



ORIGINAL ARTICLE

Robotic versus laparoscopic right colectomy for nonmetastatic pT4 colon cancer: A European multicentre propensity score-matched analysis

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Abstract

Aim: Minimally invasive surgery has been increasingly adopted for locally advanced colon cancer. However, evidence comparing robotic (RRC) versus laparoscopic right colectomy (LRC) for nonmetastatic pT4 cancers is lacking.

Methods: This was a multicentre propensity score-matched (PSM) study of a cohort of consecutive patients with pT4 right colon cancer treated with RRC or LRC. The two surgical approaches were compared in terms of R0, number of lymph nodes harvested, intra- and postoperative complication rates, overall (OS), and disease-free survival (DFS).

Results: Among a total of 200 patients, 39 RRC were compared with 78 PS-matched LRC patients. The R0 rate was similar between RRC and LRC (92.3% vs. 96.2%, respectively; $p=0.399$), as was the odds of retrieving 12 or more lymph nodes (97.4% vs. 96.2%; $p=1$). No significant difference was noted for the mean operating time (192.9 min vs. 198.3 min; $p=0.750$). However, RRC was associated with fewer conversions to laparotomy (5.1% vs. 20.5%; $p=0.032$), less blood loss (36.9 vs. 95.2 mL; $p<0.0001$), fewer postoperative complications (17.9% vs. 41%; $p=0.013$), a shorter time to flatus (2 vs. 2.8 days; $p=0.009$), and a shorter hospital stay (6.4 vs. 9.5 days; $p<0.0001$) compared with LRC. These results were confirmed even when converted procedures were excluded from the analysis. The 1-, 3- and 5-year OS ($p=0.757$) and DFS ($p=0.321$) did not significantly differ between RRC and LRC.

Conclusion: Adequate oncological outcomes are observed for RRC and LRC performed for pT4 right colon cancer. However, RRC is associated with lower conversion rates and improved short-term postoperative outcomes.

Nicola de'Angelis and Carlo Alberto Schena contributed equally to the manuscript.

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KEYWORDS

locally advanced colon cancer, minimally invasive surgery, propensity score matching, right colon cancer, robotic surgery, T4 cancer

INTRODUCTION

In recent decades, minimally invasive surgery (MIS) has been globally accepted as the gold standard treatment for right colon cancer [1–10]. Laparoscopic right colectomy (LRC) is associated with improved postoperative outcomes, including faster recovery, shorter hospital stays, lower blood loss, and similar oncological outcomes compared to those for open surgery [1–6, 8, 11–14]. Nevertheless, the safety and feasibility of laparoscopic surgery for locally advanced colonic cancer have long been a matter of debate [15–21], and concerns remain about the routine implementation of MIS for clinical T4 cancers [22]. Approximately 15% of all diagnosed colon cancers are classified as pathological T4 (pT4) cancers [23, 24]. According to the American Joint Committee on Cancer (AJCC) classification [25], locally advanced colonic cancer is classified as T4a in cases of tumour invasion of the visceral peritoneum and as T4b in cases of tumour invasion or adhesion to adjacent structures and organs [25, 26]. Radical surgical resection (i.e., R0) followed by adjuvant chemotherapy represents the gold standard for nonmetastatic pT4 colon cancers, despite being burdened by poorer prognosis and greater technical complexity when performing en bloc resections [16, 17, 22, 27]. Compelling evidence advocates laparoscopic resection over open resection for nonmetastatic pT4 colon cancers because laparoscopic resection is associated with better clinical outcomes and equivalent oncological outcomes [21, 28–32]. The robotic approach, which is a further implementation of MIS, has also been adopted for locally advanced colon cancers. However, only a few studies have analysed the outcomes of robotic surgery for T4 colon cancer [31, 33, 34], highlighting the paucity of related literature.

Therefore, this propensity score-matched (PSM) study aimed to evaluate the technical feasibility, clinical and oncological safety, and postoperative outcomes of RRC versus LRC performed for nonmetastatic pT4 right colon cancers in a European multicentre patient cohort.

MATERIALS AND METHODS**Data source, study design and population**

This study was designed as a PSM analysis of the Minimally Invasive Surgery for oncological Right Colectomy (MERCY) Study Group database [35–38]. The MERCY Study Group collaborators generated a multicentre retrospective cohort of adult patients with nonmetastatic right colon adenocarcinoma (AJCC stages 0–III) who underwent elective resection, curative-intent LRC or RRC (performed with da Vinci Surgical Platforms, Intuitive Surgical Ltd., Sunnyvale, CA, USA) in six European countries (France, Ireland,

What does this paper add to the literature?

This is the first multicentre propensity score-matched study that analysed the clinical and oncological safety of robotic versus laparoscopic right colectomy for nonmetastatic pT4 right colon cancers, demonstrating that robotic surgery provides equivalent oncological radicality than laparoscopy, being also associated with lower conversion to open surgery and improved short-term postoperative outcomes.

Italy, Spain, Switzerland and the UK) [35]. All procedures were carried out between January 2014 and December 2020 [35] by experienced colorectal surgeons (senior surgeons with at least 5 years of experience in minimally invasive colorectal surgery) who had completed their learning curve in minimally invasive right colectomy (at least 16 RRC and 25 LRC procedures [39]). All right colectomies were performed according to standardized surgical techniques, with central vascular ligation and at least standard D2-lymphadenectomy. All patients were treated and followed up after surgery according to standardized international and national protocols.

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) histologically proven pT4 adenocarcinoma; (3) right colon cancer (i.e., caecum, ascending colon or hepatic flexure); (4) AJCC TNM stage IIb/IIc (T4a/T4b, N0, M0) and TNM stage IIIb/IIIc (T4a/T4b, N+, M0); (5) curative intent; (6) elective setting; and (7) robotic (RRC) or laparoscopic (with straight instruments, LRC) approach.

