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Prognosis of Laparoscopic Surgery for Colorectal Cancer in Middle-Aged Patients: A Propensity Score-Matched Analysis

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Abstract

Background: The prognosis of middle-aged patients with CRC treated by laparoscopic resection (LR) is unclear. This study aimed to evaluate the survival outcomes of LR compared with open resection (OR) for patients with CRC and 45-65 years of age.

Methods: This retrospective cohort study used the data from a database of all consecutive colorectal resections performed between January 2009 and December 2017. Propensity score matching (PSM) was done to handle the selection bias based on age, gender, body mass index (BMI), tumor location, AJCC stage, and admission year. Univariate and multivariate COX regression model was used to identify risk factors of overall survival (OS) and progression-free survival (PFS).

Results: After PSM, 217 patients were included in each group. There were no differences in OS and PFS between the two groups (all P>0.05). There was less blood loss for LR (P<0.001), but the other complications were similar between the two groups. The multivariate analysis showed that high histological grade (hazard ratio [HR]=2.262, 95%CI: 1.334-3.836, P=0.002), stage III (HR=1.744, 95%CI: 2.360-25.406, P=0.001), stage IV (HR=47.905, 95%CI: 14.430-159.033, P<0.001), and adjuvant therapy (HR=0.547, 95%CI: 0.358-0.838, P=0.006) were independently associated with OS. High preoperative CEA (HR=1.585, 95%CI: 1.049-2.394, P=0.029), high histological grade (HR=2.128, 95%CI: 1.272-3.558, P=0.004), stage III (HR=5.562, 95%CI: 1.980-15.624, P=0.001), and stage IV (HR=26.338, 95%CI: 9.090-76.315, P<0.001), were independently associated with OS. LR was not associated with OS and PFS.

Conclusions: In middle-aged patients with CRC, OR and LR have similar survival outcomes and complications.

Background

Colorectal cancer (CRC) is the third most common cancer type in the world (1, 2). It is also the fifth leading cause of cancer death in China, and its incidence is rapidly increasing (3).

Laparoscopy is widely used in the surgical management of CRC (4). The advantages of laparoscopic procedures include less pain, quicker recovery, shorter hospital stay, and better quality of life than open surgery (5, 6). Data from randomized trials and a meta-analysis definitively established that laparoscopic colon surgery is at least equivalent to open surgery (7). Compared with open surgery, laparoscopic resection is known to minimize the surgical stress and systemic inflammatory response after surgery (8). Consequently, the postoperative immune function is better preserved with laparoscopic surgery, which may significantly increase the patient's resistance to cancer and maybe have advantages regarding the long-term outcomes (9, 10).

The incidence of CRC peaks at 74–80 years of age, and the median age at diagnosis is 70 years (11), but patients with predisposing genetic conditions will have a young-onset (12, 13). Therefore, middle-aged patients with CRC represent a population of patients that is less well studied. There are specific risk factors for the development of CRC in middle-aged individuals (14, 15). Middle-aged patients are often more fit to undergo chemotherapy than elderly patients (16). In addition, middle-aged patients often have a better socioeconomic status and have fewer comorbidities (16). Few reports examined the advantages of laparoscopic surgery compared with open surgery for CRC in middle-aged patients. The prognosis of middle-aged patients with CRC treated by laparoscopic surgery is unclear. Furthermore, most available data are from Western countries.

Therefore, this study aimed to evaluate the survival outcomes of laparoscopic surgery compared with open surgery for Chinese patients with CRC and 45–65 years of age.

Methods

Study design and patients

This retrospective cohort study used the data from a database of all consecutive colorectal resections performed at the Department of General Surgery of Mianyang Central Hospital, Sichuan Province, China, between January 2009 and December 2017. The study followed the ethical standards of the Declaration of Helsinki, as revised in 2013. This study was approved by the ethics committee of Mianyang Central Hospital. The requirement for individual consent was waived by the committee because of the retrospective nature of this study.

The inclusion criteria were: 1) radical (R0) D3 lymphadenectomy (TNM stage I-III) or palliative surgery (TNM stage IV); 2) histopathologically proven primary CRC; 3) 45–65 years of age (based on the quartiles of onset age of CRC in our database) (13); 4) no history of cancer before the CRC included in this study; 5) histological type included adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma; and (6) American Society of Anesthesiologists (ASA) class I-III.

The exclusion criteria were: 1) emergency surgery; 2) neoadjuvant treatment; 3) synchronous tumors; 4) familial adenomatous polyposis; 5) inflammatory bowel diseases; 6) primary tumor unresected; or 7) for patients with stage IV cancers, the primary tumors were not resected, or both primary and metastatic lesions were removed (including concurrent and secondary metastasis resection).

Surgery and grouping

The patients were grouped according to laparoscopic resection (LR) or open resection (OR). Patients for whom the LR was converted into OR were analyzed as part of the OR group. All surgical procedures were performed by an experienced surgeon (> 50 colorectal cancer operations/year for more than 5 years) using standardized techniques. All operations were performed or assisted by one of the team's six colorectal surgeons. The choice of the procedure was based on the patient's preference after an informed, comprehensive discussion. Conversion to an open procedure was defined as using an abdominal incision larger than necessary for specimen retrieval. According to the Japanese Society for Cancer of the Colon and Rectum, some patients underwent D3 lymphadenectomy, and others did not (17). All laparoscopic procedures were performed through a standardized medial-to-lateral approach (18). Total mesorectal excision (TME) was performed for patients with rectal cancer below the peritoneal reflection.

