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Comparing laparoscopic surgery with open surgery for long-term outcomes in patients with stage I to III colon cancer

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ABSTRACT

Background: Although the short-term advantages of laparoscopy for colon cancer (CC) over open surgery have been clearly demonstrated, there is little evidence available concerning the long-term outcomes. This study aimed to compare the long-term results of laparoscopic surgery versus open surgery in a cohort of CC patients from a single center.

Methods: A series of 443 patients consecutively operated on for stage I to III CC between January 2006 and December 2013 were followed up. Patients were divided into two groups according to the surgical technique and were compared for disease-free survival (DFS) and overall survival (OS) before and after 1:1 propensity score matching.

Results: Due to exclusions and drop-outs, the statistical analysis of the study is based on 398 patients. Open surgery was performed in 133 patients, and laparoscopic surgery was performed in 265. After propensity score matching, two comparable groups of 89 patients each were obtained. The 5-year DFS was 64.3% and 78.2% for patients in the open and laparoscopic resection groups, respectively [hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.33–1.19; P = 0.148]. A 5-year OS of 72.1% and 86.8% was observed in the open and laparoscopic resection groups, respectively (HR 0.43, 95%CI 0.20–0.94; P = 0.026). The multivariate survival analysis demonstrated better results of laparoscopy compared with open surgery for both DFS (HR 0.43, 95%CI 0.23–0.78; P = 0.004) and OS (HR 0.28, 95%CI 0.14–0.59; P < 0.001).

Conclusions: Despite the limitations of a retrospective analysis, our study confirms better results for laparoscopic surgery in terms of DFS and OS compared with open surgery in CC treatment.

1. Introduction

Although laparoscopic colectomy was described for the first time by Jacobs and coworkers [1] in 1991, its generalized adoption in colorectal cancer (CRC) treatment has been slower than expected. While a number of randomized and non-randomized studies have definitely confirmed the short-term advantages of laparoscopy when compared with traditional treatment in terms of cosmesis, pain control, bowel function, postoperative morbidity, and hospital stay [2–7], until now, evidence that laparoscopic colectomy is superior to open colectomy on a long-term basis is scanty. The long-term follow-up data from the CLASSIC and COLOR trials have demonstrated that laparoscopically assisted surgery is oncologically safe, and represents a suitable alternative to open surgery in the treatment of CRC with similar long-term results [8,9]. To our knowledge, only Lacy et al. [10] published a randomized trial reporting a significantly higher cancer-related survival in patients receiving laparoscopic colectomy compared with those undergoing open colectomy for non-metastatic colon cancer (CC).

Other retrospective and/or nonrandomised studies have reported potential survival benefits in patients undergoing laparoscopic surgery [11–15]. However, these studies are very heterogeneous, with a limited number of patients; in addition, they include rectal carcinoma, and some have an insufficient number of nodes removed and/or analyzed.

The purpose of this study was to compare the long-term

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outcomes of elective open and laparoscopic surgery in a cohort of consecutive CC patients. One of the peculiarities of this series is that the same surgeon performed all the surgical procedures following the same oncological and clinical criteria both in the open and laparoscopic groups of patients.

2. Materials and methods

A total of 849 consecutive patients with an endoscopic diagnosis of CRC or tubular adenoma with dysplasia, endoscopically unresectable, underwent elective surgery from January 2006 to December 2013 in our surgical unit. Patients with rectal cancer, those with stage IV disease, and those who had a postoperative histopathological diagnosis of tubular adenoma with dysplasia were excluded from the study, leaving 443 CC cases available for the analysis. The study, which was in compliance with the Declaration of Helsinki, was approved by the ethics committee of Careggi University Hospital.

2.1. Preoperative workup and surgical techniques

Diagnosis was determined by pancolonoscopy with multiple biopsies. In cases of incomplete colonoscopy, computed tomographic (CT) colography was performed. The pretreatment tumor stage was determined in all patients by chest and abdominal CT scan.

All study patients underwent curative standard colectomy and *en-bloc* regional lymphadenectomy. All the surgical procedures were performed either via conventional open or laparoscopic access by the same surgeon (PB), with vast experience in colorectal surgery. All laparoscopic procedures were performed through a standardized medial-to-lateral approach, with proximal ligation of vascular pedicles. Open resections were performed through a midline incision in a standard manner.