Patients with extended right colectomies with middle colic artery ligation at the origin were excluded. Patients who presented with synchronous colorectal cancer or metastatic disease, as well as those who had undergone open surgery and hand-assisted procedures, were also excluded. The type of surgical approach (i.e., robotic or laparoscopic surgery) and the type of ileocolic anastomosis (i.e., intracorporeal or extracorporeal) used depended on the surgeon's advice and preference at each centre.

This was a retrospective study dealing exclusively with anonymous clinical record data from prospectively maintained local databases routinely collected from health databases. This research was declared to the National Commission for Data Protection and Liberties (2210699) and approved by the Institutional Review Board (00011558). Personal data were collected after informing the involved patients and were treated in accordance with the ethical standards of the Helsinki Declaration. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) 2021 guidelines [40, 41].

Study outcomes and definitions

The primary outcomes were oncological results after surgical resection based on the status of the resection margins (i.e., R0) and the number of harvested lymph nodes. The secondary outcomes included operative variables, postoperative morbidity and mortality and survival rates.

Pre-, intra- and postoperative data were retrospectively collected from prospectively maintained databases. The baseline preoperative characteristics included age, sex, body mass index (BMI), American Society of Anaesthesiologists (ASA) physical status classification system, type of comorbidity, previous surgical history, Charlson comorbidity index, tumour location and neoadjuvant therapy. Intraoperative outcomes included the operating time, unplanned conversion to open surgery, estimated blood loss, tumour size, tumour stage (according to the eighth edition of the AJCC classification system [25, 26]), resection margin status (i.e., R0 or R1), and number of lymph nodes harvested. R1 resection margins were defined as the presence of viable tumour cells at ≤ 1 mm from the resection margin [26]. Intraoperative blood loss was determined by direct measurement of collected blood (from swabs, suction bottles, drainage bags, etc.). Finally, postoperative outcomes included complications (defined according to the Clavien-Dindo classification [42]), anastomotic leakage, time to flatus, time to regular diet, length of hospital stay (LOS), 30-day readmissions and mortality. Referral for adjuvant chemotherapy was determined in accordance with the standard of care after local multidisciplinary team approval. Anastomotic leakage was defined as all conditions characterized by clinical or radiological anastomotic dehiscence, with or without the need for surgical revision. All types of complications and mortality were recorded during the hospital stay or within 90 days after surgery. Additionally, the recurrence rate, disease-free survival (DFS), and overall survival (OS) were analysed and compared between the RRC and LRC groups. All patients were followed up until death or the last follow-up date (updated up to January 2023). Local recurrence was defined as any recurrence in or near the site of the original primary tumour, whereas distant recurrence was defined as any recurrence occurring as distant metastases according to the TNM classification [43, 44]. Survival was estimated based on the duration of follow-up starting from the date of surgery. Censoring was defined as the date of the last follow-up if no event occurred. DFS was defined as the interval between surgery and the date of recurrence or censoring at the last follow-up. OS was defined as the time from diagnosis to the last documented follow-up or death due to any cause.

Statistical analysis

Patients were divided into two groups according to the type of surgical approach used: RRC or LRC. All patients who required an unplanned conversion to laparoscopic (in the case of RRC) or open (in the case of RRC and LRC) approaches were maintained in their original group based on an intention-to-treat analysis. For the descriptive

analysis, means and standard deviations (SDs) are reported herein for continuous variables, whereas frequencies and percentages (%) are provided for categorical variables. Comparisons between RRC and LRC were made using student's *t* test or the Mann-Whitney test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Whenever indicated, the odds ratio (OR) and 95% confidence interval (CI) were also estimated. To lessen the selection bias inherent in a retrospective study, a PSM analysis was performed to compare the treatment (i.e., RRC and LRC) outcomes by accounting for the different covariates that might have played a role in the selection of robotic versus laparoscopic surgery [45–49]. The propensity score was obtained from a logistic regression model that included the following covariates: age, sex, ASA score, tumour size, tumour location, tumour category (pT4a/pT4b), node category (pN0/pN1/pN2), need for multivisceral resection, centre and year of surgery. Notably, the model included the year of surgery to counterbalance potential historical bias. The surgical approach (i.e., RRC vs. LRC) was entered into the regression model as the dependent variable. A 1:2 nearest neighbour case-control match without replacement was used [45–49]. The two PS-matched groups were subsequently compared with respect to the study outcomes. The OS and DFS rates at 1, 3 and 5 years were assessed using the Kaplan–Meier method and compared between groups using the log-rank (Mantel–Cox) test. As suggested by several authors [36, 50, 51], survival analysis was also conducted and reported for the entire study population.

All the statistical analyses were performed using SPSS statistical software (Statistical Package for Social Science, IBM SPSS Statistics, version 28 for Macintosh; IBM Corp., with Essential for R plug-in).

RESULTS

Study population

The study population comprised 200 patients with pT4 right colon cancer who underwent elective RRC ($n=45$) or LRC ($n=155$). The number of robotic procedures increased over time; robotic procedures were applied in 4.8% of the pT4 cases in 2014 and in 28.6% of the pT4 cases in 2020. Patients' demographic and clinical characteristics are presented in Table 1. Before matching, the RRC and LRC groups significantly differed in terms of age and ASA score, with a higher mean age and a greater frequency of ASA III in the LRC group. In terms of comorbidities, no differences were noted between RRC and LRC patients. The clinical tumour size and location and histopathological tumour characteristics were similar between the groups; however, a trend toward a greater frequency of multivisceral resection was noted in the RRC group (42.2%) than in the LRC group (27.1%) ($p=0.066$), mirroring the greater prevalence of pT4b in the RRC group (42.2%) than in the LRC group (26.5%).

After PSM, 39 RRC patients were compared to 78 LRC patients (Figure 1). The demographic, clinical and histopathological characteristics of the RRC and LRC patients after PSM are presented in

TABLE 1 Demographic, clinical, and histological characteristics of patients with pT4 right colon cancer in the RRC and LRC groups before and after propensity score matching.

