Values are presented as average ± standard deviation.

Based on the paraffin histopathological examination, we studied the histological grading of rectal neoplasms, TNM staging, resection margins, lymphovascular and perineural invasion and the number of regional lymph nodes identified in the perirectal adipose tissue. For tumor staging, we used the protocol recommended by the *American Joint Committee on Cancer (AJCC)* and *International Union against Cancer (UICC)* TNM, 6<sup>th</sup> edition.

We considered a minimum number of 10 lymph nodes necessary for an accurate staging. Starting from the premise that a large number of lymph nodes without metastases represent a positive prognostic factor, especially in IIIB and IIIC stages, we wanted to see what was the proportion of non-tumoral, respectively tumoral nodules from the total number of isolated lymph nodes.

Data were collected and analyzed using the SPSS ver. 17 software suite (SPSS Inc., Chicago, IL, USA) and are presented as mean ± standard deviations for continuous variables with Gaussian distribution, median (interquartile range) for continuous variables without Gaussian distribution, or percentages for categorical variables.

To assess the significance of the differences between groups, the Student's *t*-test (means, Gaussian populations), Mann-Whitney *U*-test (medians, non-Gaussian populations) and Fisher's exact (proportions) tests were used. Continuous variable distributions were tested for normality using D'Agostino and Pearson's test, and for equality of variances using Levene's test. The statistical significance for odds ratio (OR) was calculated according to the mid-P method for binomial distributions.

## Results

We found no significant association between the type of operation and the approach: for abdominal perineal rectal amputation, the laparoscopic approach was chosen in 23.3% of cases while for anterior rectal resection, the laparoscopic surgery was performed in 28% of cases ( $p=0.794$ ).

The demographic for the studied group consisted mostly (67.5%) of male gender patients with ages over 65 years (65.7±9.7 years). We considered all surgeries performed for rectal neoplasm. The operations were divided by way of approach (classical or laparoscopic) and depending on the type of surgery: anterior rectal resection or abdominal perineal rectal amputation (Table 1).

A significant trend was found, regarding the association between the histological grading of adenocarcinoma (grade 1 – well differentiated; grade 2 – moderately differentiated; grade 3 – poorly differentiated) and the surgical approach: using the laparoscopic approach, more well differentiated adenocarcinomas (38.1%) were operated

compared to classical approach (11.9%), the proportions being reversed for moderately differentiated adenocarcinomas: 78% of the laparoscopic operations, compared to 52.4% of the classical operations (Table 2; Figures 1 and 2).

**Table 2 – Adenocarcinoma grading according to type of surgical approach**

	Tumor grading			P
	1	2	3	
Classical approach	7 (11.9%)	46 (78%)	6 (10.2%)	0.029
Laparoscopic approach	8 (38.1%)	11 (52.4%)	2 (9.5%)	

Values are presented as number of individuals and (percentage from the total cases for the respective approach).

Patients who underwent laparoscopic surgery were younger (62.4±10.7 years), compared to patients who underwent classic surgery (66.9±9.2 years); however, the differences had no statistical significance ( $p=0.068$ ).

Considering that obtaining a number of 10 or more lymph nodes available for analysis after the surgical operation is a success, we observed no significant differences ( $p=0.717$ ) regarding the success rate between the laparoscopic (success rate: 85.7%) and the classical approach (success rate: 88.1%). The success rate comparison is presented in Table 3.

**Table 3 – Comparison of success rates in the two types of approach**

	≥10 lymph nodes	<10 lymph nodes	P
Classical approach	52 (88.1%)	18 (85.7%)	0.717
Laparoscopic approach	18 (85.7%)	3 (14.3%)	

The non-significant differences between the two types of approaches were also valid regarding the average number of lymph nodes obtained: 20 lymph nodes in the classical approach vs. 18 lymph nodes in the laparoscopic approach ( $p=0.109$ ; Table 4).

**Table 4 – Comparison of the number of lymph nodes according to the type of surgical approach**

	Classical approach	Laparoscopic approach	P
Median lymph nodes obtained	20	18	0.109
Interquartile range	14	14	
Minimum–Maximum	2–54	6–46	

We noted that positive lymph nodes were associated mostly with stages IIIB and IIIC rectal cancers (Table 5; Figure 3).

**Table 5 – Distribution of lymph nodes with metastases**

Tumor stage	0	I	IIIA	IIIB	IIIC
Positive lymph nodes (classic approach)	1	5	1	13	11
Positive lymph nodes (laparoscopic approach)	5	14	0	2	3
Total number of cases with positive lymph nodes (%)	6 (16.6%)	19 (26.3%)	1 (100%)	15 (83.3%)	14 (87.5%)

A series of differences were observed regarding the tumor stages operated by the two approaches: using classical approach were operated tumors in more advanced stages (Table 6).