All the patients were thoroughly informed about the surgical procedure and the study, and gave written consent for the investigation.

The choice of the surgical procedure was based primarily on the patient's own preference and on his/her history of previous abdominal surgery. Laparoscopic or open surgery was performed regardless of the clinical stage.

Tumors were staged according to the current American Joint Commission on Cancer/International Union Against Cancer TNM staging system [16].

2.2. Adjuvant therapy and follow-up schedule

Adjuvant therapy was administered according to the pathological stage and the oncologist's recommendation. During the entire study period, the chemotherapy regimen including fluorouracil, leucovorin, and oxaliplatin was used as standard adjuvant treatment [17]. Apart from the stage, the primary reasons for a patient not receiving chemotherapy were his/her refusal, medical decision (mainly based on age), and/or inadequate health conditions.

All patients were included in an oncological follow-up program. The patients were followed up at periodic intervals at our ambulatory center and through periodic phone calls. The follow-up schedule included a clinical check-up and serum carcinoembryonic antigen (CEA) level evaluation every 6 months in the first 2 years and then once a year, chest and abdominal CT scan or liver ultrasound once a year, and colonoscopy performed 1 year after surgery and then again at the third and fifth year of follow-up.

Follow-up documentation, date of tumor recurrence, date of tumor-related or unrelated deaths, overall survival (OS), and disease-free survival (DFS) were assessed. OS was defined as the time from the date of primary treatment to the date of death from any cause. DFS was defined as the time from primary treatment to the date of first recurrence or death, whichever occurred first. Locoregional or distant recurrences were detected by imaging and, whenever possible, confirmed by histological examination. Observation times of patients alive without recurrence were censored at the date of the last follow-up information.

2.3. Statistical analysis

A 1:1 nearest-neighbour matching based on the propensity score was used to minimize the potential selection bias due to the retrospective study design. The propensity score represents the probability of undergoing laparoscopic surgery conditional to a pattern of clinical characteristics for each patient and was estimated using a logistic regression model that included the following covariates: year of surgery, sex, age at surgery, body mass index (BMI) category, American Association of Anesthesiologists (ASA) score, tumor site, and previous abdominal surgery (no vs. minor vs. major surgery). Each patient of the laparoscopic group was matched with a patient of the open surgery group who had the closest estimated propensity score. Patients for whom matching could not be performed were excluded from the propensity score-matched population. Patient demographic and clinical characteristics were summarized as frequencies and percentages. Continuous variables were reported as mean $\pm$ standard deviation or median and interquartile range (IQR). The following demographic and clinical variables were investigated: year of surgery, sex, age at the time of intervention, previous abdominal surgery, BMI category, ASA score, tumor site, pathological T and N stages, number of evaluated nodes, type of surgical approach, and medical treatment. In all analyses, age was categorized according to the quintiles of its distribution. The distributions of categorical variables in the two treatment groups were compared using the chi-square test and the McNemar test before and after matching, respectively. Differences in continuous variables were assessed with the Wilcoxon-Mann–Whitney and Wilcoxon signed-rank tests before and after matching, respectively. The standardized mean differences (d) were also reported as an estimate of group divergence [18]. Median follow-up time was estimated according to the Kaplan-Meier reverse method [19]. All the variables were investigated for their impact on DFS and OS. For univariate analysis, estimates of DFS and OS rates were calculated according to the Kaplan-Meier product-limit method [20]. Hazard ratios and their 95% confidence intervals (Cis) were also calculated by means of the Cox proportional hazard model. The multivariate Cox regression model was fitted to evaluate the independent effect on DFS and OS of any factors whose p value was $\leq$0.20 at the univariate analysis. The likelihood ratio test was used to test the statistical significance of all coefficients. The Cox proportional hazard model was stratified by the matched pairs in the propensity score matching analyses. The consistency of the intervention effect according to the pathological stage was investigated with a pre-planned interaction test. Data were analyzed using the statistical software SAS 9.2 (SAS Corporation, Cary, NC). A two-sided p value $\leq$ 0.05 was considered statistically significant. This manuscript was written according to the STROBE statement for the reporting of observational studies [21].

3. Results

The overall study population consisted of 443 patients with stage I to III CC who underwent a curative resection for CC. Twenty-nine patients (6.6%) were lost to follow-up, ten patients (2.3%) were excluded for synchronous CC, and six patients (1.4%) were excluded for metachronous CC during the study period. Therefore, 398

Table 1
Patient and tumor characteristics by surgical approach before and after propensity score matching.

