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ORIGINAL RESEARCH

Laparoscopic surgery facilitates administration of adjuvant chemotherapy in locally advanced colon cancer: propensity score analyses

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Purpose: The aim of this study was to evaluate the impact of a laparoscopic approach on long-term oncological outcomes in curative intent surgery for pT4 colon cancer, in both overall and stratified subgroups with distinct clinical entities.

Patients and methods: Patients with a pT4N0-2M0 colon cancer from four centers between 2000 and 2014 were included. Laparoscopic and open approaches were compared according to the intention-to-treat principle. Propensity scores were used to adjust for baseline differences between the groups in three manners: i) as a linear predictor in a Cox regression model, ii) to create a 1:1 matched cohort, and iii) to stratify patients into four groups with an increasing chance of receiving laparoscopy.

Results: In total, 424 patients were included. After 1:1 matching, a laparoscopic approach correlated with higher rates of radical resection, lower morbidity, and a higher percentage of patients receiving adjuvant chemotherapy. This translated into better 5-year disease-free survival (52% vs 40%, HR 0.70; 95% CI 0.50–0.96) and 5-year overall survival (68% vs 57%, HR 0.66; 95% CI 0.43–0.99). These results were confirmed in the other two propensity score analyses. In the multivariable models, adjuvant chemotherapy remained independently associated with better survival, whereas surgical approach lost significance.

Conclusions: In locally advanced colon cancer, an intentional laparoscopic approach in experienced hands seems to decrease morbidity and to increase the proportion of patients receiving adjuvant chemotherapy. Receiving adjuvant chemotherapy was independently associated with improved survival.

Keywords: T4 colon cancer, laparoscopy, lower GI

Synopsis

In this multicenter propensity score analyses of 424 pT4N0-2M0 colon cancer patients who underwent curative intent surgery, laparoscopic surgery compared to open was associated with reduced postoperative morbidity and a higher percentage of patients receiving adjuvant chemotherapy, which translated into improved survival.

Introduction

Resection of locally advanced (T4) colon cancer stage is still regarded as a relative contraindication for laparoscopic surgery, because radicality of the resection (R0) might be jeopardized, thereby impacting the long-term oncological outcome.[1]

Laparoscopic surgery for colon cancer has become widely accepted and implemented in routine practice for localized disease (pT1-3). Both favorable short-term

and long-term benefits have been demonstrated,[2–5] including less postoperative complications, shorter hospital stay, lower risks of adhesion-related small bowel obstruction, and incisional hernia compared to open surgery.[6] In the multicenter randomized COLOR trial,[7] the noninferiority of laparoscopic surgery for pT1-4 colon cancer in terms of oncological outcomes (3-year disease-free survival, DFS) was suggested. However, clinically suspected tumor invasion of adjacent structures (cT4b stage) and emergency surgery were exclusion criteria. Due to a conversion rate of about 50% for the remaining T4 tumors in the COLOR data, the authors presumed the open approach to be most appropriate for T4 colon cancer.

Experience with laparoscopic surgery for T4 tumors increases, and the concerns on achieving radicality of resection may be outdated. Accumulating series of laparoscopic resections of T4 colon cancer are published,[8–18] and two recent meta-analyses[19,20] show comparable rates of R0 resections and long-term oncological outcomes after laparoscopic versus open surgery. However, only a limited body of evidence is available and is restricted to retrospective series with substantial allocation bias.[19,20] Also, emergency cases and multivisceral resections (MVR, pT4b) were often excluded in the previous series.

The aim of this multicenter cohort study was to evaluate long-term oncological outcomes after curative intent laparoscopic surgery for pT4 colon cancer and compare it to open surgery using propensity score analyses in order to correct for allocation bias.

Methods

Patients and databases

In this cohort study, four prospectively maintained databases of the University Hospital Leuven, the Dutch (teaching) St. Antonius Hospital, and two Dutch university medical centers (Radboud UMC and Amsterdam UMC) were combined (centers 1–4). The database of center 1 contained all consecutive patients who underwent resection of colon cancer between January 2004 and July 2013. The databases of centers 2 and 3 included all pT4 colorectal cancer patients undergoing surgery between January 2000 and December 2013, and between January 2000 and December 2007, respectively. The database of center 4 included all pT4 colon cancer patients who underwent surgery between January 2004 and December 2014. Patients undergoing a curative intent pT4N0-2M0 primary colon cancer resection were included. Patients with a macroscopic incomplete (R2) resection or with an inadequate pathological or surgical report were excluded. Adjuvant chemotherapy was administered according to the national protocols: indicated in high-risk stage II and stage III, consisting of 5-flourouracil or capecitabine and preferably combined with oxaliplatin (FOLFOX or CAPOX) since 2005, for a total duration of 6 months. Follow-up was performed according to the national protocol and data were collected until April 2018.[21,22] This study was waived from the review of the medical ethics boards, since the prospective data collection did not interfere with the psychological integrity of the patients. The study is reported in accordance with the STROBE checklist.

Variables and outcomes

The pT4 stage was subdivided into pT4a and pT4b according to TNM7:[23] pT4a refers to tumors perforating the visceral peritoneum and pT4b refers to tumors directly invading other organs or structures. MVR could be either limited or extensive: limited additional resection included the abdominal wall, the omentum, or the ovaries, and extensive resection was defined as resections including the pancreas, spleen, kidney, liver, stomach, bladder, ureters, uterus, or additional bowel segments.

The primary outcome measures were DFS and overall survival (OS). Secondary outcomes were radicality of resection, classified as R0 (radical resection) and R1 (microscopically irradical resection) resections, administration of adjuvant chemotherapy, and postoperative complications (<30 days or in hospital). Postoperative complications were registered if the Clavien–Dindo[24] (CD) score was 2 or higher. Postoperative morbidity was defined as CD 2–4, and postoperative mortality as CD5.

Statistical analyses

The laparoscopic converted procedures were included in the laparoscopic group according to "intention-to-treat principle". For each patient, a propensity score was calculated, displaying the probability of receiving laparoscopic surgery based on a multivariable logistic regression model including (potential) confounding baseline variables. Potential confounders were variables only affecting outcome measures, and true confounders were variables affecting both choice for surgical approach and outcome measures.[25] Confounders included age, emergency setting, tumor location (right/left), MVR (none/limited/extended), N-stage, and histopathology. The choice for variables

included in the model was based on identified (potential) confounders in the previous series.[8,9,11,19] Due to multicollinearity between MVR and T4 subcategory (T4a/T4b), the latter was not included in the propensity score calculation.