**Table 6 – The relationship between tumor stage and surgical approach**

Tumor stage	0	I	Ila	Ilb	IIla	IIlb	IIlc
Classical approach (%)	4 (6.8%)	11 (18.6%)	14 (23.7%)	1 (1.7%)	1 (1.7%)	13 (22%)	15 (25.4%)
Laparoscopic approach (%)	2 (9.5%)	8 (38.1%)	3 (14.3%)	0 (0%)	0 (0%)	5 (23.8%)	3 (14.3%)
Total (%)	6 (7.5%)	19 (23.8%)	17 (21.2%)	1 (1.2%)	1 (1.2%)	18 (22.5%)	18 (22.5%)

### Tumor invasion

We observed a significant association between the tumor grade and lymphovascular invasion (small vessel and venous invasion), while the relationship between tumor grade and perineural (Pn) invasion was not significant. In our study, the lymphovascular invasion was identified more frequently moderately and poorly differentiated adenocarcinomas (Table 7; Figure 4).

**Table 7 – The association between tumor grade and tumor invasion**

Tumor grade	1	2	3	P
Lymphovascular invasion	2 (13.3%)	16 (28.1%)	6 (75%)	0.022
Perineural (Pn) invasion	0 (0%)	4 (7%)	1 (12.5%)	0.212

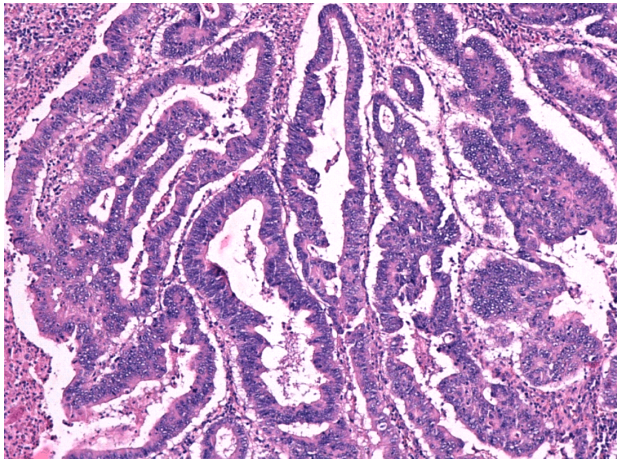
Poorly differentiated adenocarcinoma was a significant risk factor for lymphovascular invasion (OR=9;  $p=0.008$ ), while the increase in the risk for Pn invasion (Figure 5) was not statistically significant (OR=2.4;  $p=0.418$ ).

The laparoscopic approach proved to be efficient in terms of reaching oncological resection limits, without statistical significance, regarding not reaching oncological resection limits (OR=0.737;  $p=0.639$ ). We have to mention that in 15 (18.8%) cases, the resection limits could not be evaluated and thus these cases were excluded from the risk analysis. According to our analysis, a positive resection limit (R1) was encountered in the classical approach in three cases (representing 6.7% of this approach) compared to only one case in the laparoscopic approach (representing 5%) (Table 8).

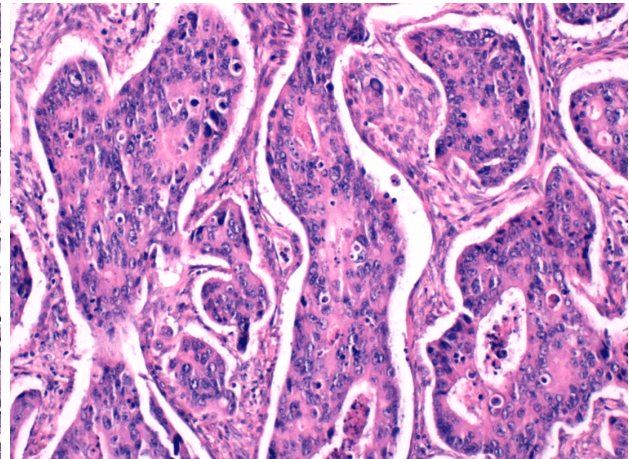
**Table 8 – Comparison of the number of the oncological resection limits according to the type of surgical approach**

	Classical approach	Laparoscopic approach	P
R0	42 (71.1%)	19 (90.4%)	0.639
R1	3 (6.7%)	1 (5%)	
RX	14 (23.7%)	1 (4.7%)	

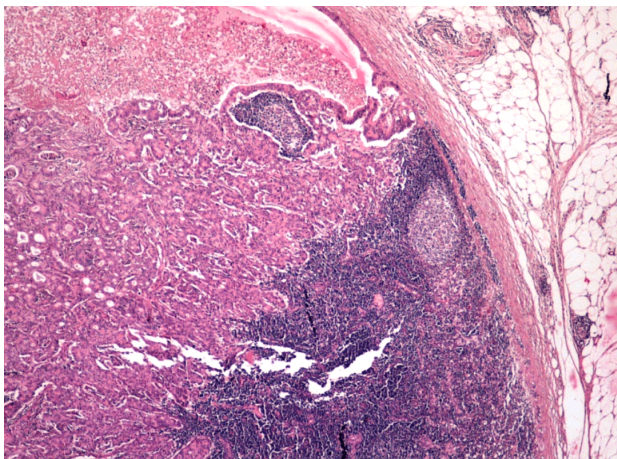
Values are presented as number of individuals and (percentage from the total cases for the respective approach).