Variables	Before PSM (n = 200)			After PSM (n = 117)		
	RRC group (n = 45)	LRC group (n = 155)	p-value	RRC group (n = 39)	LRC group (n = 78)	p-value
Demographic and clinical variables						
Male, n (%)	23 (51.1)	75 (48.4)	0.866	19 (48.7)	38 (48.7)	1
Age (mean [SD])	66.24 (17.05)	72.33 (12.41)	0.025	68.35 (14.26)	70.38 (13.42)	0.344
Age >75 years, n (%)	13 (28.9)	75 (48.4)	0.026	11 (28.2)	33 (42.3)	0.160
BMI (mean [SD])	26.78 (3.91)	26.40 (5.02)	0.253	26.08 (3.59)	26.54 (5.68)	0.657
Obesity (BMI ≥ 30 kg/m ²), n (%)	8 (20.5)	31 (23.8)	0.829	5 (12.8)	15 (19.2)	0.440
ASA, n (%)			0.004			0.588
I	6 (13.3)	9 (5.8)		4 (10.3)	6 (7.7)	
II	30 (66.7)	82 (52.9)		26 (66.7)	46 (59)	
III	8 (17.8)	60 (38.7)		8 (20.5)	25 (32)	
IV	1 (2.2)	4 (2.6)		1 (2.5)	1 (1.3)	
Cardiovascular diseases, n (%)	16 (35.6)	65 (41.6)	0.394	16 (41)	33 (42.3)	0.958
Pulmonary diseases, n (%)	2 (4.4)	16 (10.3)	0.265	2 (5.1)	10 (12.8)	0.369
Kidney diseases, n (%)	3 (6.7)	12 (7.7)	0.553	3 (7.7)	5 (6.4)	0.900
Neurocognitive disorders, n (%)	1 (2.2)	10 (6.5)	0.287	1 (2.6)	2 (2.6)	0.922
Diabetes, n (%)	9 (20)	30 (19.4)	0.646	9 (23.1)	12 (15.4)	0.593
Comorbidity >1, n (%)	19 (42.2)	66 (42.6)	0.604	17 (43.6)	35 (44.9)	0.958
Charlson comorbidity score (mean [SD])	5.16 (2.21)	5.31 (2.40)	0.631	5.16 (2.21)	5.38 (1.89)	0.554
Previous abdominal surgery, n (%)	15 (33.3)	59 (38.1)	0.599	13 (33.3)	32 (41)	0.546
Patients with multivisceral resection, n (%)	19 (42.2)	42 (27.1)	0.066	15 (38.5)	22 (28.2)	0.295
Organs involved						
Abdominal wall	4	7		3	3	
Omentum	10	20		8	12	
Duodenum	4	2		3	2	
Small bowel	1	1		1	0	
Gallbladder	3	7		3	4	
Bladder	1	1		1	0	
Pararenal fats	0	1		0	1	
Liver (wedge)	1	0		1	0	
Gonadic vessel	1	0		1	0	
Fallopian tube	0	1		0	1	
Stomach (wedge)	0	4		0	3	
Sigmoid colon	1	0		0	0	
Patients >1 extra-colic organ resected*, n (%)	6 (31.6)	4 (9.5)	0.057	5 (33.3)*	3 (13.6)*	0.228
Preoperative imaging assessment on computed tomography scan						
Clinical tumour size (largest dimension, cm) (mean [SD])	4.58 (1.91)	5.24 (2.36)	0.268	4.58 (1.92)	5.54 (2.31)	0.122
Tumour location, n (%)			0.721			0.988
Caecum	15 (33.3)	62 (40)		13 (33.4)	25 (32.1)	
Ascending colon	19 (42.3)	59 (38.1)		16 (41)	33 (42.3)	
Hepatic flexure	11 (24.4)	34 (21.9)		10 (25.6)	20 (25.6)	

TABLE 1 (Continued)

Variables	Before PSM (n = 200)			After PSM (n = 117)		
	RRC group (n = 45)	LRC group (n = 155)	p-value	RRC group (n = 39)	LRC group (n = 78)	p-value
Histopathological variables						
Stage of disease AJCC			0.369			0.829
Stage II (pT4 N0 M0)	12 (26.7)	54 (34.8)		10 (25.6)	22 (28.2)	
Stage III (pT4 N1 or N2 M0)	33 (73.3)	101 (65.2)		29 (74.4)	56 (71.8)	
pT stage, n (%)			0.063			0.412
pT4a	26 (57.8)	114 (73.5)		23 (59)	53 (66.9)	
pT4b	19 (42.2)	41 (26.5)		16 (41)	25 (33.1)	
pN stage, n (%)			0.272			0.921
N0	12 (26.7)	54 (34.8)		10 (25.6)	22 (28.2)	
N1	20 (44.4)	49 (31.6)		18 (46.2)	33 (42.3)	
N2	13 (28.9)	52 (33.6)		11 (28.2)	23 (29.5)	
Lymphovascular invasion, n (%)	23 (51.1)	88 (56.8)	0.502	19 (48.7)	45 (57.7)	0.432
Perineural invasion, n (%)	12 (26.7)	58 (37.4)	0.216	10 (25.6)	31 (39.7)	0.154
Tumour size (largest dimension, cm) (median [SD])	4.51 (1.91)	4.77 (1.92)	0.393	4.53 (2.02)	4.97 (1.79)	0.245
Tumour grade, n (%)			0.779			0.910
Well differentiated	9 (20)	37 (23.9)		8 (20.5)	18 (23.1)	
Moderately differentiated	18 (40)	64 (41.3)		15 (38.5)	31 (39.7)	
Poorly differentiated	18 (40)	54 (34.8)		16 (41)	29 (37.2)	
Adjuvant treatment, n (%)	35 (77.8)	107 (69)	0.351	29 (74.4)	57 (73.1)	1

Note: Significant *p*-values are indicated in bold.

Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anaesthesiology; BMI, body mass index; LRC, laparoscopic right colectomy; PSM, propensity score matching; RRC, robotic right colectomy; SD, standard deviation; TNM, tumour, nodes and metastasis score.