The propensity score was used in three different manners to adjust for group differences, all with distinct advantages and disadvantages.[25,26] Firstly, the propensity score was used as a linear predictor in Cox regression analyses (referred to as "Regression adjusted"), from which an estimated effect was derived. In this way, the entire cohort could be included in the analysis. In order to minimize baseline differences before statistical comparison, the propensity score was used for 1:1 matching with a caliper width of 0.02 and using matching without replacement (referred to as "Matched cohort"). Besides comparison of the two matched cohorts, the excluded cohort of open surgery after matching was analyzed and compared to the included matched open cohort. Thirdly, the propensity score was used to subdivide patients into four strata based on quartiles of the propensity scores, creating an equal distribution of confounding variables within the four strata (referred to as 'Strata 1–4'). For each stratum, baseline and outcome variables were compared between laparoscopic and open subgroups. This method uses the entire cohort and creates clinically relevant subgroups from a surgical perspective. In addition, sensitivity analyses were performed for MVR and emergency surgery.

Differences in baseline characteristics between subgroups were assessed using a chi-square test for categorical variables or a Fisher's exact test in case of low counts (<5). For normally distributed continuous variables, mean and SD were reported. The survival analyses were performed using Kaplan–Meier and Cox regression analyses. A p-value of <0.05 was considered statistically significant in the multivariable analyses. For statistical analyses, PASW Statistics, version 24 (SPSS inc., Chicago, IL) was used.

Results

Patients

A total of 424 patients that underwent macroscopic complete (R0/R1) resection of primary pT4N0-2M0 colon cancer in one of the four participating centers were included (Figure S1). Mean age was 69 years (SD 12) and 51% of patients were male. Laparoscopic surgery was performed in 131 patients (31%), of which 33 procedures were converted (25%). A MVR was performed in 171 patients (40%) and emergency surgery in 60 patients (14%). Median follow-up was 48 months (IQR 22–60). Baseline characteristics are displayed in Table 1. The following baseline characteristics were significantly different for the laparoscopic and open groups, respectively: emergency setting (5% vs 18%, p<0.001), MVR (31% vs 45%, p=0.014), and T4 subcategory (T4a: 81% vs 66%, p=0.002).

Numbers of performed resections between the centers were 164 (39%) in center 1, 113 (27%) in center 2, 90 (21%) in center 3, and 57 (13%) in center 4 with significantly different laparoscopy rates (42%, 24%, 3%, and 56%, respectively; p<0.001) and conversion rates (38%, 11%, 67%, and 6%, respectively; p=0.001). No differences in case mix were found between centers 2, 3, and 4, while center 1 showed higher rates of elective surgery and lower rates of MVRs and pT4b tumors (Table S1).

Unadjusted analysis of outcome measures

The R0 resection rate was higher in the laparoscopic group as compared to the open group (99% vs 93%, p=0.010). The postoperative morbidity rate was lower after laparoscopic surgery (27% vs 46%, p<0.001) and postoperative mortality rates were comparable (2% vs 3%, p=0.357). Adjuvant chemotherapy was more often administered after laparoscopic surgery (60% vs 44%, p=0.004). Laparoscopy was significantly associated with better 5-year DFS (52% vs 38%, p=0.008) and 5-year OS (68% vs 57%, p=0.023) (Tables 2 and S2, Figures 1 and 2).

Regression adjusted analysis

The distributions of propensity scores are displayed in Figure 1. After adjusting for the propensity score in regression models, R0 resection rate (OR 0.16; 95% CI 0.02–1.25) as well as postoperative mortality (OR 0.73; 95%CI 0.14–3.68) were comparable between the two approaches, while postoperative morbidity was lower (OR 0.48; 95% CI 0.30–0.77) and the rate of administration of adjuvant chemotherapy higher (OR 1.94; 95% CI 1.25–3.03) after laparoscopic surgery. Five-year DFS was significantly better in the laparoscopic group (HR 0.70; 95% CI 0.52–0.94), without significant benefit for 5-year OS (HR 0.73; 95%CI 0.50–1.06) (Figure 2).

Propensity matched analysis

In Figure 1, the distributions of propensity scores are displayed for the propensity matched cohort. Within the propensity matched cohort (n=262), no baseline differences were found between the laparoscopic and open groups (Table 3), apart from the center. The excluded open group

Table 1 Baseline characteristics of the entire cohort for the laparoscopic and the open group

		Lap (n=131)		Open (n=293)		
		n	%	n	%	*p*-Value
Gender	Male	68	52%	148	51%	0.790
	Female	63	48%	145	49%	
Age	≤60	29	22%	73	25%	0.783
	61–70	37	28%	75	26%	
	71–80	41	31%	99	34%	
	≥81	24	18%	46	16%	
Hospital	Center 1	69	53%	95	32%	<0.001
	Center 2	27	21%	86	29%	
	Center 3	3	2%	87	30%	
	Center 4	32	24%	25	9%	
Location tumour	Right	56	43%	126	43%	0.961
	Left/transverse	75	57%	167	57%	
Surgical procedure	(Extended) right hemicolectomy	60	46%	127	43%	0.140
	Transverse resection	0	0%	8	3%	
	(Extended) left hemicolectomy	13	10%	42	14%	
	(Low) anterior/sigmoid resection	51	39%	94	32%	
	Subtotal/panprocto-colectomy	7	5%	22	8%	
Setting	Elective	125	95%	239	82%	<0.001
	Emergency	6	5%	54	18%	
Neoadjuvant therapy	Yes	5	4%	14	5%	0.681
	No	124	96%	279	95%	
MVR	No	91	69%	162	55%	0.014
	Yes, limited	19	15%	50	17%	
	Yes, extended	21	16%	81	28%	
Conversion		33	25%	NA		NA
pT-stage	T4a	106	81%	193	66%	0.002
	T4b	25	19%	100	34%	
pN-stage	N0	64	49%	139	47%	0.963
	N1	38	29%	88	30%	
	N2	29	22%	66	23%	
Histology	Adenocarcinoma (well diff)	94	72%	197	67%	0.333
	Adenocarcinoma (poorly/undiff)	15	11%	50	17%	
	Mucinous/signet ring cells	22	17%	46	16%	

Abbreviations: Lap, laparoscopic approach; MVR, multivisceral resection; NA, not applicable; Open, open approach; pT/N, pathological T/N-stage; Undiff, undifferentiated; Well diff, well differentiated.

