



# The Effect of Resection Methods on Outcomes in Colorectal Cancers: Does Conversion Matter?

## Kolorektal Kanselerde Rezeksiyon Metodunun Sonuçlara Etkisi: Konversiyon Önemli mi?

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### ABSTRACT

**Aim:** In this study, we aim to evaluate the short and long-term outcomes of patients undergoing conversion from laparoscopy to open surgery compared to other methods (laparoscopy and open surgery).

**Method:** The data of 98 patients, who underwent elective surgery due to colorectal cancer in a single center, were retrospectively analyzed. Based on the resection method, patients were divided into three groups: laparoscopy, open and conversion. The demographic characteristics, comorbidity, colonic localization, colonic transit properties, preoperative metastasis, resection type, morbidity and mortality, lymph node metastasis, stage, follow-up duration, recurrence and overall survival data were recorded and compared.

**Results:** The morbidity incidence was highest in the conversion group (63.6%) ( $p=0.012$ ). There was no statistical difference in the morbidity subgroup analyses between laparoscopy and open surgery groups ( $p=0.752$ ), whereas the incidence of morbidity in the conversion group was statistically higher than both the laparoscopy and open surgery groups ( $p=0.009$  and  $p=0.025$ , respectively). During follow-up, recurrence was observed in two patients (4.50%) in the laparoscopy group and in two patients (4.50%) in the open surgery group. There was no difference one, two, and three-year survival rates among the three groups.

**Conclusion:** In colorectal cancers, morbidity is observed more frequently in patients in the early stage of the disease who undergo conversion; however, with regard to short and long-term oncological outcomes, there is no difference in resection methods.

**Keywords:** Colorectal cancer, laparoscopy, open surgery, conversion

### ÖZ

**Amaç:** Çalışmamızda kolorektal kanselerde laparoskopiden açığa konversiyon ve diğer yöntemlerin (laparoskopik ve açık cerrahi) kısa ve uzun dönemde sonuçlarının değerlendirilmesi amaçlanmıştır.

**Yöntem:** Mayıs 2013 ile Aralık 2016 tarihleri arasında kolorektal kanser nedeniyle aynı merkezde elektif opere edilen 98 hastanın medikal verileri retrospektif olarak değerlendirildi. Hastalar rezeksiyon metoduna göre laparoskopik ( $n=44$ ), açık ( $n=43$ ) ve konversiyon ( $n=11$ ) olarak üç gruba ayrıldı. Gruplarda hastaların demografik özellikler, komorbidite varlığı, tümörün kolonik yerleşimi, kolonoskopide geçiş özellikleri, preoperatif metastaz, rezeksiyon tipi, morbidite ve mortalite, lenf bezi metastazı ve hastalık evresi, takip süreleri, nüks ve genel sağkalım verileri kaydedildi ve karşılaştırıldı.

**Bulgular:** Kolorektal kanser nedeniyle 44 (44,89%) laparoskopik, 43 (43,87%) açık ve 11 (11,2%) konversiyon kolon rezeksiyonu uygulandı. Demografik özellikler, komorbidite, tümör lokalizasyonu, rezeksiyon tipi, operasyon süresi, mortalite, stage ve sağkalım açısından gruplar arasında farklılık saptanmadı. Morbidite en sık konversiyon grubunda (63,6%) olduğu görüldü ( $p=0,012$ ). Morbidite alt grup analizleri yapıldığında laparoskopik ve açık cerrahi grupları arasında istatistiksel farklılık bulunmazken ( $p=0,752$ ); konversiyon grubunda morbidite görülme oranı hem laparoskopik grubundan hem de açık cerrahi grubundan istatistiksel olarak daha yüksek bulundu (sırasıyla  $p=0,009$  ve  $p=0,025$ ). Takip döneminde nüks laparoskopik grubunda 2 (4,50%) hastada, açık cerrahi grubunda 2 (4,50%) hastada görüldü. Konversiyon grubunda hastalık nüksü görülmedi. Bir, iki ve üç yıllık sağkalım açısından gruplar arasında farklılık görülmedi.

**Sonuç:** Kolorektal kanselerde erken dönemde konversiyon uygulanan hastalarda morbidite daha sık görülmekte; ancak kısa ve uzun dönem onkolojik sonuçlarda rezeksiyon metodları arasında farklılık bulunmamaktadır.