Variable	Total		Open surgery		Laparoscopy		P value[a]	d
	No.	%	No.	%	No.	%		
Before PS matching	N = 398		N = 133		N = 265			
Year of surgery								
2006–2007	78	19.6	43	32.3	35	13.2	<0.001	0.49
2008–2009	101	25.4	33	24.8	68	25.7		
2010–2011	118	29.6	29	21.8	89	33.6		
2012–2013	101	25.4	28	21.1	73	27.5		
Sex								
Male	204	51.3	72	54.1	132	49.8	0.416	0.09
Female	194	48.7	61	45.9	133	50.2		
Age, years								
Median (IQR)	72 (62–79)		75 (65–81)		71 (60–78)		<0.001	0.39
I quintile	80	20.1	15	11.3	65	24.5	0.005	0.43
II quintile	76	19.1	28	21.1	48	18.1		
III quintile	79	19.9	22	16.5	57	21.5		
IV quintile	82	20.6	32	24.0	50	18.9		
V quintile	81	20.3	36	27.1	45	17.0		
Previous abdominal surgery								
No	223	56.0	49	36.8	174	65.7	<0.001	0.75
Minor	146	36.7	59	44.4	87	32.8		
Major	29	7.3	25	18.8	4	1.5		
BMI category								
Underweight	24	6.0	9	6.8	15	5.7	0.090	0.27
Normal	142	35.7	48	36.1	94	35.5		
Overweight	168	42.2	47	35.3	121	45.6		
Obese	64	16.1	29	21.8	35	13.2		
ASA score								
I	29	7.3	3	2.3	26	9.8	<0.001	0.47
II	163	40.9	44	33.1	119	44.9		
III	179	45.0	72	54.1	107	40.4		
IV	27	6.8	14	10.5	13	4.9		
Tumor site								
Right colon	151	37.9	48	36.1	103	38.9	0.033	0.27
Transverse colon	43	10.8	22	16.5	21	7.9		
Descending and Pelvic colon	204	51.3	63	47.4	141	53.2		
pT								
pT1, pT2	116	29.2	26	19.6	90	34.0	0.003	0.33
pT3, pT4	282	70.8	107	80.4	175	66.0		
pN								
pN0	277	69.6	91	68.4	186	70.2	0.226	0.18
pN1	81	20.4	24	18.1	57	21.5		
pN2	40	10.0	18	13.5	22	8.3		
UICC stage								
I	103	25.9	26	19.6	77	29.1	0.105	0.23
II	170	42.7	64	48.1	106	40.0		
III[b]	125	31.4	43	32.3	82	30.9		
Adjuvant CT								
No	236	59.3	83	62.4	153	57.7	0.371	0.10
Yes	162	40.7	50	37.6	112	42.3		
After PS matching	N = 178		N = 89		N = 89			
Year of surgery								
2006–2007	42	23.6	22	24.7	20	22.5	0.795	0.09
2008–2009	50	28.1	26	29.2	24	27.0		
2010–2011	44	24.7	21	23.6	23	25.8		
2012–2013	42	23.6	20	22.5	22	24.7		
Sex								
Male	92	51.7	47	52.8	45	50.6	0.871	0.05
Female	86	48.3	42	47.2	44	49.4		
Age, years								
Median (IQR)	73 (64–79)		73 (65–80)		72 (64–79)		0.845	0.04
I quintile	24	13.5	11	12.4	13	14.6	0.831	0.20
II quintile	39	21.9	21	23.6	18	20.2		
III quintile	37	20.8	19	21.3	18	20.2		
IV quintile	42	23.6	18	20.2	24	27.0		
V quintile	36	20.2	20	22.5	16	18.0		
Previous abdominal surgery								
No	88	49.4	43	48.3	45	50.6	0.769	0.14
Minor	84	47.2	44	49.4	40	44.9		
Major	6	3.4	2	2.3	4	4.5		
BMI category								
Underweight	6	3.4	3	3.4	3	3.4	0.739	0.09
Normal	68	38.2	33	37.1	35	39.3		

(*continued on next page*)

Table 1 (*continued*)