(n=162) after 1:1 matching contained more emergency cases as compared to the included open group (29% vs 5%, $p<0.001$) as well as more MVRs (57% vs 29%, $p<0.001$) and more pT4b tumors (44% vs 21%, $p<0.001$).

Laparoscopic surgery as compared to open surgery in the 1:1 matched cohort revealed higher R0 resection rates (99% vs 95%, $p=0.030$), lower postoperative morbidity (27% vs 72%, $p<0.001$), a trend toward lower postoperative mortality (2% vs 8%, $p=0.051$), and comparable rates of administration of adjuvant chemotherapy (60% vs 54%, $p=0.301$). Five-year DFS was significantly better in the laparoscopic group (52% vs

40%, p=0.038), as well as 5-year OS (68% vs 57%, p=0.044) (Figure 1). Survival rates of patients that were excluded from the open group after propensity matching were comparable with the included open group (5-year DFS 37%, p=0.664 and 5-year OS 57%, p=0.914).

Propensity score–based strata

After dividing the entire cohort into four strata based on quartiles of the propensity scores, with stratum 1 containing the lowest propensity for laparoscopic surgery, the R0 resection rates were higher in all strata (although nonsignificant), postoperative morbidity, mainly CD2 complications, was lower in stratum 4 (22% vs 43%, p=0.031), adjuvant chemotherapy higher in strata 2 and 3 and survival outcomes favorable in all strata (although nonsignificant) after laparoscopic surgery vs open (Table 2 and Figure 2). Baseline characteristics of the four strata are provided in Table S3–S6. Stratum 1 contains all emergency cases as well as the highest percentage of extended MVRs (50%). Stratum 2 also includes a high percentage of MVRs (limited MVR 30%, extended MVR 47%), whereas the MVR rates of strata 3 and 4 are 16% and 0%, respectively.

Sensitivity analyses

After sensitivity analyses, no subgroup of patients (eg emergency setting) could be identified in which oncological outcomes of laparoscopic surgery were inferior to outcomes after open surgery (Table 2 and Figure 2). In the "no-MVR" subgroup, DFS and OS were significantly better, and in the extended MVR and elective cases, more adjuvant chemotherapy was administered after laparoscopic surgery as compared to open surgery. For elective cases also, a significant better DFS was seen after laparoscopy.

Adjuvant chemotherapy

Post hoc analyses showed that after adjusting for adjuvant chemotherapy in the Cox regression models, the beneficial effect of laparoscopic surgery on DFS and OS did not remain significant, neither in the unadjusted nor in the regression adjusted and the 1:1 matched cohort. In every multivariable model, adjuvant chemotherapy was significantly associated with improved DFS (HR 0.46; 95% CI 0.35–0.61, HR 0.54; 95% CI 0.41–0.71 and HR 0.37; 95% CI 0.24–0.56, respectively) and OS (HR 0.49; 95% CI 0.33–0.72, HR 0.44; 95% CI 0.31–0.62 and HR 0.31; 95% CI 0.19–0.51, respectively), both in stage II and stage III subgroups (data not shown).

Discussion

In this multicenter series of 424 pT4N0-2M0 colon cancer patients who underwent curative intent surgery, laparoscopic surgery was associated with reduced postoperative morbidity and a higher percentage of patients receiving adjuvant chemotherapy. The multivariable models revealed an independent association of adjuvant chemotherapy with improved survival, but not surgical approach. This suggests that laparoscopic surgery facilitates the administration of adjuvant chemotherapy by improving postoperative recovery and reducing complication rates, with ultimate gain in survival.

Table 2 Short-term oncological outcomes after laparoscopic and open surgery

	Lap/Open	Radicality			Adj. chemo		
		Lap	Open	*p*-Value	Lap	Open	*p*-Value
Unadjusted	131/293	130 (99%)	271 (93%)	0.010*	75 (60%)	127 (44%)	0.004
Propensity score adjusted models							
Matched cohort	131/131	130 (99%)	123 (95%)	0.030*	75 (60%)	68 (54%)	0.301
Stratum 1	15/90	15 (100%)	78 (89%)	0.191	9 (53%)	41 (47%)	0.233
Stratum 2	32/75	31 (97%)	68 (92%)	0.317	20 (69%)	28 (37%)	0.004
Stratum 3	39/69	39 (100%)	66 (96%)	0.257	26 (70%)	33 (45%)	0.027
Stratum 4	45/59	45 (100%)	59 (100%)		20 (44%)	25 (46%)	0.920
Sensitivity analyses							
No MVR	91/162	90 (99%)	157 (97%)	0.298	53 (60%)	74 (48%)	0.061
Limited MVR	19/50	19 (100%)	45 (90%)	0.152	7 (44%)	17 (34%)	0.338
Extended MVR	21/81	21 (100%)	69 (89%)	0.103	15 (71%)	36 (44%)	0.028
Elective	125/239	124 (99%)	223 (95%)	0.027*	72 (60%)	107 (46%)	0.010
Emergency	6/54	6 (100%)	48 (89%)	0.516	3 (60%)	20 (39%)	0.330

Abbreviations: Adj. chemo, adjuvant chemotherapy; Lap, laparoscopic approach; MVR, multivisceral resection; Open, open approach; Unadjusted, the unadjusted (entire) cohort.