*Percentage calculated of number of patients with multivisceral resection.

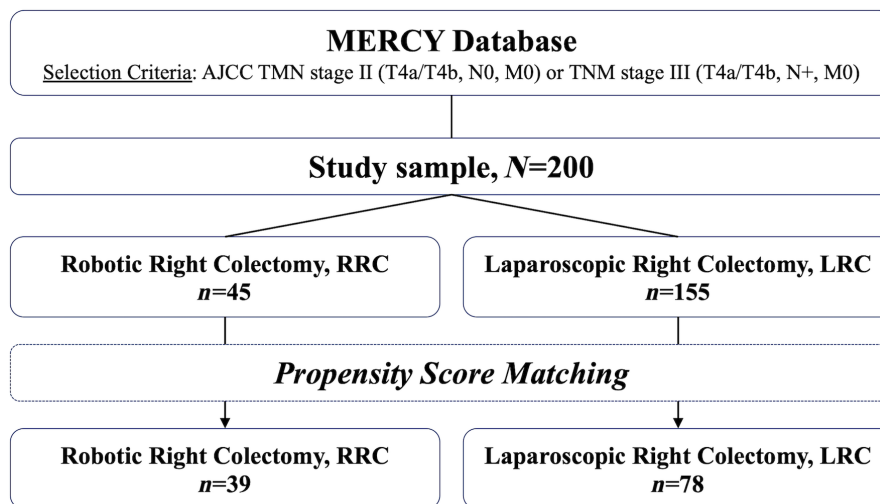


FIGURE 1 Flowchart of the study population selection and propensity score matching.

Table 1. The groups were well balanced (all respective *p*-values >0.05); furthermore, the propensity score showed adequate discrimination accuracy between the treatment groups (with an area under the curve [AUC] of 0.71; range: 0.61–0.82). Overall, 76 (65%)

cancers were classified as T4a (59% in the RRC group vs. 67.9% in the LRC group), and 41 (35%) were classified as T4b (41% in the RRC group vs. 32.1% in the LRC group). Overall, 86 patients (73.5%) received adjuvant treatment, without difference between the groups.

Pathological outcomes

The pathological outcomes are displayed in Table 2. An R0 resection was obtained in the vast majority of patients (94.9%), without a significant difference between RRC and LRC (92.3% for RRC vs. 96.2% for LRC; $p=0.399$). A microscopic residual tumour (i.e., R1) was detected in three (7.7%) and three (3.8%) patients in the RRC and LRC groups, respectively, whereas no macroscopic residual disease (i.e., R2) was observed. At least 12 lymph nodes were retrieved during most right colectomies in both the RRC (97.4%) and LRC (96.2%) groups ($p=1$), but the average number of lymph nodes harvested during the operation (documented in the pathology report) was slightly greater in the RRC group (29.2 [median: 27] lymph nodes) than in the LRC group (26.3 [median: 23] lymph nodes; $p=0.076$).

Operative and postoperative outcomes

Operative and postoperative outcomes are displayed in Table 2. Focusing on intraoperative outcomes, RRC and LRC had comparable mean operating times (193 min for RRC vs. 198 min for LRC; $p=0.750$). RRC was associated with significantly less intraoperative blood loss (36.9 mL for RRC vs. 95.2 mL for LRC; mean difference: -58.3 mL; $p<0.0001$) and a lower conversion rate (5.1% for RRC vs. 20.5% for LRC; $p=0.032$; OR: 0.21; 95% CI: 0.04–0.96) than LRC. In the RRC group, conversion to open surgery was due to technical difficulties related to invasion of the duodenum ($n=2$) during multivisceral resection, whereas in the LRC group, conversion was required due to bleeding ($n=2$), invasion of adjacent organs ($n=11$), or technical difficulties related to tumour size ($n=3$). Conversion to open surgery was more frequent during LRC requiring a multivisceral resection (36.4%) than during LRC not associated with a multivisceral resection (14.3%) ($p=0.058$). Ileocolic anastomosis was performed intracorporeally more frequently in the RRC group (74.4%) than in the LRC group (34.6%) (OR=5.47; 95% CI: 2.3–12.9; $p<0.0001$). Stapled anastomoses were performed in the great majority of patients (77.8%), with a significant difference between the groups (97.4% of stapled anastomosis in the RRC group vs. 67.9% in the LRC group; $p<0.0001$). The hand-sewn anastomoses were all extracorporeal and were performed mainly during laparoscopic procedures (96.2%). Only one anastomosis in the RRC group was hand-sewn; this was an extracorporeal anastomosis performed during a converted procedure.

Only two (2.6%) intraoperative complications occurred (bleeding), both during laparoscopic procedures. Focusing on postoperative outcomes, RRC was associated with fewer complications (17.9% for RRC vs. 41% for LRC; $p=0.013$; OR=0.31; 95% CI: 0.12–0.80), a shorter time to flatus (2 days for RRC vs. 2.85 days for LRC; mean difference=0.85 day; $p=0.009$) and a shorter LOS (6.4 days for RRC vs. 9.5 days for LRC; mean difference=3.15 days; $p=0.004$). No group-related differences were noted for the severity of postoperative complications according to the Clavien–Dindo classification

TABLE 2 Intra- and postoperative outcomes in patients with pT4 right colon cancer in the RRC and LRC groups after propensity score matching ($n=117$).