Variable	Total		Open surgery		Laparoscopy		P value[a]	d
	No.	%	No.	%	No.	%		
Overweight	69	38.8	34	38.2	35	39.3		
Obese	35	19.6	19	21.3	16	18.0		
ASA score								
I	5	2.8	3	3.4	2	2.3	0.783	0.20
II	64	36.0	34	38.2	30	33.7		
III	94	52.8	43	48.3	51	57.3		
IV	15	8.4	9	10.1	6	6.7		
Tumor site								
Right colon	71	39.9	33	37.1	38	42.7	0.521	0.11
Transverse colon	23	12.9	12	13.5	11	12.4		
Descending and Pelvic colon	84	47.2	44	49.4	40	44.9		
pT								
pT1, pT2	46	25.8	18	20.2	28	31.5	0.110	0.26
pT3, pT4	132	74.2	71	79.8	61	68.5		
pN								
pN0	114	64.0	59	66.3	55	61.8	0.323	0.27
pN1	37	20.8	14	15.7	23	25.8		
pN2	27	15.2	16	18.0	11	12.4		
UICC stage								
I	39	21.9	18	20.2	21	23.6	0.581	0.14
II	74	41.8	40	44.9	34	38.2		
III*	65	36.5	31	34.9	34	38.2		
Adjuvant CT								
No	103	57.9	53	59.5	50	56.2	0.720	0.07
Yes	75	42.1	36	40.5	39	43.8		

Abbreviations: d, standardized mean difference; PS, propensity score; IQR, interquartile range; BMI, body mass index; CT, chemotherapy.
[a] Chi-square for heterogeneity, Wilcoxon-Mann-Whitney, McNemar, or Wilcoxon signed-rank test.
[b] pN0/N1c cases were included in the stage III group.

Table 2
Number of retrieved lymph nodes by surgical approach before and after propensity score matching.

Variable	Total		Open surgery		Laparoscopy		P value[a]	d
	No.	%	No.	%	No.	%		
Before PS matching	N = 398		N = 133		N = 265			
Mean ± SD	23.2 ± 11.9		24.3 ± 12.9		22.7 ± 11.3		0.203	0.13
Median (IQR)	22 (14–30)		22 (16–31)		22 (13–29)		0.351	0.10
Number of retrieved nodes								
<12	64	16.1	19	14.3	45	17.0	0.490	0.07
≥12	334	83.9	114	85.7	220	83.0		
After PS matching	N = 178		N = 89		N = 89			
Mean ± SD	22.8 ± 12.0		23.8 ± 12.7		21.7 ± 11.2		0.249	0.18
Median (IQR)	21 (13–29)		21 (16–30)		19 (12–29)		0.209	0.15
Number of retrieved nodes								
<12	32	18.0	12	13.5	20	22.5	0.185	0.24
≥12	146	82.0	77	86.5	69	77.5		

Abbreviations; d, standardized mean difference; PS, propensity score; SD, standard deviation; IQR, interquartile range.
[a] Unpaired Student *t*-test, Wilcoxon-Mann-Whitney, chi-square for heterogeneity, paired Student *t*-test, Wilcoxon signed-rank, or McNemar test.

(89.8%) patients were considered eligible for the analyses: 133 underwent open resections, and 265 underwent laparoscopic resections. The conversions (52 cases, 19.6%) were included in the laparoscopic resection group according to the intention-to-treat principle.

Data concerning individual, demographic, and CC stage of the 398 patients are shown in Table 1. At baseline, significant imbalances between the two groups were found for year of surgery ($P < 0.001$, $d = 0.49$), age at surgery ($P < 0.001$, $d = 0.39$), previous abdominal surgery ($P < 0.001$, $d = 0.75$), ASA score ($P < 0.001$, $d = 0.47$), tumor site ($P = 0.033$, $d = 0.27$), and pathological T status ($P = 0.003$, $d = 0.33$).

After propensity score matching, 89 patients comprized each of the two groups. Twenty-two (24.7%) of the laparoscopic group were conversions. Demographic, clinical, and tumor characteristics of the 178 patients are reported in Table 1, and no differences in the distributions for any of the variables were found.