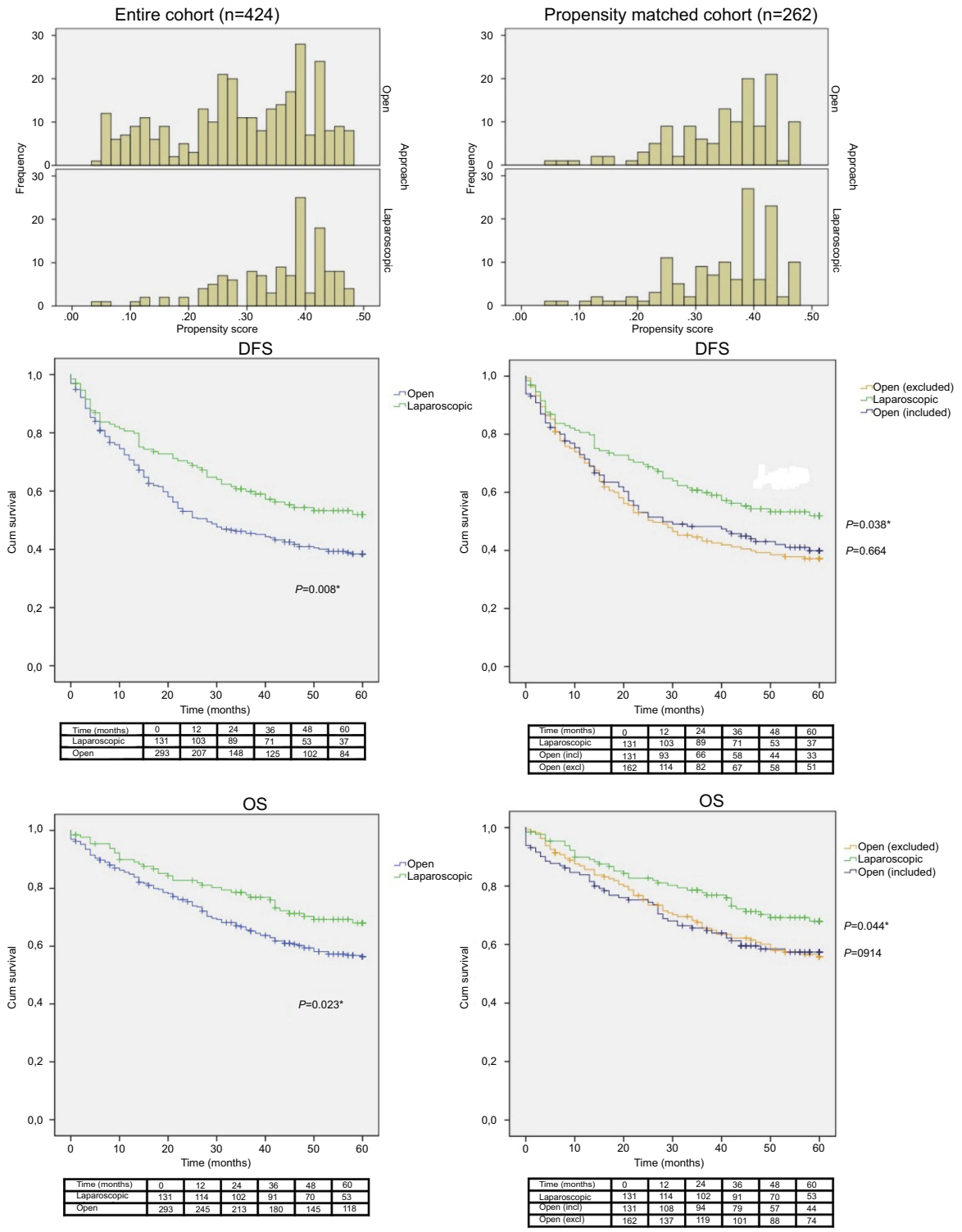

Figure 1 Propensity score distribution, disease-free survival (DFS), and overall survival (OS) in the entire cohort and the propensity matched cohort.
Abbreviations: Laparoscopic, laparoscopic approach; Open, open approach; DFS, disease-free survival; OS, overall survival; cum, cumulative; open (excl), open approach, excluded from the matched cohort; open (incl), open approach, included from the matched cohort.

A recently published Chinese expert series[27] similarly observed higher survival rates after laparoscopic surgery (5-year DFS 57% vs 40%, p=0.053, 5-year OS 61% vs 47%, p=0.060). The increased likelihood of receiving adjuvant chemotherapy due to better recovery from minimally invasive surgery has also recently been observed.