Variables	RRC group ($n=39$)	LRC group ($n=78$)	<i>p</i> -value
Intraoperative variables			
Operative time (min) (mean [SD])	192.97 (38.68)	198.31 (65.98)	0.750
Conversion to laparotomy, <i>n</i> (%)	2 (5.1)	16 (20.5)	0.032
Operative blood loss (mL) (median [SD])	36.9 (36.1)	95.2 (82.23)	<0.0001
Type of side-to-side anastomosis, <i>n</i> (%)			
Intracorporeal	29 (74.4)	27 (34.6)	<0.0001
Use of ICG fluorescence, <i>n</i> (%)	4 (10.3)	3 (3.8)	0.220
Intraoperative complication, <i>n</i> (%)	0	2 (2.6)	0.552
Postoperative variables			
Number of transfused patients, <i>n</i> (%)	3 (7.7)	8 (10.3)	0.750
Time to flatus (mean [SD])	2 (0.87)	2.85 (1.56)	0.009
Return to regular diet (mean [SD])	3.21 (2.35)	4.40 (2.95)	0.109
Postoperative morbidity, <i>n</i> (%)	7 (17.9)	32 (41)	0.013
Patients with >1 complication*, <i>n</i> (%)	3 (42.9)	12 (37.5)	1
Dindo–Clavien classification*, <i>n</i> (%)			
I/II	5 (71.4)	21 (65.6)	0.366
III/IV	1 (14.3)	10 (31.3)	
V	1 (14.3)	1 (3.1)	
Wound infection, <i>n</i> (%)	0	2 (2.6)	0.552
Prolonged ileus, <i>n</i> (%)	3 (7.7)	6 (7.7)	1
Intra-abdominal abscess, <i>n</i> (%)	1 (2.6)	5 (6.4)	0.662
Anastomotic leakage, <i>n</i> (%)	2 (5.1)	7 (9)	0.716
Hospital stay, days (mean [SD])	6.38 (5.1)	9.5 (6)	0.004
Mortality at 90 days, <i>n</i> (%)	1 (2.6)	1 (1.3)	1
Readmission within 60 days, <i>n</i> (%)	0	7 (9)	0.094
Pathological variables			
Harvested lymph nodes (mean [SD])	29.2 (11.99)	26.3 (13.10)	0.076
≥12, <i>n</i> (%)	38 (97.4)	75 (96.2)	1

TABLE 2 (Continued)

Variables	RRC group (n = 39)	LRC group (n = 78)	p-value
Resection margin status, n (%)			
RO	36 (92.3)	75 (96.2)	0.399

Note: Significant *p*-values are indicated in bold.

Abbreviations: ICG, indocyanine green; LRC, laparoscopic right colectomy; RRC, robotic right colectomy; SD, standard deviation; TNM, tumour, nodes and metastasis score.

*The percentage refers to the number of patients with postoperative complication.

($p=0.366$); more specifically, considering the main types of postoperative complications, no difference was noted for the occurrence of anastomotic leakage, postoperative ileus, wound infections, intra-abdominal abscess, blood transfusion, and mortality, whereas hospital readmission showed a trend toward a higher frequency in the LRC group (9% vs. 0%; $p=0.094$). The overall 90-day mortality was 1.7% ($n=2$); one patient per group died due to sepsis.

As a sensitivity analysis, we compared RRC and LRC with respect to postoperative outcomes after excluding the converted cases ($n=18$). The results are consistent with those observed for the entire PS-matched sample. In particular, RRC was associated with significantly less blood loss ($p=0.001$), fewer postoperative complications

(16.2% vs. 40.3%; $p=0.014$), a shorter time to flatus ($p=0.026$), a shorter time to regular diet ($p=0.035$), and a shorter hospital stay ($p=0.001$) than LRC. No group-related differences were noted for the operating time, anastomotic leakage, ileus, severity of postoperative complications, RO status, hospital readmission rate or number of harvested lymph nodes.

Survival

The mean follow-up time was 23.2 (SD: 19.9; range 1–92 months). The OS and DFS curves are shown in Figures 2 and 3, respectively. The 1-, 3- and 5-year OS rates were 86%, 58.2% and 29.1%, respectively, for the RRC group and 87.5%, 58.1% and 39.6%, respectively, for the LRC group ($p=0.757$). The 1-, 3-, and 5-year DFS rates were 77.7%, 48.6% and 27.8%, respectively, for the RRC group and 63.4%, 49.4% and 36.6%, respectively, for the LRC group ($p=0.321$). Disease recurrence over the entire follow-up period was observed in 14 (35.9%) patients in the RRC group and 29 (37.7%) patients in the LRC group ($p=1$). Overall, 8 (6.8%) patients had local recurrences, and 43 (36.8%) patients had distant metastases, without differences between the RRC and LRC groups ($p=0.877$).

Survival analyses of the entire study sample (without PSM, $n=196$) revealed similar OS and DFS rates. In particular, the 1-,