**Anahtar Kelimeler:** Kolorektal kanser, laparoskopik, açık cerrahi, konversiyon

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## Introduction

Laparoscopic surgical interventions have been widely used in benign and malignant colorectal diseases since 1990.<sup>1</sup> There are many advantages to laparoscopic resection compared to conventional open surgery; including less postoperative pain, uncompromised pulmonary functions, no conspicuous incision, quicker mobilization and recovery time, and a decrease in morbidity and hospitalization time.<sup>2</sup> Furthermore, as therapeutic properties are not negatively affected after laparoscopic interventions, postoperative adjuvant treatments can be started earlier.<sup>3</sup> Despite the ongoing discussion as to whether laparoscopic resections can ensure better results than open surgery, they are performed with increasing frequency.<sup>4,5</sup> However, although their short term and oncological outcomes are similar, the percentage of laparoscopic resections performed is still lower than open surgery.<sup>6</sup>

In the catalogue of minimally invasive surgical interventions, the term “conversion” has now been added to the classic resection methods. Conversion is defined as termination of the laparoscopic procedure for cause and switching to open surgery via mid-line incision. The conversion rate for colorectal cancers usually varies between 1.9% and 40.9%.<sup>7</sup> Conversion from laparoscopy to open surgery is not only considered as a complication, but also there is limited data to show whether identical outcomes to full laparoscopic resection can be obtained. While studies usually focus on outcomes for laparoscopy and open surgery, the results of conversion as a separate group are either not evaluated or are added into the open surgery outcomes. The postoperative outcomes of patients undergoing conversion are also not clear: when conversion cases are compared with laparoscopy and open surgery cases, exact data on operation time, hospitalization duration, morbidity, mortality and oncologic outcomes is not yet available.<sup>8,9,10</sup> Consequently, there is ongoing debate about whether laparoscopic interventions should be recommended to all patients with colorectal pathology, and how to identify patients at risk of conversion.

In this retrospective study, we aimed to compare the short and long-term outcomes of cases converted from laparoscopy to open surgery with other methods (laparoscopy and open surgery) over a three-year follow-up period.

## Materials and Methods

### Study Population

Medical data from a total of 98 patients undergoing elective resection for colorectal cancer, in a single center between May 2013 and December 2016, were retrospectively evaluated. All operations were carried out in a single

center by a single surgical team. A total of 21 patients were excluded from the study for several reasons: their surgery was for benign causes (diverticulitis, inflammatory bowel disease); they underwent emergency surgery or were diagnosed with colorectal cancer during the surgery; palliative interventions (stent, etc.) were applied to the area of malignancy; the surgery was due to recurrent colorectal cancer. A total of 98 patients who complied with our criteria were included in the study. Detailed information about the operation was provided to the participating patients and a written informed consent was obtained from each one. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were divided into three groups based on the resection method: laparoscopy (n=44), open (n=43), and conversion (n=11). Demographic characteristics of the patients; comorbidity; colonic localization of the tumor; colonic transit properties during colonoscopy; preoperative metastasis; resection type; morbidity and mortality; lymph node metastasis and stage of the disease; follow-up duration; recurrence and overall survival data were recorded and compared.

The presence of a carcinoma in all patients with colorectal cancer was confirmed histologically with a preoperative colonoscopy. For preoperative staging in cases with colon cancer, imaging was performed using computed tomography and magnetic resonance imaging (MRI), if necessary. In cases of rectal cancer, a routine pelvic MRI was taken.

### The Surgical Technique

The resection types used were right or left hemicolectomy, anterior or low anterior resection (LAR) or abdominoperineal resection. Laparoscopic surgical intervention could not be performed in patients with invasion of surrounding organs, with a history of intraabdominal operation, or in cases of technical problems. Hybrid laparoscopy was avoided and anastomoses were applied intracorporeally. In all laparoscopy, open, and conversion methods, the tumor was resected en bloc, along with any surrounding areas invaded by the tumor, and local lymph nodes, following the no-touch technique.<sup>11</sup> Ostomies were routinely created if patients had a history of radiotherapy in the rectal region or anastomosis in the lower rectum.

A liquid diet and oral enteral supplement was administered preoperatively to all patients undergoing resection. The night prior to surgery, all patients were administered with a low molecular weight heparin derivative (Clexane 8000 anti-Xa IU/0,8, Aventis), and prophylaxis for deep vein thrombosis. There was no particular bowel preparation in the preoperative period. Following post-operative gas emission, a liquid diet was started and patients who could

tolerate oral intake and developed no signs of morbidity were discharged. In terms of preoperative evaluation and postoperative care, there was no difference in approach for patients in the various groups. In the postoperative period, patients were called for checkup three times in the first year and biannually in the second and third years for full evaluation.

### Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM Corp. released 2012), IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, New York, USA). Descriptive data was expressed as mean ± standard deviation (minimum:maximum) or median (minimum:maximum). The Shapiro-Wilk test was used to assess whether the variables followed normal distribution or not. According to normality test results, either one way analysis of variance or Kruskal-Wallis test were used for comparing the operation types. Categorical variables were compared using the Fisher-Freeman-Halton, Fisher's exact, and chi-square tests. The log-rank test was used to determine the difference in the Kaplan-Meier curves for disease-free survival time. The mean survival time was reported. A p value of <0.05 was considered statistically significant.

## Results

In treating our patients for colorectal cancer, we carried out laparoscopic surgery on 44 (44.89%) patients, open surgery in 43 (43.87%) patients, and laparoscopic conversion resection in 11 (11.2%). The demographic characteristics, presence of comorbidity, colonic localization of the cancer, colonic transit features noticed during colonoscopy, and the presence of preoperative metastasis for the three groups are presented in Table 1. Demographically, age, gender and body mass index (BMI) values were similar among the three groups and no statistical differences were found (p=0.467, p=0.341, p=0.542, respectively). Although comorbidity was more frequently observed in the conversion group, no statistically significant differences were detected among the three groups (p=0.182).

In all groups, the tumor was most frequently localized in the left colon (Table 1). In the laparoscopy and open surgery groups, the second most frequent localization was the rectum; and in the conversion group, it was the right colon; however, no statistical difference was observed among the groups in terms of tumor localization (p=0.362). In the preoperative period, liver metastases were observed in the laparoscopy and open surgery groups, but not in the conversion group (p=0.361). In the preoperative period,

**Table 1.** Demographic and histopathologic features

	Laparoscopy (n=44)	Open (n=43)	Conversion (n=11)	P
Age	63.64±12.33 (35:84)	63.42±12.83 (31:83)	63.36±8.50 (53:82)	0.467*
Gender (F/M)	21(47.70%) / 23 (52.3%)	14 (32.60%) / 29 (67.40%)	4 (36.40%) / 7 (63.60%)	0.341**
BMI	25.40 (19.20:35.10)	25.60 (18.60:40.70)	26.10 (19.50:45.70)	0.542***
Comorbidity	26 (59.10%)	22 (51.20%)	9 (81.80%)	0.182**
Tumor localization				
Right colon	8 (18.2%)	10 (23.3%)	4 (36.40)	
Left colon	19 (43.2%)	17 (39.6%)	5 (45.5%)	0.362****
Rectum	17 (38.6%)	16 (37.2%)	2 (18.2%)	
Passage during				
Colonoscopy				
Normal	12 (27.30%)	15 (34.90%)	4 (36.40%)	
Narrows	32 (72.8%)	28 (65.1%)	7 (63.7%)	0.892****
Preoperative metastasis	3 (6.80%)	6 (14%)	0	0.361****
Preoperative pathology				
HGD	8 (18.20%)	7 (16.30%)	3 (27.30%)	
Adenocarcinoma	36 (81.2%)	36 (83.7%)	8 (72.7%)	0.702**

\*ANOVA test, \*\*Chi-square test, \*\*\*Kruskal-Wallis test, \*\*\*\*Fisher-Freeman-Halton test

Data were presented as mean ± standard deviation (minimum:maximum), median (minimum:maximum) or n (%)

F: Female, M: Male; HGD: High grade dysplasia, BMI: Body mass index

patients with metastases were reviewed by the oncology council and underwent resection as their first-line therapy. The histopathology diagnosis in the preoperative period was high grade dysplasia for 18.6% of the patients and adenocarcinoma for 81.4% of the patients (p=0.702). Neoadjuvant chemotherapy and radiotherapy was given to 17 patients (17.3%) with rectal cancer.

The resection type and method, duration of operation, postoperative morbidity and mortality in the three groups are presented in Table 2. LAR and right hemicolectomy were the most frequently performed resection types in all three groups. Subtotal colectomy was performed only in the open surgery group. Laparoscopy was performed in nine patients (52.9%), open surgery in six patients (35.2%), and conversion from laparoscopy was required in two patients (11.7%) receiving neoadjuvant chemotherapy and radiotherapy. The operation duration was similar in all three groups (p=0.298). Ileostomy was performed in four patients (9.09%) in the laparoscopy group, 14 patients (32.5%) in the open surgery group, and in three patients (27.2%) in the conversion group.