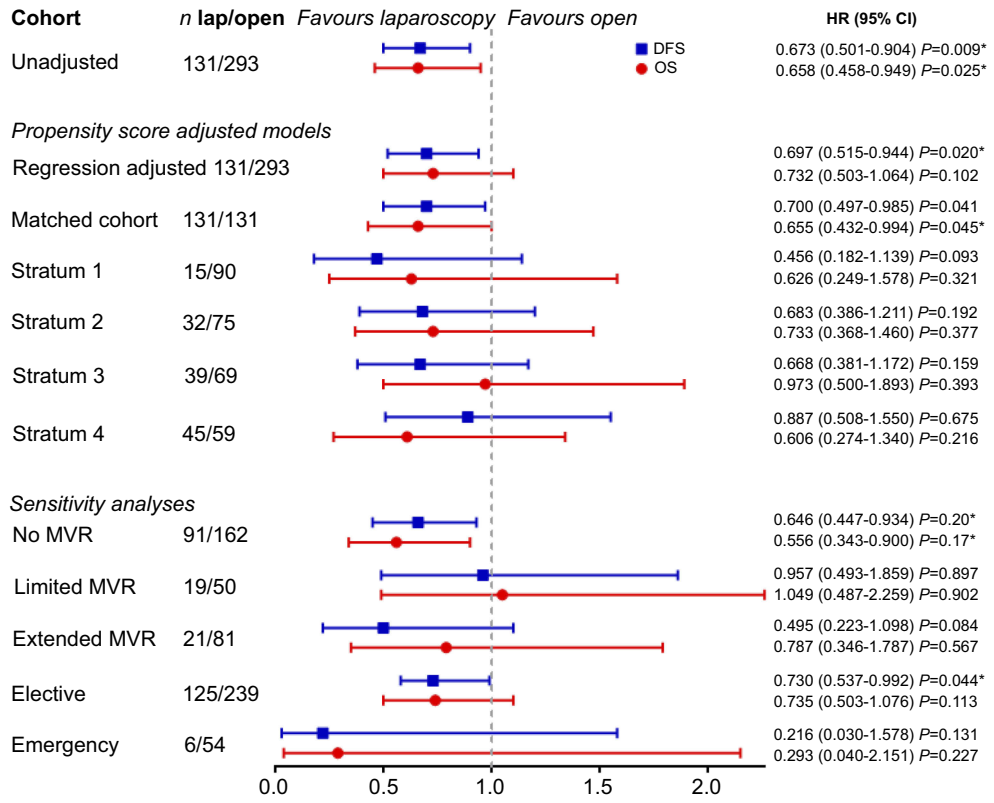

Figure 2 Disease-free (DFS) and overall survival (OS).
Abbreviations: Lap, laparoscopic approach; MVR, multiviscersal resection; Open, open approach; unadjusted, the unadjusted (entire) cohort; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Lee et al reported higher rates and less delay to the initiation of adjuvant chemotherapy after laparoscopic surgery for stage III colon cancer in a propensity matched cohort of 66,266 patients, ultimately resulting in improved survival. But this is a new insight that has not previously been described in the literature.[28] In randomized controlled trials, such as the COLOR trial,[7] comparable rates of adjuvant chemotherapy and survival after laparoscopic and open surgery are likely related to strict inclusion of relatively fit patients with small tumors, being operated upon in the elective setting. Therefore, randomized controlled trials have restricted external validity. We hypothesize that more extended application of laparoscopy by experienced surgeons in routine practice is now going to shed a different light on the impact of minimally invasive surgery. The most pronounced differences in administration of adjuvant chemotherapy between laparoscopy and open surgery were found in the extended MVR subgroup (71% vs 44%) and in the emergency setting (60% vs 39%), suggesting that minimizing surgical trauma is only becoming clinically relevant in such high-risk patients. Two series including substantial numbers of T4b cases also reported higher rates of adjuvant chemotherapy after laparoscopic as compared to open surgery (63% vs 37%, p=0.047 and 71% vs 57%, p=0.513).[13,16]

The main reason why T4 colon cancer has been considered a contraindication for laparoscopic surgery was the concern about achieving complete resection with negative margins, especially in the case of local ingrowth (pT4b). In this multicenter series, a 100% R0 resection rate in 40 patients requiring MVR was found. Four studies assessed outcomes after laparoscopic resection of pT4b colon cancer in relatively small cohorts of 15–23 patients.[9,11,13,20,29] R0 resection rates were 83%, 93%, 96%, and 100%, respectively. For experienced surgeons in open MVR who also completed the learning curve for laparoscopic colon surgery, the laparoscopic approach might eventually facilitate dissection in locally advanced cases. This is related to the magnified view at high resolution with a 30-degree camera that enables optimal visualization from different angles, which, for example, might improve dissection from the retroperitoneum below a bulky tumor as compared to median laparotomy. It is often considered that tactile feedback is missing in laparoscopy, but there is still an indirect sense of firmness of tissues. Furthermore, high-quality MVR has become more and more dependent on thorough preoperative

Table 3 Baseline characteristics of the matched cohort for the laparoscopic and the open group

		Lap (n=131)		Open (n=131)		*p*-Value	Open excl (n=162)	
		n	%	n	%		n	%
Gender	Male	68	52%	68	52%	1.000	80	49%
	Female	63	48%	63	48%		82	51%
Age	≤60	29	22%	31	24%	0.924	42	26%
	61–70	37	28%	37	28%		38	24%
	71–80	41	31%	43	33%		56	35%
	≥81	24	18%	20	15%		26	16%
Hospital	Center 1	69	53%	47	36%	<0.001	48	30%
	Center 2	27	21%	28	21%		58	36%
	Center 3	3	2%	45	34%		42	26%
	Center 4	32	24%	11	8%		14	9%
Location tumour	Right	56	43%	51	39%	0.530	75	46%
	Left/transverse	75	57%	80	61%		87	54%
Surgical procedure	(Extended) right hemicolectomy	60	46%	51	39%	0.071	76	47%
	Transverse resection	0	0%	5	4%		3	2%
	(Extended) left Hemicolectomy	13	10%	20	15%		22	13%
	(Low) anterior/sigmoid resection	51	39%	44	34%		50	31%
	Subtotal/panprocto-colectomy	7	5%	11	8%		11	7%
Setting	Elective	125	95%	124	95%	0.776	115	71%
	Emergency	6	5%	7	5%		47	29%
Neoadjuvant therapy	Yes	5	4%	8	7%	0.409	6	4%
	No	124	96%	123	93%		156	96%
MVR	No	91	70%	93	71%	0.747	69	43%
	Yes, limited	19	15%	15	12%		35	22%
	Yes, extended	21	16%	23	17%		58	36%
Conversion		33	25%	NA		NA	NA	
pT-stage	T4a	106	81%	103	79%	0.645	90	56%
	T4b	25	19%	28	21%		72	44%
pN-stage	N0	64	49%	63	48%	0.830	76	47%
	N1	38	29%	42	32%		46	28%
	N2	29	22%	26	20%		40	25%
Histology	Adenocarcinoma (well diff)	94	72%	96	73%	0.872	101	62%
	Adenocarcinoma (poorly/undiff)	15	11%	16	12%		34	21%
	Mucinous/signet ring cells	22	17%	19	15%		27	17%

Abbreviations: Lap, laparoscopic approach; MVR, multivisceral resection; NA, not applicable; Open, open approach; Open excl, open approach, excluded from the matched cohort; pT/N, pathological T/N-stage; Undiff, undifferentiated; Well diff, well differentiated.

anatomical planning of the surgical planes of dissection. Performing minimally invasive surgery increases the skills in intraoperative recognition of (disturbed) anatomy. The proven better hemostatic dissection with less blood loss also favors the laparoscopic approach. Even if a larger incision is needed for extraction of a bulky pT4b tumor, laparoscopy might be the preferred approach by reducing surgical stress response and because of flexibility in the site of extraction to reduce the risk of incisional hernia (eg Pfannenstiel).