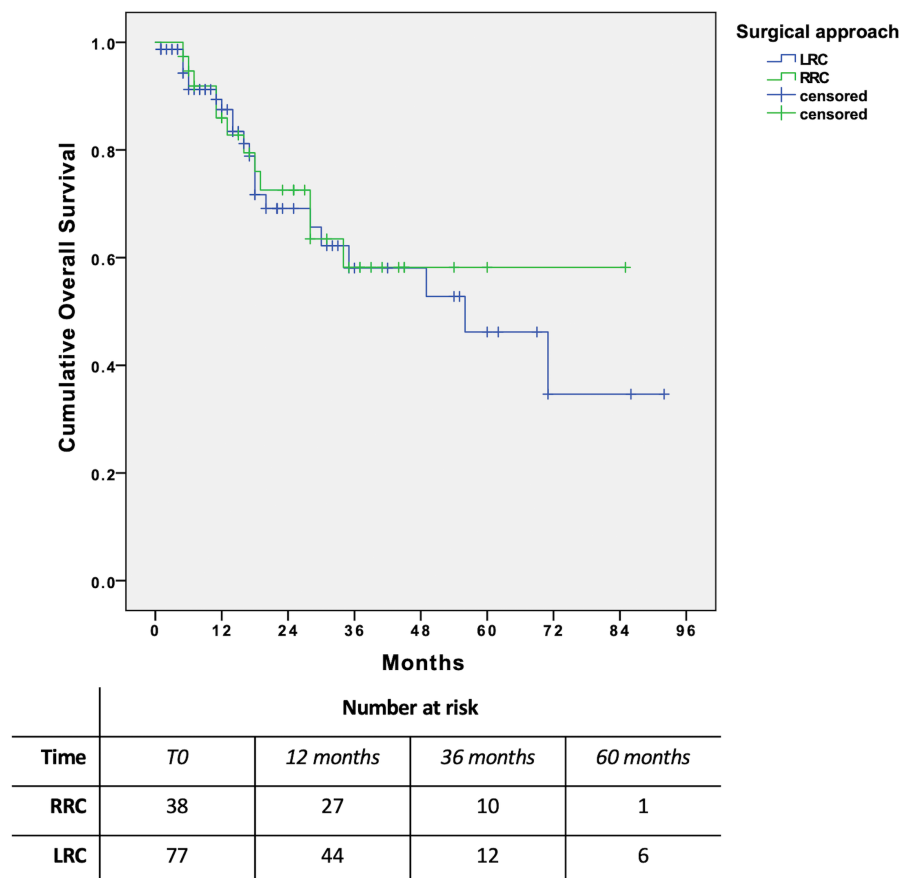


FIGURE 2 Kaplan–Meier curve of overall survival.

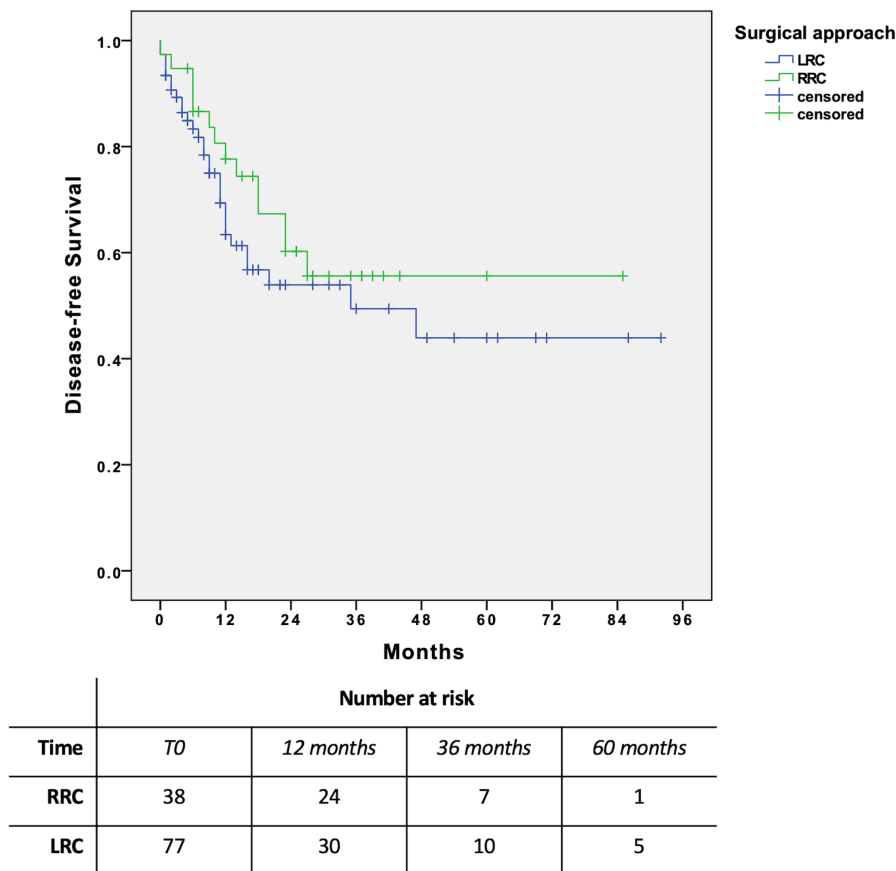


FIGURE 3 Kaplan–Meier curve of disease-free survival.

3- and 5-year OS rates were 87.7%, 60.1% and 40%, respectively, for the RRC group ($n=44$) and 85.3%, 67.6% and 53.4%, respectively, for the LRC group ($n=152$) ($p=0.992$). The 1-, 3- and 5-year DFS rates were 77.8%, 52.6% and 39%, respectively, for the RRC group and 72%, 56.9% and 50.8%, respectively, for the LRC group ($p=0.654$).

DISCUSSION

To the best of our knowledge, this study is the first multicentre PSM analysis comparing short- and long-term outcomes between RRC and LRC for nonmetastatic pT4 right colon cancer patients. The present results suggest that, facing comparable oncological outcomes (R0, number of harvested lymph nodes, OS and DFS), RRC is associated with significantly better peri- and postoperative outcomes in terms of reduced conversion to laparotomy, lower perioperative blood loss, lower morbidity and faster recovery than LRC.

Achieving R0 resection with adequate lymph node clearance is the pillar of surgical oncology [52, 53]. In the case of T4 colon cancer, achieving negative margins may require technically demanding procedures, potentially including en bloc resection of adjacent tumour-invaded organs (i.e., in patients with pT4b disease). This also represents the reason why T4 cancer has been considered an exclusion criterion in most randomized controlled trials comparing MIS to open surgery for colorectal cancer [1, 6–8, 11], limiting the body of

evidence concerning locally advanced cancer. However, MIS, including robotic surgery, has also been increasingly adopted for patients with pT4-stage disease [21, 28–32, 34]. During the past decade, the number of minimally invasive colectomies performed worldwide for locally advanced colon cancer has increased exponentially. Between 2010 and 2014, approximately 35% of pT4 colon cancer cases recorded in the National Cancer Database in the USA were treated laparoscopically or robotically [31]. Similarly, Pacheco and Harris-Gendron in the USA reported a shift toward robotic surgery for T4 colorectal cancers (4.1% robotic resections in 2010 vs. 19.1% in 2017) [33], which is consistent with the data observed in the MERCY database. Globally, in the MERCY European multicentre cohort, the use of robotic surgery has shown an increasing trend over time, particularly for intracorporeal anastomosis [35] but also for pT4 colon cancer.