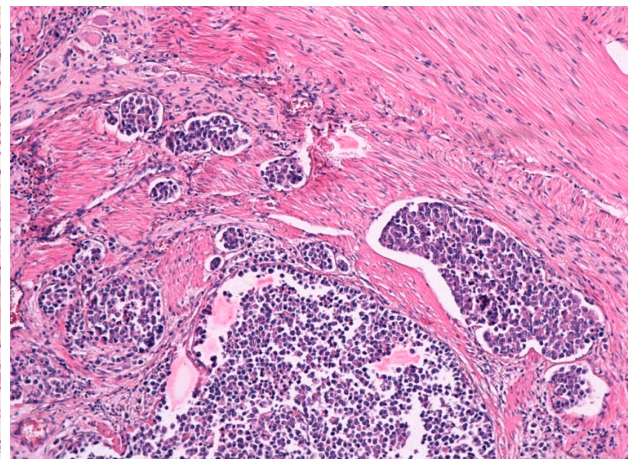
**Figure 1 – Moderately differentiated adenocarcinoma of the rectum: there is still a glandular configuration, but the glands are irregular and very crowded. HE staining,  $\times 100$ .**



**Figure 2 – Poorly differentiated rectal adenocarcinoma: sheets of cells, just a few glandular lumina are visible. HE staining,  $\times 200$ .**

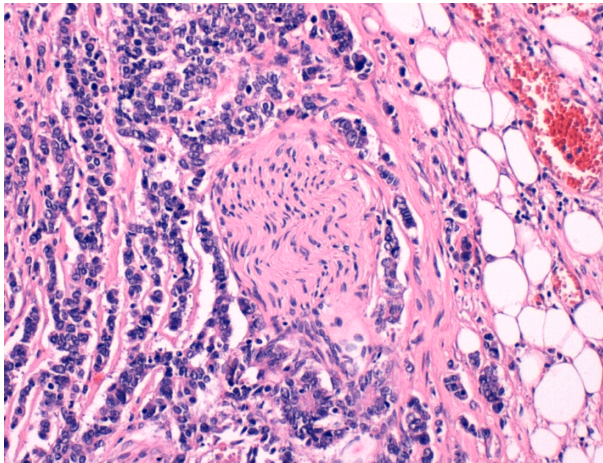


**Figure 3 – Lymph node metastases from rectal adenocarcinoma. HE staining,  $\times 100$ .**



**Figure 4 – Lymphovascular invasion in a high-grade rectal carcinoma. HE staining,  $\times 100$ .**





**Figure 5** – *Cross-section of a nerve surrounded by neoplastic cells (perineural invasion in a high grade rectal carcinoma). HE staining,  $\times 200$ .*

## Discussion

While analyzing the lymph nodes isolated from the perirectal adipose tissue, we noticed an adequate number of isolated lymph nodes in both classical and laparoscopic approach [4]. Despite the high number of isolated lymph nodes in the classical approach, through the laparoscopic surgery there were enough lymph nodes isolated for an effective tumor staging. Tumoral lymph nodes were found mostly in stages IIIB and IIIC tumors [5, 6].

We also focused on the degree of tumor invasion for both ways of approach, analyzing both lymphovascular (LV) and perineural (Pn) invasion. We considered Pn invasion an adverse prognostic factor. We wanted to investigate if there was any connection between the histological tumor grade and tumor invasion for the selected cohort. Therefore, we noticed a positive association between the invasion, along with the increase of tumor grade. Pn invasion was identified mostly in patients with G3 rectal adenocarcinoma.

In both ways of approach, regardless of the tumor stage, oncological resection limits (R0) were aimed at and obtained, thus making laparoscopic surgery oncologically feasible.

We identified a possible limitation of the study: a possible bias generated by the fact that according to the best-care principle, the more advanced rectal cancers were operated using the open surgery approach, thus the prognostic of these cases may be negatively influenced when compared to the laparoscopic approached cases.

In cases of advanced stage rectal cancers (IIIB, IIIC) from the studied cohort operated through laparoscopic procedure, oncological limits were obtained. We aim at obtaining a comparable number of cases of advanced stage rectal cancers operated by laparoscopic approach, in order to strengthen the role of laparoscopic surgery in rectal neoplasia.