Occurrence of severe postoperative complications is an important factor that precludes the use of adjuvant chemotherapy.[30] Postoperative infection requiring re-intervention (CD3) or ICU admission (CD4) were highest in the extended MVR and emergency subgroups undergoing open

surgery (31% and 28%, respectively). This likely reduced the possibilities of administration of adjuvant chemotherapy in these subgroups. Moreover, it has been increasingly described in the literature that postoperative complications have an independent adverse effect on oncological outcomes, possibly related to upregulation of inflammatory cytokines that enhance tumor progression.[31–33]

Previously published series comparing laparoscopic and open surgery for pT4 colon cancer often address the issue of allocation bias with more advanced cases in the open subgroup contained. In this analysis, we have attempted to overcome this bias by using propensity scores and by not excluding MVR and emergency cases. Propensity scores control for baseline differences inherent to observational studies.[25] However, the present analysis might still be subject to allocation bias. We have only roughly subdivided MVRs in "limited" and "extended", while still the more complex extended MVRs could be assigned to the open subgroup. Furthermore, the number of emergency cases were limited. We did not correct for effects such as tumor size, presence of intraabdominal infections, presence of adhesions, body mass index, and comorbidity. Consequently, hidden confounding by allocation to laparoscopic or open surgery (selecting patients) could have occurred for which propensity score analyses do not correct. Nonetheless, we have implemented the propensity scores using different manners and results were comparable amongst all analyses. This represents the best achievable evidence, as new RCTs comparing surgical approach in T4 colon cancer are unlikely to be conducted. Previous RCTs comparing surgical techniques have struggled with differences in completion of learning curves amongst the participating surgeons.[34–36] Rouanet et al proposed to compare a series of expert centers that apply different surgical techniques as an alternative for RCTs, in this way overcoming the problems of learning curves and allocation bias.[37] Our study approaches this methodology to some extent, by including two centers (1 and 4) with relatively high laparoscopic surgery rates (42% and 56%), and one participating hospital applying open surgery in 97% of cases, with comparable case mixes. However, the conversion rate of 38% in center 1 suggests that the learning curve has not been fully completed during the study period.

Another limitation of the study is the retrospective data collection with difficulties in the uniformity of defining variables and potential underestimation of the postoperative complication rate. However, postoperative complication rates among the four hospitals were comparable or even higher than previously published.[38]

Conclusion

In conclusion, this multicenter cohort study showed that laparoscopic surgery for pT4 colon cancer was associated with a lower risk of postoperative morbidity and a higher chance of receiving adjuvant chemotherapy. Receiving adjuvant chemotherapy was independently associated with better survival, which indicates an indirect impact of surgical approach on oncological outcome. However, these results might not be generalizable due to the level of experience in advanced laparoscopic surgery. Centralization of care for pT4 colon cancer should be aimed for, and future series of expert centers performing laparoscopic surgery for T4 colon cancer, especially in the more technically challenging cases, should further confirm our hypothesis.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

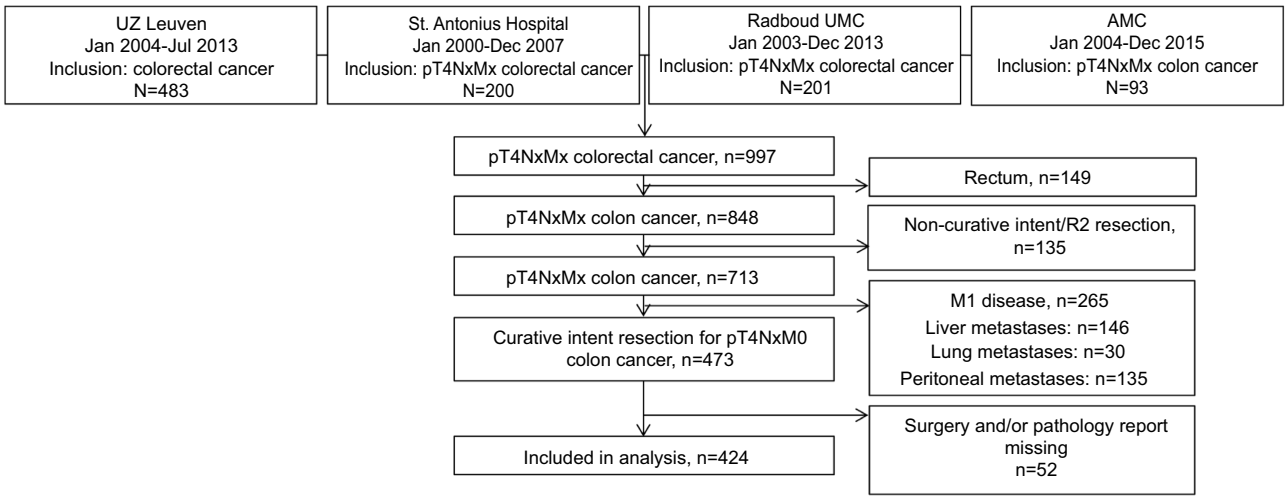

Figure S1 Patients included in the analysis.

Abbreviations: pT/N, pathological T/N-stage; R2, macroscopically irradical resection; M1, metastatic disease; UZ, University hospital Leuven; Radboud UMC, Radboud University Medical Centre; AMC, Amsterdam University Medical Centre, location academic medical centre; Jan, January; Jul, July; Dec, December.

Table S1 Case-mix and outcomes per hospital for the laparoscopic and the open group