In the overall population, there was a mean of 23.2 lymph nodes identified in the specimens, and 83.9% of the patients had 12 or more retrieved/analyzed lymph nodes (Table 2). After propensity score matching, a mean of 22.8 retrieved/analyzed lymph nodes was assessed and 12 or more lymph nodes were analyzed in 82.0% of the patients (Table 2). The open and laparoscopic group of patients did not differ in the average number of retrieved/analyzed lymph nodes, either before or after propensity score matching ($P = 0.351$, $d = 0.10$ and $P = 0.209$, $d = 0.15$, respectively). In addition, the probability of having 12 or more lymph nodes retrieved/analyzed did not differ between the two surgical techniques either before or after propensity score matching ($P = 0.490$, $d = 0.07$ and $P = 0.209$, $d = 0.15$, respectively) (Table 2).

Table 3
Long-term outcomes before and after propensity score matching[a] (univariate analysis).

Variable	Open surgery	Laparoscopy	HR (95% CI)	P Value[b]
Before propensity score matching	N = 133	N = 265		
Disease-free survival				
Events - no. (%)	55 (41.4)	43 (16.2)		
5-year disease-free survival, %[a]	64.3 (54.8–72.3)	81.0 (74.7–85.9)	0.39 (0.26–0.58)	<0.001
Overall survival				
Deaths – no. (%)	49 (36.8)	26 (9.8)		
5-year overall survival, %[a]	71.1 (61.8–78.6))	87.4 (81.3–91.5)	0.28 (0.18–0.46)	<0.001
After propensity score matching	N = 89	N = 89		
Disease-free survival				
Events - no. (%)	36 (40.4)	18 (20.2)		
5-year disease-free survival, %[a]	64.3 (52.3–74.0)	78.2 (66.8–86.0)	0.63 (0.33–1.19)	0.148
Overall survival				
Deaths – no. (%)	31 (34.8)	11 (12.4)		
5-year overall survival, %[a]	72.1 (60.0-81-0)	86.8 (75.9–93.0)	0.43 (0.20–0.94)	0.026

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Values in parentheses are 95% CI.
[b] Likelihood-ratio test.

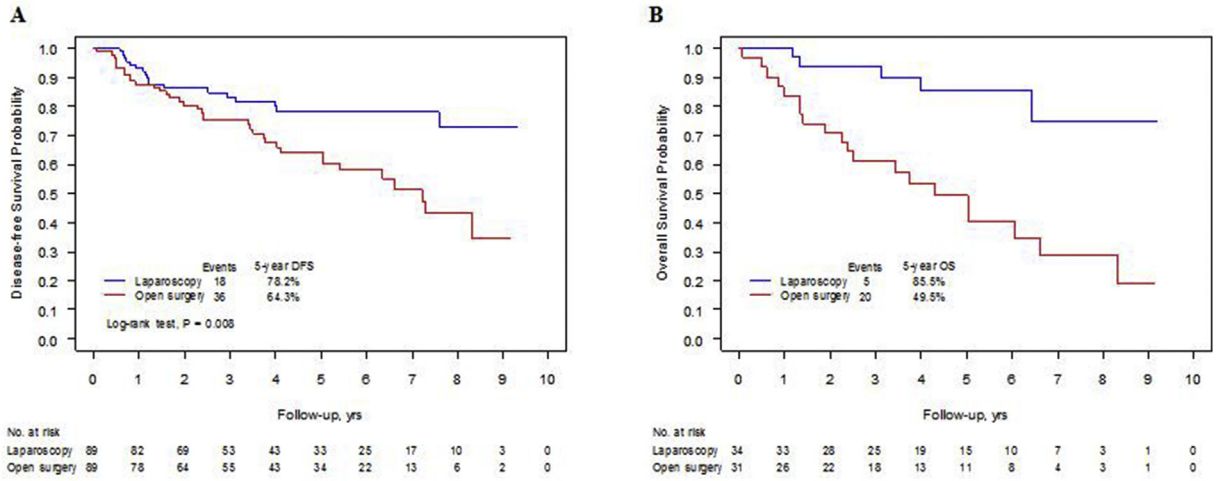

Fig. 1. Kaplan-Meier estimates of disease free (A) and overall survival (B) according to the intervention technique after propensity score matching. (2-column fitting image).

3.1. Long-term results

In the 178 patients analyzed after propensity score matching, the median follow-up time was 60.2 months (IQR 36.3–87.3 months). Recurrences occurred in 31 cases (17.4%), and 42 patients (23.6%) died.