The reasons for conversion surgery were: local invasion in 5 patients (45.4%); severe adhesions in 2 patients (18.1%); severe intestinal dilatation in 2 patients (18.1%); narrow pelvis in 1 patient (9%); and ureteral injury in 1 patient (9%).

The most frequent cause of morbidity in all three groups was wound site infection and postoperative morbidity was most frequently observed in the conversion group (63.6%) (p=0.012; Table 2). When morbidity subgroup analyses were performed, no statistical difference was found between the laparoscopy and open surgery groups (p=0.752),

whereas the incidence of morbidity in the conversion group was statistically higher than that of both the laparoscopy group and the open surgery group (p=0.009 and p=0.025, respectively). Anastomotic leakage was observed in one patient (1.02%) in the laparoscopy group, and in one patient (1.02%) in the open surgery group. Two deaths occurred in the open surgery group: one due to hepatic failure (1.02%) and one due to myocardial infarction (1.02%); and one death in the conversion group ensued because of necrotizing fasciitis (1.02%). No mortalities were recorded in the laparoscopy group. There was no statistically significant difference between the subgroups in terms of mortality (p=0.098).

Following resection, pathology samples were examined, and stage and presence of metastases in the lymph node were evaluated for the three groups (Table 3). Similar numbers of lymph nodes were removed in all three groups (p=0.178) and no difference in terms of tumor size was detected among the three groups (p=0.626). When patient stages were evaluated, the most frequently observed stage in all three groups was stage 3 (45.5%, 37.2% and 63.6%, respectively). Statistical analysis for the stages revealed no significant difference among the three groups (p=0.701).

Recurrence rate in the follow-up period, mean follow-up duration and overall survival values were presented in Table 3. In the follow-up period, recurrence was seen in two patients (4.50%) in the laparoscopy group, and in two patients (4.50%) in the open surgery group. No recurrence was observed in the conversion group. In terms of recurrence, no statistically significant differences were observed among the groups (p=1.00). The groups also had similar one, two, and three-year survival rates (Figure 1).

**Table 2.** Resection method, morbidity and mortality

	Laparoscopy (n=44)	Open (n=43)	Conversion (n=11)	P
Resection type				
Right hemicolectomy	8 (18.20%)	10 (23.30%)	4 (36.40%)	
Left hemicolectomy	5 (11.3%)	3 (7%)	1 (9.10%)	
LAR	30 (68.20%)	23 (53.50%)	4 (36.40%)	0.153*
APR	1 (2.30%)	3 (7%)	2 (18.20%)	
Subtotal colectomy	0	4 (9.30%)	0	
Operation duration (min.)	180 (90:300)	180 (120:420)	180 (120:270)	0.298**
Morbidity	9 (20.50%)	10 (23.30%)	7 (63.60%)	<b>0.012*</b>
Mortality	0	2 (4.70%)	1(9.10%)	0.098*

\*Fisher-Freeman-Halton test, \*\*Kruskal-Wallis test

Data were presented as median (minimum:maximum) or n (%)

LAR: Low anterior resection, APR: Abdominoperineal resection

## Discussion

Although laparoscopic resection for colorectal cancer is becoming more common, it is still used less frequently than open surgery.<sup>12</sup> Apart from oncological factors, this is most likely because of the technical difficulties involved in laparoscopic techniques and the steep learning curve required.<sup>13</sup> More surgical experience and anatomical awareness is required for oncologic resections performed on segments of the colon in different intra-abdominal locations,

when compared to other laparoscopic interventions. With every laparoscopically completed surgery (colon mobilization, dissection and ligation of large veins, resection and anastomosis of the specimen), the surgeon's recognition of anatomic structures and surgical experience increases.<sup>14</sup> As the procedures become more complex, conversion becomes a more significant complication. Although the level of surgical experience is often said to have no bearing on the decision to convert from laparoscopic to open surgery, some studies have noted that conversion is more likely to be adopted in the early stages of the learning curve.<sup>7</sup> In our study, we observed that although conversion was performed in our early cases where our laparoscopic experience was inadequate; as our experience increased and better preoperative evaluations were made, conversion became unnecessary.