The feasibility of robotic surgery, particularly for T1–T3 right colon cancer [54], has been explored in recent years. On the one hand, many authors have reported theoretical advantages, such as a higher rate of textbook outcomes [55], shorter LOS [56–58], lower conversion rate [55–57, 59, 60], reduced time to flatus [60] and faster learning curve [39, 61], for RRC than for LRC. However, the only randomized controlled trial comparing RRC versus LRC published thus far showed similar short- and long-term outcomes between the two surgical approaches [9, 10]. Nevertheless, evidence is limited, particularly when evaluating the role of robotic surgery in the subset of patients with pT4 stage right colon cancer [62] (Table 3).

TABLE 3 Summary of the relevant literature about the outcomes of robotic surgery in patients with T4 colon cancer.

First author and year	Parascandola et al. (2021) ³⁴	El-Sharkawy et al. (2021) ³¹	Pacheco & Harris-Gendron (2022) ³³	Present study
Study design	Retrospective PSM study	Retrospective PSM study	Retrospective study	Retrospective PSM study
Study time frame	2010–2016	2010–2014	2015–2017	2014–2020
Data source	National Cancer Database	National Cancer Database	National Cancer Database	MERCY database
Country	United States of America	United States of America	United States of America	Europe (multicentre)
Total sample (n)	26 260	21 998	27 319	200
Sample after PSM (n)	2628	11 224		117
Surgical approach	Open surgery (n = 876)	Open surgery (n = 5612)	Open surgery (n = 14239)	Laparoscopic surgery w(n = 78)
Right colon cancer, n (%)	390 (44.5)	379 (43.3)	396 (45.2)	78 (100)
Multivisceral resection, n (%)	n/a	n/a	n/a	22 (28.2)
Operative time (min) (mean/median [SD/range])	n/a	n/a	n/a	198.31 (65.98)
Conversion to open surgery, n (%)	/	180 (20.6)	1681 (22.3)*	16 (20.5)
Overall postoperative morbidity, n (%)	n/a	n/a	n/a	32 (41)
Mortality, n (%)	34 (3.9)	17 (1.9)	20 (2.3)	1 (1.3)***
Length of hospital stay (mean/median [SD/range])	n/a	n/a	8.66 (7.51)	9.5 (6)
RO, n (%)	719 (82.1)	756 (86.3)	736 (84)	75 (96.2)
Lymph nodes harvested (mean [SD])	n/a	n/a	n/a	26.3 (13.10)
≥12 harvested lymph nodes, n (%)	781 (89.2)	824 (94.1)	821 (93.7)	75 (96.2)
Overall survival rates	45.5% at 5 years	51.8% at 5 years	51.6% at 5 years	86% at 1 year, 58.2% at 3 years and 29.1% at 5 years
Disease-free survival rates	n/a	n/a	n/a	77.7% at 1 year, 48.6% at 3 years and 27.8% at 5 years

Note: Statistically significant results are shown in bold.

Abbreviations: MIS, minimally invasive surgery; n/a, not assessed; PSM, propensity score matching; SD, standard deviation.

*Calculated on the overall MIS population (n = 7532). ***Mortality at 60 days.



A retrospective study conducted by Parascandola et al. compared robotic, laparoscopic, and open resection for the management of pT4 colon cancer [34]. Based on the National Cancer Database in the United States, 876 cases of T4 colon cancer per treatment approach were analysed after applying PSM. Compared with open surgery, laparoscopic and robotic colectomies were associated with significantly higher odds of harvesting 12 or more lymph nodes, shorter time from surgery to chemotherapy, decreased mortality hazards, and increased OS [34]. Moreover, there was no significant difference between the robotic and laparoscopic approaches in terms of short- or long-term oncological outcomes, apart from a decreased odds of conversion to laparotomy in the robotic group. However, in the study by Parascandola et al. [34], no distinction was made between the different procedures required for the resection of pT4 colon cancer lesions, which included partial, subtotal, or total colectomies. Less than half of the cancers (43.2%–45.2%, depending on the surgical approach group) were located at the level of the ascending colon, hepatic flexure, or caecum. Thus, the sample was highly heterogeneous despite the similar stage (T4) because, although debated, right and left colon cancers present significant differences in terms of genetic components, pathophysiology, and prognosis [63–66].

Based on the National Cancer Database, sponsored by the American College of Surgeons and the American Cancer Society in the United States, El-Sharkawy et al. [31] published a PSM analysis aimed at comparing survival outcomes between patients who underwent MIS (laparoscopic and robotic) and those who underwent open surgery for pT4 colon cancer. Overall, 34.2% of patients underwent MIS, but unfortunately, the specific rate of robotic and laparoscopic procedures was not reported. Additionally, the exact location of T4 colon cancer was not described. Notably, a high rate of conversion from MIS to open surgery was described (22.3%), supporting the complexity of MIS resection for pT4 cancer and most likely indicating variable surgeon expertise in MIS among the numerous facilities (>1500) that contributed to the cohort. Nevertheless, compared with open surgery, MIS was associated with improved postoperative mortality, surgical margins, lymph node harvest and five-year survival [31]. In particular, the advantage of an adequate lymph node harvest (≥ 12) associated with MIS was also reported by Pacheco and Harris-Gendron [33] based on 2015–2017 data from the National Cancer Database.

In contrast to the previous literature, which essentially consisted of heterogeneous retrospective databases, the present study involved a PSM analysis of a very specific cohort of patients, namely, those presenting with nonmetastatic pT4 right colon cancer treated by experienced surgeons via a minimally invasive approach. Despite its retrospective nature, the homogeneity of the sample concerns not only the cancer stage (pT4) but also the tumour location (only right colon cancer) and the type of MIS. Moreover, the PSM method allowed us to compare RRC and LRC considering most of the clinical and pathological variables that might influence the choice of surgical technique, including the surgical centre and the year of surgery, thus providing more precise insights into the outcomes of RRC and LRC for pT4 right colon cancer.