Univariate analysis showed that the 5-year DFS was 64.3% in the open surgery and 78.2% in the laparoscopic resection groups (HR 0.63, 95%CI 0.33–1.19; P = 0.148) (Table 3 and Fig. 1). The 5-year OS was 72.1% for patients in the open resection group and 86.8% for patients undergoing laparoscopic surgery (HR 0.43, 95%CI 0.20–0.94; P = 0.026) (Table 3 and Fig. 1). When the multivariate analysis was performed, adjusting for sex, age at surgery, previous abdominal surgery, ASA score, and Union for International Cancer Control (UICC) stage, the results of laparoscopic surgery on long-term outcomes appeared significantly better both for DFS (HR 0.43, 95%CI 0.23–0.78; P = 0.004) and for OS (HR 0.28, 95%CI 0.14–0.59; P < 0.001).

When patients were stratified by pathological stage, the differences in the impact of the two surgical techniques on both DFS (P = 0.923, test for interaction) and OS (P = 0.838, test for interaction) were similar in the different strata.

To assess the robustness of the primary propensity score matching analysis, the statistical evaluation of long-term results was also performed on the whole population of 398 patients. More importantly and similarly to the aforementioned findings in the propensity score group, univariate analysis produced evidence of an advantage in DFS and OS for the laparoscopically treated patients in the whole population (Table 3). Moreover, the univariate models identified the following parameters as being statistically significant predictive factors for both DFS and OS: age at surgery, previous abdominal surgery, ASA score, pT and pN categories, and UICC stage (Table 4). Multivariate analysis identified previous abdominal surgery, ASA score, and advanced stage disease as the strongest independent prognostic factors for worse results in terms of both DFS and OS, whereas sex and age at surgery were associated with OS only. Moreover and more importantly, at multivariate analysis, the laparoscopic approach was confirmed to have better results in terms of both DFS (HR 0.60, 95%CI 0.39–0.94; P = 0.025) and OS (HR 0.40, 95%CI 0.24–0.69; P < 0.001) when compared with open surgery (Table 5).

4. Discussion

The main finding of the present article is that the laparoscopic treatment of CC patients has better long-term results when compared with open surgery, both in the overall and propensity score matched populations under study. These results appear to

Table 4
Univariate analysis in 398 patients.

Variable	Disease-free survival			Overall survival		
	5-year DFS	HR (95% CI)	P value[a]	5-year OS	HR (95% CI)	P value[a]
Year of surgery						
2006–2007	80.8%	1 (ref.)	0.269	87.2%	1 (ref.)	0.254
2008–2009	74.3%	1.37 (0.77–2.46)		78.2%	1.49 (0.79–2.81)	
2010–2011	77.3%	1.36 (0.73–2.55)		85.8%	1.20 (0.57–2.53)	
2012–2013	NE	2.04 (1.01–4.13)		NE	2.29 (0.96–5.47)	
Sex						
Male	73.3%	1 (ref.)	0.135	78.7%	1 (ref.)	0.103
Female	77.2%	0.74 (0.49–1.10)		84.8%	0.68 (0.43–1.09)	
Age						
I quintile	85.5%	1 (ref.)	<0.001	95.3%	1 (ref.)	<0.001
II quintile	82.8%	1.04 (0.47–2.33)		93.5%	1.66 (0.54–5.06)	
III quintile	78.5%	1.59 (0.76–3.29)		87.1%	2.48 (0.86–7.14)	
IV quintile	75.3%	2.33 (1.17–4.63)		76.7%	5.62 (2.14–14.8)	
V quintile	51.7%	3.36 (1.72–6.57)		53.7%	8.51 (3.27–22.1)	
Previous abdominal surgery						
No	78.4%	1 (ref.)	<0.001	83.6%	1 (ref.)	<0.001
Minor	75.5%	1.43 (0.93–2.19)		84.6%	1.21 (0.73–2.00)	
Major	48.9%	3.83 (2.09–7.03)		50.1%	5.01 (2.63–9.54)	
BMI category						
Underweight	70.8%	1 (ref.)	0.851	75.0%	1 (ref.)	0.824
Normal	76.6%	0.72 (0.32–1.63)		79.7%	0.77 (0.32–1.86)	
Overweight	74.9%	0.82 (0.37–1.81)		80.9%	0.72 (0.30–1.73)	
Obese	74.4%	0.85 (0.35–2.05)		89.9%	0.62 (0.23–1.68)	
ASA score						
I	96.6%	1 (ref.)	<0.001	96.3%	1 (ref.)	<0.001
II	82.3%	6.83 (0.93–50.1)		91.1%	4.63 (0.62–34.7)	
III	70.7%	12.3 (1.70–89.0)		75.4%	11.3 (1.55–82.3)	
IV	28.6%	31.4 (4.11–239.6)		38.5%	34.9 (4.49–270.8)	
Tumor site						
Right colon	72.6%	1 (ref.)	0.488	78.1%	1 (ref.)	0.336
Tr. colon	83.5%	0.69 (0.33–1.41)		89.4%	0.64 (0.28–1.45)	
Desc./pelvic	75.4%	0.83 (0.54–1.25)		82.6%	0.73 (0.45–1.17)	
pT						
pT1, pT2	92.0%	1 (ref.)	<0.001	92.0%	1 (ref.)	<0.001
pT3, pT4	68.1%	5.90 (2.86–12.2)		77.3%	4.99 (2.29–10.9)	
pN						
pN0	81.3%	1 (ref.)	<0.001	86.5%	1 (ref.)	0.002
pN1	67.5%	1.75 (1.10–2.79)		75.3%	1.80 (1.07–3.05)	
pN2	48.6%	3.11 (1.82–5.32)		62.2%	2.95 (1.60–5.44)	
UICC stage						
I	91.0%	1 (ref.)	<0.001	91.0%	1 (ref.)	<0.001
II	76.2%	4.13 (1.94–8.80)		84.9%	3.37 (1.48–7.69)	
III[b]	60.8%	6.16 (2.91–13.1)		70.2%	5.34 (2.39–12.0)	
Adjuvant CT						
No	76.1%	1 (ref.)	0.507	79.2%	1 (ref.)	0.543
Yes	74.0%	1.15 (0.77–1.71)		85.6%	0.87 (0.54–1.38)	