Laparoscopic resection rates in colorectal cancers vary between 27.7% and 51.1%; in our study, laparoscopic resection was performed in 44.8% of the cases.<sup>15,16</sup> Studies show that surgery time is significantly longer in laparoscopic resections (mean 216±53 min) than in open surgery (mean 172±48 min); while the exact length of time cannot be determined in conversion cases.<sup>17</sup> Moreover, as the experience of the surgical team increases, operation time decreases.<sup>18</sup> However, in our study, there was little difference in operation duration in the three groups. This could be due to the long surgery time and the limited number of patients in the three groups.

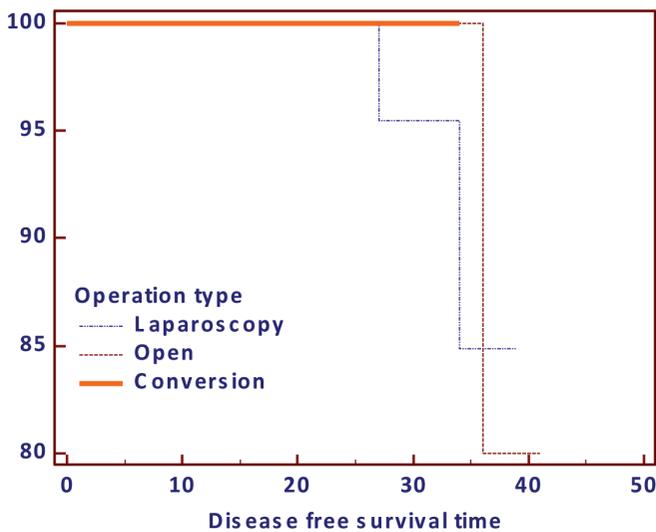


Figure 2. Disease free survival

Table 3. Lymph node metastases, stages, recurrence and average follow-up time

	Laparoscopy (n=44)	Open (n=43)	Conversion (n=11)	p
Removed lymph node	17 (8:31)	18 (10:95)	17 (11:24)	0.178*
Lymph node metastasis	0 (0:7)	0 (0:19)	1 (0:10)	0.462*
Tumor size (mm)	42.50 (10:150)	50 (10:140)	55 (20:100)	0.626*
Stage				
1	9 (20.50%)	8 (18.60%)	2 (18.20%)	0.701**
2	12 (27.30%)	14 (32.60%)	1 (9.10%)	
3	20 (45.50%)	16 (37.20%)	7 (63.60%)	
4	3 (6.80%)	5 (11.60%)	1 (9.10%)	
Recurrence rate	2 (4.50%)	2 (4.70%)	0	1.00**
Follow-up duration (months)	37.92	40	26.1	0.840
1 year survival (%)	100%	100%	100%	
2 years survival (%)	95.70	100%	100%	
3 years survival (%)	86.10%	80%	100%	

\*Kruskal-Wallis test, \*\*Fisher-Freeman-Halton test  
Data were presented as median (minimum:maximum) or n (%)

Reported conversion rates vary between 2% and 44% and the conversion rate in our study was 11.2%.<sup>7,19,20</sup> Causes of conversion can be listed as patient-related factors (male gender, obesity, history of abdominal surgery, tumor size, neoadjuvant treatment); surgeon-related factors (surgical experience, technical facilities, patient volume); the surgical area to be resected (narrow pelvis particularly in male patients); intraoperative complications (organ injury, uncontrollable bleeding and anastomosis difficulties).<sup>16,21</sup> In addition, in terms of resection type, rectum, proctectomy and left colon resections have higher rates of conversion.<sup>22</sup> Patients with Crohn's disease and malignant cases have higher conversion rates than those with benign diseases (inflammatory diseases, diverticulitis).<sup>16,22</sup> Advanced age is not a factor which increases the conversion rate but high conversion rates have been observed in obese patients (BMI >30 kg/m<sup>2</sup>).<sup>23,24</sup> A history of abdominal surgery is not considered as a contraindication for surgical laparoscopic interventions, although it is a relative contraindication. While a history of abdominal and pelvic surgery increases the risk of conversion, a history of appendectomy and cholecystectomy are not reported to increase the risk of conversion.<sup>9</sup> However, in our study, conversion was necessary in 18.1% patients with a history of appendectomy due to severe cohesive adhesion. Relatively high conversion rates in our cases were assumed to be due to the inexperience of one surgeon. The most frequent causes of conversion were intraabdominal severe cohesive adhesion and invasion of the tumor into the surrounding tissue.