RO resection was achieved in 92.3% of patients who underwent RRC and 96.2% of those who underwent LRC, but these two groups were not significantly different. In a recent meta-analysis by Podda et al. [32], RO resection was obtained in 91.6% of laparoscopic colectomies for pT4 tumours, whereas Parascandola et al. [34] achieved negative margins in 86.3% of laparoscopic resections and 84% of robotic resections. In this study, as in the previous literature [31, 33, 34], the mean number of harvested lymph nodes was greater in the RRC group than in the LRC group; however, when assessing the frequency of retrieving 12 or more lymph nodes, no difference was noted between RRC and LRC (97.4% vs. 96.2%, respectively), suggesting that adequate oncological resection can be achieved with both minimally invasive surgical approaches. However, it is not possible to conclude based on the present retrospective data whether the robotic approach allows for more precise central ligation, facilitating more extended lymphadenectomy (e.g., complete mesocolic excision, CME), than does LRC. Moreover, there is a lack of international consensus on the role and technical requirements of CME [67], which deserves further focused trials.

When addressing intraoperative outcomes, RRC performed for pT4 right colon cancer is associated with a significantly lower rate of conversion (5.1% vs. 20.5%) to open surgery. Notably, all operators were experienced surgeons in MIS and robotic surgery, which may explain the low rate of conversion in the RRC group. Conversely, the rate of conversion in the LRC group was similar to that previously reported for T4 colon cancers [31, 34], which might reflect the inherent drawbacks of laparoscopy with straight instruments in complex colorectal resection, namely, the limited range of motion, the lack of flexible instruments, the two-dimensional view, and the poor ergonomics, particularly when multivisceral resection is needed. This can also explain the reduced blood loss (36.9 mL vs. 95.2 mL) and greater rate of intracorporeal anastomosis (74.4% vs. 34.6%) in the RRC group than in the LRC group. Several studies have suggested that unplanned conversion from MIS to open right colectomy may negatively impact postoperative recovery, morbidity and survival [35, 38, 68–70]. However, this finding was not confirmed in the present study, as it was in previous investigations [31, 34], where the oncological outcomes associated with RRC or LRC did not differ. Moreover, when excluding converted procedures from the analyses, the postoperative outcomes, namely, the rate of postoperative complications and recovery, remained significantly better in the RRC group than in the LRC group, suggesting that the observed results are related to the surgical approach and cannot be explained only by the higher rate of conversion to laparotomy observed in the LRC group.

In the present study, the operating times of the RRC and LRC groups were comparable (192.9 min vs. 198.3 min, respectively). This result is likely related to the experience of the surgical teams involved, but it also suggests that robotic platforms may facilitate complex surgical gestures in locally advanced disease (i.e., T4 tumours), helping to overcome the aforementioned drawbacks of laparoscopy [35, 39].

RRC procedures were also associated with significantly improved postoperative outcomes, including shorter time to flatus

(−0.85 day), reduced overall postoperative morbidity (OR=0.31), and shorter LOS (−3.15 days). Based on recent evidence, performing an intracorporeal instead of an extracorporeal anastomosis during minimally invasive right colectomy might lead to potential benefits, such as reduced short-term morbidity, faster recovery, and shorter LOS [36, 71–76]. Moreover, these results are consistent with several studies that reported improved in-hospital and short-term outcomes in patients who underwent robotic colectomy [77–82]. However, regarding the type and severity of postoperative complications, there was no significant difference between RRC and LRC in terms of anastomotic leakage or severe Clavien–Dindo complications.

Focusing on the long-term outcomes, the 1-, 3- and 5-year OS and DFS in the present study were similar between the RRC and LRC groups, both in the PSM and entire cohorts, and were consistent with previous results shown in other studies on T4 colon cancer [20, 31, 32, 83–85]. According to the meta-analysis by Podda et al. [32], laparoscopic colectomy for T4 colon cancer was associated with pooled 3- and 5-year OS rates of 77.8% and 49.9%, respectively, and with pooled 3- and 5-year DFS rates of 64.1% and 54.9%, respectively.

Although this study represents the first multicentre PSM analysis of RRC versus LRC for pT4 right colon cancer, the current results should be interpreted with caution considering several limitations. First, the retrospective design is associated with potential selection and reporting bias, providing a limited number of routinely collected variables for analyses. In an effort to mitigate this limitation, only experienced colorectal surgeons and referral centres applying enhanced recovery protocols were included. In addition, we utilized a PSM analysis to make RRC and LRC comparable despite the absence of randomization. Indeed, when RCTs are not available, the best evidence might be obtained from a nonrandomized study with a PSM design based on a prospectively maintained database and an intention-to-treat analysis [86]. Finally, it was not possible to perform a cost-effectiveness analysis of RRC versus LRC because the specific costs of surgical instruments, operating room occupancy, maintenance of the robotic platforms, and hospital stay were not available or estimable due to considerable variance across countries or within Europe. Nevertheless, it must be emphasized that the higher financial costs associated with RRC over LRC represent a major barrier to the widespread adoption of robotic platforms; thus, future studies with cost–benefit analyses are advocated [82]. However, since RRC could be associated with better perioperative outcomes (i.e., reduced conversion to laparotomy, lower perioperative blood loss, lower morbidity, and faster recovery than LRC), this could impact the perioperative costs and the burden of pT4 colon cancer on both the patient and the health care provider.

In conclusion, the present study provides evidence to support the feasibility of MIS for nonmetastatic pT4 right colon cancer. Compared with LRC, RRC appears to be technically feasible, providing oncological adequacy and improved short-term postoperative outcomes, such as a lower risk of conversion to open surgery, reduced blood loss, a greater rate of intracorporeal anastomosis, lower

morbidity, and a shorter LOS. Thus, the present results support the application of robotic surgery in performing complex colonic resections in oncological patients.

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CONFLICT OF INTEREST STATEMENT

The authors confirm that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This research was declared to the National Commission for Data Protection and Liberties (2210699) and approved by the Institutional Review Board (00011558). Personal data were collected after informing the involved patients and were treated in accordance with the ethical standards of the Helsinki Declaration.

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