Abbreviations: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; CT, chemotherapy.
[a] Likelihood-ratio test.
[b] pN0/N1c cases were included in the stage III group.

confirm those from a previous single-center randomized surgical study of stage III CC [10] and from two randomized trials that have investigated the non-inferiority of laparoscopy in long-term oncological outcome [8,9]. Our results are also consistent with those from a few non-randomized studies, which have shown that laparoscopic resection is associated with significantly better DFS and cancer-related survival in patients with stage III CC [11–15]. The compliance of our study, at variance from some of these previous reports [10,13,14], with the UICC recommendation of at least 12-node evaluation for correct stage determination, seems to strengthen our findings.

The conversion rate of 19.6% is consistent with some of the previous reports [2–4,22], whereas it may appear high when compared with more recent ones [23,24]. However, a policy of early conversion was followed in our study, since it always took place before vascular ligation/division and it was primarily confined to the earliest period of our series. Conversions were exclusively due to anatomic or technical reasons such as relevant and diffuse coalescence of the mesenteries, and postoperative adhesions and/or difficulties in a correct exposure of the operating field.

The univariate analysis on the entire study population showed a statistically significant advantage both in DFS and OS for laparoscopic surgery. Despite the overall homogeneity of our series (same surgeon, same oncologic radicality, rectal cancer and non-elective surgery excluded), the significance of this finding is mitigated by the retrospective nature of our study with potential selection biases, as demonstrated by the unbalanced distribution of patients between the two groups (laparoscopic/open surgery) for year of surgery, age at surgery, presence/absence of previous abdominal surgery, ASA score, tumor site, and pathological T status. For this reason and with the purpose of compensating for the consequent drawbacks, statistical analysis was also approached by means of propensity score, which confirmed at the univariate analysis the statistically significant positive impact of laparoscopic surgery on

Table 5
Multivariate analysis in 398 patients.