		Center 1		*Center 2*		*Center 3*		*Center 4*		
		n	%	***n***	%	***n***	%	***n***	%	***p-value***
Lap/open		69/95	42%/58%	27/85	24%/76%	3/85	3%/97%	32/25	56%/44%	<0.001
Conversion		26	38%	3	11%	2	67%	2	6%	0.001
		n (lap/open)	*% within hospital*	*n (lap/open)*	*% within hospital*	*n (lap/open)*	*% within hospital*	*n (lap/open)*	*% within hospital*	*p-value*
Age	≤60	13/18	19%	5/23	25%	1/22	26%	10/10	35%	0.291
	61–70	21/28	30%	6/20	23%	0/24	27%	10/3	23%	
	71–80	21/29	31%	11/30	36%	2/30	36%	7/10	29%	
	≥81	14/20	21%	5/13	16%	0/11	12%	5/2	12%	
Location tumor	Right	26/41	41%	14/38	46%	0/36	40%	16/11	47%	0.682
	Left/transverse	43/54	59%	13/48	54%	3/51	60%	16/14	53%	
Setting	Elective	67/80	90%	27/68	84%	3/71	82%	28/20	84%	0.344
	Emergency	2/15	10%	0/18	16%	0/16	18%	4/5	16%	
MVR	No	49/63	68%	22/42	58%	0/44	49%	20/12	56%	0.011
	Yes, limited	8/11	12%	3/23	23%	2/12	16%	6/4	18%	
	Yes, extended	12/21	20%	2/20	19%	1/31	36%	6/9	26%	
pT-stage	T4a	60/72	80%	24/49	65%	1/57	64%	21/15	63%	0.005
	T4b	9/23	20%	3/37	35%	2/30	36%	11/10	37%	
pN-stage	N0	33/49	50%	14/38	46%	0/43	48%	17/9	46%	0.792
	N1	21/28	30%	7/27	30%	2/27	32%	8/6	25%	
	N2	15/18	20%	6/21	24%	1/17	20%	7/10	30%	
Radicality	R0	68/93	98%	27/78	94%	3/78	92%	32/22	95%	0.128
	R1	1/2	2%	0/7	6%	0/7	8%	0/3	5%	
Adjuvant chemotherapy	Yes	45/56	63%	11/58	39%	2/52	37%	16/12	47%	0.000
	No	21/37	37%	16/28	61%	1/31	63%	13/12	53%	
Postoperative complications	Yes	19/45	40%	2/27	26%	3/49	58%	11/13	42%	<0.001
	No	50/49	60%	25/49	74%	0/38	42%	21/12	58%	

Abbreviations: Lap, laparoscopic approach; MVR, multivisceral resection; Open, open approach; pT/N, pathological T/N-stage. R0, microscopically radical resection; R1, microscopically irradical resection.

Table S2 Short-term outcomes after laparoscopic and open surgery; postoperative morbidity

	Lap/ Open	Postop Complications (CD2)			Postop Complications (CD3/4)			Postop Mortality (CD5)		
		Lap	Open	*p-value*	Lap	Open	*p-value*	Lap	Open	*p-value*
Unadjusted	131/293	19 (15%)	66 (23%)	0.057	14(11%)	61(21%)	0.012	2 (2%)	8 (3%)	0.357
Propensity score adjusted models										
Matched cohort	131/131	19 (15%)	41 (31%)	0.001	14 (11%)	45 (34%)	0.001	2 (2%)	8 (6%)	0.051
Stratum 1	15/90	5 (33%)	20 (22%)	0.350	1 (7%)	23 (26%)	0.182	0 (0%)	5 (5.6%)	0.455
Stratum 2	32/75	6 (19%)	15 (20%)	0.882	2 (6%)	19 (25%)	0.032	1 (3%)	1 (1%)	0.511
Stratum 3	39/69	5 (13%)	14 (20%)	0.327	5 (13%)	12 (17%)	0.531	0 (0%)	1 (1%)	0.639
Stratum 4	45/59	3 (7%)	17 (29%)	0.005	6 (13%)	7 (12%)	0.822	1 (2%)	1 (2%)	0.681
Sensitivity analyses										
No MVR	91/162	9 (10%)	37 (23%)	0.010	11 (12%)	28 (17%)	0.272	1 (1%)	3 (2%)	0.546
Limited MVR	19/50	4 (21%)	10 (20%)	1.000	1 (5%)	8 (16%)	0.237	1 (5%)	2 (4%)	0.626
Extended MVR	21/81	6 (29%)	19 (24%)	0.627	2 (10%)	25 (31%)	0.048	0 (0%)	3 (4%)	0.371
Elective	125/239	17 (14%)	55 (23%)	0.032	13 (10%)	46 (19%)	0.030	2 (2%)	5 (2%)	0.745
Emergency	6/54	2 (33%)	11 (20%)	0.602	1 (17%)	15 (28%)	0.559	0 (0%)	3 (6%)	0.725

Abbreviations: CD, Clavien-Dindo score; Lap, laparoscopic approach; MVR, multivisceral resection; Open, open approach; Unadjusted, the unadjusted (entire) cohort.

Table S3 Baseline characteristics of stratum 1 (lowest propensity for laparoscopic surgery) for the laparoscopic and the open group

		Laparoscopic (n=*15*)		*Open* (n=*90*)		*p*-value
		n	%	*n*	%	
Gender	Male	7	47%	53	59%	0.376
	Female	8	53%	37	41%	
Age	≤60	3	20%	27	30%	0.621
	61-70	3	20%	15	17%	
	71-80	8	53%	35	39%	
	≥81	1	7%	13	14%	
Hospital	Center 1	5	33%	24	27%	0.001
	Center 2	2	13%	26	29%	
	Center 3	1	7%	31	34%	
	Center 4	7	47%	9	10%	
Location tumour	Right	10	67%	36	40%	0.054
	Left/transverse	5	33%	54	60%	
Surgical procedure	(Extended) right hemicolectomy	8	53%	36	40%	0.811
	Transverse resection	0	0%	3	3%	
	(Extended) left hemicolectomy	1	7%	12	13%	
	(Low) anterior/sigmoid resection	5	33%	31	34%	
	Subtotal/panprocto-colectomy	1	7%	8	9%	
Setting	Elective	9	60%	36	40%	0.147
	Emergency	6	40%	54	60%	
Neoadjuvant therapy	Yes	0	0%	2	2%	0.762
	No	13	100%	88	98%	
MVR	No	4	27%	29	32%	0.911
	Yes, limited	3	20%	17	19%	
	Yes, extended	8	53%	44	49%	
Conversion		4	27%			
T-stage	T4a	8	53%	45	50%	0.811
	T4b	7	47%	45	50%	
N-stage	N0	9	60%	40	44%	0.515
	N1	4	27%	30	33%	
	N2	2	13%	20	22%	
Histology	Adenocarcinoma (well diff)	8	53%	49	54%	0.570
	Adenocarcinoma (poorly/undiff)	6	40%	27	30%	
	Mucinous/signet ring cells	1	7%	14	16%	

Abbreviations: Lap, laparoscopic approach; MVR, multivisceral resection; NA, not applicable; Open, open approach; pT/N, pathological T/N-stage; Undiff, undifferentiated; Well diff, well differentiated.