The use of laparoscopic surgery as a method of surgical treatment for patients with colorectal cancer has been a controversial subject. In time, there were many debates aiming to establish whether its use as a routine treatment

for patients with rectal cancer is efficient with regard to attaining oncological resection limits, by extracting an adequate specimen of resection for tumor staging (through isolated satellite lymph nodes). Many argued against the use of laparoscopic surgery in the treatment of rectal cancer, giving counter arguments such as the risk of tumor relapse, as well as anatomical aspects (narrow pelvis, major nerve involvement).

In this regard, the CLASICC trial (a seven-year multi-center, randomized clinical trial following patients with colorectal cancer from 27 UK centers), annulled the use of laparoscopic-assisted anterior resection for cancer of the rectum as a routine choice of treatment for patients with rectal cancer, even though the study concluded that laparoscopic surgery for cancer of the colon is as effective as open surgery in the short term and is likely to produce similar long-term outcomes [7]. The study was later infirmed in recent years by the COLOR II, COLOR III [7, 8] trials, as well as by ongoing studies regarding laparoscopic approach for rectal cancer.

The COLOR II trial is a seven-year randomized clinical trial, comparing laparoscopic and open surgery for rectal cancer (conducted from January 20, 2004 to May 4, 2010). It included 1103 patients undergoing surgery for rectal cancer, divided randomly either for laparoscopic approach or for classic approach, treated in 30 centers and hospitals from eight different countries in Europe, Canada and South Korea. Histologically, it followed the occurrence of positive circumferential resection limits and median tumor distance to distal resection margin. Positive residual tumor (R1) was traced in 56 (10%) out of 588 patients who underwent laparoscopic surgery, and in 30 (10%) out of 300 patients who underwent open surgery ( $p=0.850$ ). Median tumor distance to distal resection margin did not differ significantly between the groups [3 cm (interquartile ratio – IQR 2–4.8) vs. 30 cm (IQR 1.8–5), respectively;  $p=0.676$ ] [9].

The COLOR III trial adds on to the latter by introducing total mesorectal excision (TME) as an essential component of the surgical management of rectal cancer in both open and laparoscopic procedure. The primary endpoint involved in this study was the existence of clear circumferential resection margin (CRM) [10].

From our experience, apart from the clinical healing, which is clearly more rapid after laparoscopic surgery, we identified similar results regarding oncological safety in patients undergoing laparoscopic surgery and patients undergoing open surgery. In our study, oncological resection limits (R0) were obtained. R1 was encountered in the classical approach in three cases (representing 6.7% of this approach) compared to only one case in the laparoscopic approach (representing 5%).

A similar oncological adequacy between laparoscopic and open surgery through a meta-analysis based on randomized clinical trials and prospective non-randomized controlled trials regarding the short-term benefits of laparoscopy in rectal cancer treatment. The study included an assessment of oncological limits attained after laparoscopic surgery in rectal cancer. The authors reported involvement of circumferential margin in 7.9% of the patients who

underwent laparoscopic surgery and in 6.9% of those submitted to open surgery. Thus, the study concluded an overall relative risk (RR) of 1 (95% confidence interval 0.73–1.35) with no heterogeneity. Significantly, more lymph nodes were retrieved after open surgery [11].

In the current study, we considered a number of 10 or more lymph nodes necessary for accurate tumor staging. In this regard we did not notice any significant differences between open surgery and laparoscopic surgery ( $p=0.717$ ).

There are ongoing studies that evaluate the impact of neoadjuvant radiotherapy on pathological lymph nodes (LN) status regarding survival rate. It is becoming more obvious that neoadjuvant oncological treatment can reduce tumor stage [10, 12, 13].

In this regard, we had only two documented patients from the studied cohort who underwent neoadjuvant radiotherapy. We need further documentation on this matter.

Oncological resection limits and accurate tumor staging are necessary for a better outcome [14, 15]. Associated oncological treatment improves the outcome [16, 17].

In the treatment of rectal cancer, a multidisciplinary team consisting of an experienced surgeon in colorectal surgery, a pathologist and an oncologist is needed.

Laparoscopic colorectal surgery has a better short-term postoperative outcome compared to open surgery [18–21]. Our focus for this cohort is to expand the monitoring of the studied cohort over a period of five years for tumor recurrence, quality of life, survival rate [3, 22, 23]. We also aim at developing a database to monitor patients undergoing neoadjuvant radiotherapy related to oncological resolution.

## ✉ Conclusions

In both approaches, independent of the tumor stage, oncological resection limits (R0) and satellite lymph node based staging were aimed for and could be obtained. No significant differences were noted between the laparoscopic surgery group and the open surgery group. We can conclude that the laparoscopic approach demonstrated its oncological feasibility in the rectal cancer surgical treatment.

## Conflict of interests

The authors declare that they have no conflict of interests.

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