Variable	Disease-free survival		Overall survival	
	HR (95% CI)	P value[a]	HR (95% CI)	P value[a]
Sex				
Male	1 (ref.)	0.060	1 (ref.)	0.034
Female	0.65 (0.42–1.02)		0.57 (0.34–0.97)	
Age				
I quintile	1 (ref.)	0.276	1 (ref.)	0.002
II quintile	0.79 (0.35–1.76)		1.36 (0.44–4.19)	
III quintile	1.42 (0.66–3.05)		2.62 (0.87–7.83)	
IV quintile	1.24 (0.59–2.59)		3.55 (1.25–10.1)	
V quintile	1.72 (0.80–3.70)		5.82 (1.97–17.2)	
Previous abdominal surgery				
No	1 (ref.)	0.028	1 (ref.)	0.029
Minor	1.27 (0.79–2.03)		0.75 (0.42–1.34)	
Major	2.69 (1.35–5.37)		2.13 (1.00–4.52)	
ASA score				
I	1 (ref.)	0.004	1 (ref.)	0.009
II	4.32 (0.58–32.1)		2.08 (0.27–16.0)	
III	4.73 (0.62–36.0)		2.16 (0.27–17.1)	
IV	13.9 (1.69–114.6)		7.92 (0.92–68.1)	
UICC stage				
I	1 (ref.)	<0.001	1 (ref.)	<0.001
II	3.24 (1.50–7.04)		2.14 (0.91–5.02)	
III	6.53 (3.02–14.1)		5.03 (2.18–11.6)	
Intervention technique				
Open surgery	1 (ref.)	0.025	1 (ref.)	<0.001
Laparoscopy	0.60 (0.39–0.94)		0.40 (0.24–0.69)	

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Likelihood-ratio test.

OS. As far as DFS, which appeared greater in the laparoscopic group without attaining significance at univariate analysis, two remarks must be made. First, the measurements of the relative risk and their CIs obtained in the two populations, matched and non-matched, were almost identical for DFS. Second, propensity score matching induced a reduction of the total number of the events included in the analysis, thus decreasing the statistical power of the study. The combination of these two facts seems to strengthen the meaning of the finding of better results in the laparoscopic group also for DFS, despite significance is not attained at univariate analysis. Moreover, and even more importantly, in the propensity score multivariate analysis, which was performed to improve the precision of the hazard ratio estimates, the significantly favorable role of the laparoscopic technique was confirmed for both DFS and OS, similarly to what was shown by the multivariate analysis in the whole population.

If the advantage of laparoscopy, which is also detected in each of the different CC stages, is added to all the previous remarks, the conclusion in our series that the laparoscopic option improves the long-term results of surgery seems to be entirely justified. Furthermore, it suggests the strategic significance of a laparoscopic option despite variable conversion rates, which each series, ours included, presents.

Some possible explanations have been previously provided that could account for improved long-term results of laparoscopy. They include the diminished surgical stress and postoperative pain due to less tissue and tumor manipulation, as well as the decrease in postoperative complication rates and blood transfusions with a better preservation of the early postoperative cellular immune response [25,26]. Consistent with these data, better preserved and/or earlier recovered humoral immunity has been recently shown in laparoscopically treated CRC [27]. This may play a significant prognostic role, as it has been shown that better preserved immunity may reduce the occurrence of postoperative cancer recurrence/metastasis [28,29]. Moreover, in their experimental mouse model, *Pera* and coworkers [30] reported significantly higher postoperative serum interleukin-6 and vascular endothelial growth factor (VEGF) levels in a CC open surgery group when compared with the corresponding laparoscopic group. These increased levels of systemic pro-inflammatory cytokines and VEGFs were associated with increased angiogenesis and tumor growth. Recently, it has also been reported that the expression of VEGF is correlated with tumor infiltration, metastatic spread, and poor prognosis both for CC and gastric cancer [31–33]. The whole set of these data may help to explain why a less invasive surgical approach might result in improved long-term outcomes.

In conclusion, in a confirmed general picture of good long-term results in the treatment of CC, this study highlights the oncologic effectiveness of laparoscopy when compared with open surgery as testified to by the same number of retrieved/examined nodes in the two groups. Moreover and most importantly, this study produces evidence of better results of laparoscopy in terms of DFS and OS. Therefore, our data support minimally invasive surgery as the gold standard for the surgical treatment of patients with non-advanced CC.

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Conflicts of interest

Maria Novella Ringressi, Luca Boni, Giancarlo Freschi, Stefano Scaringi, Gianpiero Indennitate, Ilenia Bartolini, Paolo Bechi and Antonio Taddei have no conflicts of interest or financial ties to disclose.

Authors' contribution

MNR, PB and AT carried out the clinical procedures and have been involved in drafting the manuscript or revising it critically for important content. GF, IB, SS and GI were involved in the recruitment of patients and contributed to acquisition of the data. LB, MNR and PB were involved in analysis and interpretation of the data. All authors read and approved the final manuscript.

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