Table S4 Baseline characteristics of stratum 2 for the laparoscopic and the open group

		Laparoscopic (n=*32*)		*Open* (n=*75*)		*p*-value
		n	%	*n*	%	
Gender	Male	16	50%	33	44%	0.568
	Female	16	50%	42	56%	
Age	≤60	8	25%	20	27%	0.416
	61-70	14	44%	21	28%	
	71-80	7	22%	25	33%	
	≥81	3	9%	9	12%	
Hospital	Center 1	19	59%	20	27%	0.001
	Center 2	5	16%	25	33%	
	Center 3	2	6%	22	29%	
	Center 4	6	19%	8	11%	
Location tumour	Right	15	47%	30	40%	0.510
	Left/transverse	17	53%	45	60%	
Surgical procedure	(Extended) right hemicolectomy	14	44%	32	43%	0.673
	Transverse resection	0	0%	2	3%	
	(Extended) left hemicolectomy	4	13%	6	8%	
	(Low) anterior/sigmoid resection	12	37%	33	44%	
	Subtotal/panprocto-colectomy	2	6%	2	3%	
Setting	Elective	32	100%	75	100%	
	Emergency	0	0%	0	0%	
Neoadjuvant therapy	Yes	30	94%	65	87%	0.240
	No	2	6%	10	13%	
MVR	No	7	22%	18	24%	0.525
	Yes, limited	12	38%	20	27%	
	Yes, extended	13	41%	37	49%	
Conversion		16	50%			
T-stage	T4a	17	53%	30	40%	0.210
	T4b	15	47%	45	60%	
N-stage	N0	15	47%	39	52%	0.874
	N1	9	28%	20	27%	
	N2	8	25%	16	21%	
Histology	Adenocarcinoma (well diff)	21	66%	47	63%	0.955
	Adenocarcinoma (poorly/undiff)	8	25%	20	27%	
	Mucinous/signet ring cells	3	9%	8	11%	

Abbreviations: Lap, laparoscopic approach; MVR, multivisceral resection; NA, not applicable; Open, open approach, pT/N: pathological T/N-stage, Undiff: undifferentiated; Well diff, well differentiated.

Table S5 Baseline characteristics of stratum 3 for the laparoscopic and the open group

		Laparoscopic (n=*39*)		*Open* (n=*69*)		*p*-value
		n	%	*n*	%	
Gender	Male	21	54%	38	55%	0.902
	Female	18	46%	31	45%	
Age	≤60	15	38%	21	30%	0.151
	61-70	2	5%	12	17%	
	71-80	15	39%	30	44%	
	≥81	7	18%	6	9%	
Hospital	Center 1	23	59%	23	33%	<0.001
	Center 2	8	21%	21	30%	
	Center 3	0	0%	19	28%	
	Center 4	8	21%	6	9%	
Location tumour	Right	22	56%	41	59%	0.761
	Left/transverse	17	44%	28	41%	
Surgical procedure	(Extended) right hemicolectomy	22	56%	39	57%	0.167
	Transverse resection	0	0%	2	3%	
	(Extended) left hemicolectomy	2	5%	11	16%	
	(Low) anterior/sigmoid resection	13	33%	12	17%	
	Subtotal/panprocto-colectomy	2	5%	5	7%	
Setting	Elective	39	100%	69	100%	
	Emergency	0	0%	0	0%	
Neoadjuvant therapy	Yes	3	8%	0	0%	0.045
	No	36	92%	69	100%	
MVR	No	35	90%	56	81%	0.239
	Yes, limited	4	10%	16	19%	
	Yes, extended	0	0%	0	0%	
Conversion		8	21%			
T-stage	T4a	36	92%	59	86%	0.369
	T4b	3	8%	10	14%	
N-stage	N0	9	23%	19	28%	0.877
	N1	16	41%	27	39%	
	N2	14	36%	23	33%	
Histology	Adenocarcinoma (well diff)	28	71%	47	69%	0.862
	Adenocarcinoma (poorly/undiff)	1	3%	3	4%	
	Mucinous/signet ring cells	10	26%	19	28%	

Abbreviations: Lap, laparoscopic approach; MVR, multivisceral resection; NA, not applicable; Open, open approach; pT/N, pathological T/N-stage; Undiff, undifferentiated; Well diff, well differentiated.

Table S6 Baseline characteristics of stratum 4 (highest propensity for laparoscopic surgery) for the laparoscopic and the open group

		Laparoscopic (n=*45*)		*Open* (n=*59*)		*p*-value
		n	%	*n*	%	
Gender	Male	24	53%	24	41%	0.200
	Female	21	47%	35	59%	
Age	≤60	3	7%	5	9%	0.694
	61–70	18	40%	27	46%	
	71–80	11	24%	9	15%	
	≥81	13	29%	18	31%	
Hospital	Center 1	22	49%	28	48%	<0.001
	Center 2	12	27%	14	24%	
	Center 3	0	0%	15	25%	
	Center 4	11	24%	2	3%	
Location tumour	Right	9	20%	19	32%	0.165
	Left/transverse	36	80%	40	68%	
Surgical procedure	(Extended) right hemicolectomy	16	36%	20	34%	0.263
	Transverse resection	0	0%	1	2%	
	(Extended) left hemicolectomy	6	13%	13	22%	
	(Low) anterior/sigmoid resection	21	47%	18	31%	
	Subtotal/panprocto-colectomy	2	4%	7	12%	
Setting	Elective	45	100%	59	100%	
	Emergency	0	0%	0	0%	
Neoadjuvant therapy	Yes	0	0%	2	3%	0.212
	No	45	100%	57	97%	
MVR	No	45	100%	59	100%	
	Yes, limited	0	0%	0	0%	
	Yes, extended	0	0%	0	0%	
Conversion		5	14%			
T-stage	T4a	45	100%	59	100%	
	T4b	0	0%	0	0%	
N-stage	N0	31	69%	41	70%	0.981
	N1	9	20%	11	19%	
	N2	5	11%	7	12%	
Histology	Adenocarcinoma (well diff)	37	82%	54	91%	0.155
	Adenocarcinoma (poorly/undiff)	0	0	0	0%	
	Mucinous/signet ring cells	8	18%	5	9	

Abbreviations: Lap, laparoscopic approach; MVR, multivisceral resection; NA, not applicable; Open, open approach; pT/N, pathological T/N-stage; Undiff, undifferentiated; Well diff: well differentiated.