When the outcomes of patients undergoing laparoscopy or conversion surgery are compared, a higher rate of morbidity is seen in both groups compared to those having open surgery, according to the literature.<sup>25</sup> While no difference in terms of morbidity and mortality are reported between conversion patients and the open surgery group in this report, another study reports a higher complication rate and a longer period of hospitalization in conversion patients compared to those having laparoscopy or open surgery.<sup>8,26</sup> The morbidity rate is reported as 23% after laparoscopy, 11-20% after open surgery, and 35.2% after conversion.<sup>16,27,28,29</sup> Although the incidence of wound site infection and incisional hernia decreases following laparoscopic resections; postoperative ileus, anastomosis leakage, wound site infection and duration of hospitalization increase in patients undergoing conversion.<sup>16</sup>

In our study, morbidity was also most frequently observed in the conversion group. The incidence of wound site infection, is reported as the most frequent cause of morbidity: 10-12% in open surgery cases and 32.1% in conversion patients.<sup>30</sup> In our study, the most frequent cause of morbidity in all three

groups was wound site infection; and in morbidity subgroup analysis, the morbidity incidence was found to be higher in the conversion group than in either the laparoscopy or open surgery groups. Likewise, reported incidences of anastomosis leakage are 2.4-6.8% after open surgery, 2.7% after laparoscopy, but 25% after conversion.<sup>25,31</sup> However, in our study, anastomosis leakage was observed in laparoscopy and open surgery groups but not in the conversion group. In conversion patients, the incidence of mortality is reported to be 3.5%.<sup>32</sup> In our cases, mortality was observed in 9.09% of the conversion group.

In colorectal cancer cases, lymph nodes have a prognostic value in determining the stage. Studies report that as surgeons gain more experience, the number of lymph nodes removed increases and that at least 12 lymph nodes should be removed for a sufficient lymph node dissection.<sup>33</sup> Analysis of resected pieces has shown that 14-19 lymph nodes are removed in laparoscopic resections whereas 15-23 lymph nodes are removed in open surgical resections.<sup>15,34</sup> In our study, the number of removed lymph nodes was similar in all groups and no statistically significant differences were found between the resection methods.

The average tumor size in colorectal cancers is 3.5 (1-7) cm in the laparoscopic group and 3.9 (1-8) in the open surgery group.<sup>34</sup> In our study, although average tumor size was larger in the conversion group, no statistically significant difference was found among the groups.

When stages are analyzed in patients with colorectal cancer, stage 3 is reported as the most common stage in both laparoscopy and open surgery groups (34.2%, 37.7%, respectively).<sup>15</sup> In our study, our cases were also most frequently stage 3. Although stage 3 was relatively more frequently observed in the conversion group, no statistically significant difference was found among the groups.

Three and five-year survival rates are also similar in laparoscopy and open surgery groups.<sup>6,35</sup> When overall survival is evaluated over a 10-year period, it is 45.3% in laparoscopic resections and 40.9% in open surgical resections.<sup>15</sup> Disease-free survival rate is 64.9% in laparoscopic resections and 59.8% in open surgical resections.<sup>15</sup> In our study, one, two, and three-year survival rates revealed no statistical differences between the resection methods.

Nonetheless, there are some limitations in the interpretation of the data in our study. First of all, the number of patients included in our study and in the resection type subgroups is relatively small. Also, although groups were assigned according to the resection method used, there were biological differences between colon and rectal cancers. Linking high rates of conversion to open laparoscopy to

surgical inexperience is only an assumption. Finally, the inability to perform randomization among the groups, and the retrospective nature of the study are also limitations.

In conclusion, in patients with colorectal cancer, laparoscopic resections can be performed safely and effectively, with similar results to open surgery. To overcome the technical difficulties and understand the two-dimensional anatomical structures of laparoscopy, a learning curve is required. However, we have limited data on the conversion outcomes following minimal invasive surgery. Therefore, there is no consensus of opinion on whether to recommend laparoscopic interventions to every patient with colorectal pathology, or how to identify patients with a higher risk of conversion. Despite the indisputable success of laparoscopic surgery, we believe that selection of appropriate patients and clarification of the reasons for conversion are of utmost importance in giving the best results after laparoscopic colectomy.

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** External and internal peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: U.E.E., H.M.Ç., Concept: U.E.E., Design: H.M.Ç., Data Collection or Processing: U.E.E., H.M.Ç., Analysis or Interpretation: U.E.E., H.M.Ç., Literature Search: H.M.Ç., Writing: U.E.E.

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