Adjuvant therapy

According to the patient's postoperative general condition or compliance and the physicians' experience, the patients with T3-4 or stage III-IV disease were considered for 5-fluorouracil-based chemotherapy. Patients with rectal cancer were considered for radiotherapy using a four-field box technique to the pelvis consisting of 45-50.4 Gy in 25–28 fractions (19).

Postoperative complications

Postoperative complications were those occurring within 30 days after surgery. Anastomosis-related complications (leakage, stenosis, or intraluminal bleeding) were confirmed by X-ray, endoscopy, or angiography. Intra-abdominal collections and abscesses were proven by ultrasound or computed tomography scans and concomitant systemic inflammatory response lasting ≥ 24 h. Postoperative hemorrhage was defined as a blood loss of > 300 mL according to the drainage volume. The severity of postoperative complications was assessed according to the Clavien-Dindo classification (20).

Data collection

Preoperative variables (age, gender, tumor location, and preoperative CEA), intraoperative data (operation time, blood loss, and the number of lymph nodes harvested), and postoperative data (largest tumor diameter, American Joint Committee on Cancer (AJCC) stage, histological grade, postoperative complications, and length of postoperative hospital stay) were recorded.

The tumor was staged according to the seventh American Joint Commission on Cancer (AJCC) TNM classification (21). Tumor location was classified as right-sided tumors (cecum, ascending colon, hepatic flexure, and transverse colon), left-sided tumors (splenic flexure, descending colon, and sigmoid colon), and rectal cancer.

Follow-up

The patients were routinely followed at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years, and then annually. The last follow-up was in December 2020. Local recurrence was defined as a recurring tumor limited to the previous tumor resection site or adjacent organs. Distant recurrence was defined as any tumor recurrence outside the primary site of the disease. Overall survival (OS) was measured from the date of surgery to death from any cause. Progression-free survival (PFS) was measured from the time of operation to the date of progression or death from any cause. Lost to follow-up was defined as the complete impossibility of seeing or contacting the patients, either by phone, mail, or e-mail.

Propensity score matching (PSM)

To mitigate the selection bias due to the retrospective nature of this study, PSM was done to handle the selection bias and to estimate the prognosis of the two groups. Propensity scores were obtained by logistic regression analysis of age, gender, body mass index (BMI), tumor location, AJCC stage, and admission year. One-to-one pair matching without replacement and a nearest-neighbor matching algorithm with calipers less than 0.1 were performed using SPSS 26 (IBM, Armonk, NY, USA).

Statistical analysis

Data are presented as means ± standard deviations for continuous variables and as numbers and percentages for categorical variables. The characteristics of the two groups were compared using the independent t-test for continuous variables and either the chi-square test or Fisher's exact test for the categorical variables. Survival analysis was performed using the Kaplan-Meier method and compared using the log-rank test. The patients lost to follow-up were censored at their last visit. Variables with $P < 0.05$ in the univariate analyses were entered into a multivariate Cox regression analysis using the forward method. Statistical analyses were performed using SPSS 26.0 (IBM, Armonk, NY, USA). Two-sided P-values < 0.05 were considered statistically significant.

Results

Clinicopathological characteristics

Figure 1 presents the flowchart of the patients' enrollment. A total of 997 patients were identified as potentially eligible. Patients with emergency surgery (e.g., acute intestinal obstruction or perforation and acute bleeding) (n = 184), familial adenomatous polyposis (FAP) (n = 4), synchronous tumors (n = 19), preoperative adjuvant treatment (n = 121), inflammatory bowel diseases (n = 5), other types of cancers (n = 5) (except for adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma), without resection of the primary tumor (n = 4), and patients who underwent resection of the primary tumor and metastasis in two different surgical sessions (n = 18) were excluded. Finally, 637 patients were included.

Eight patients (3.0%) converted from LR to OR because of a fixed tumor (n = 3), technical difficulty (n = 1), bleeding (n = 1), extensive adhesions (n = 1), and large incision for specimen retrieval (n = 2). The LR and OR groups included 265 (41.6%; 56.0 ± 5.8 years of age) and 372 (58.4%; 55.9 ± 5.6 years of age) patients, respectively. Before matching, the higher frequency of admission in 2014–2017 (74.0% vs. 41.1%, P < 0.001), higher frequency of rectal tumor (67.9% vs. 56.7%, P = 0.001), lower frequency of right-sided tumors (14.0% vs. 26.3%, P = 0.001), less blood loss (102 ± 97 vs. 196 ± 151 ml, P < 0.001), a lower rate of intraabdominal bleeding (1.1% vs. 3.8%, P = 0.042), a higher rate of wound infection (3.8% vs. 1.1%, P = 0.022), and lower use of postoperative therapy (62.6% vs. 79.0%, P < 0.001) were observed in the LR group compared with the OR group (Table 1). The differences between the two groups of age, gender, tumor size, preoperative CEA, histological grade, number of LNs, and AJCC stage were not significant (all P > 0.05) (Table 1).

Table 1
Characteristics of the patients

	Before matching (n = 637)			After matching (n = 434)		
	LR (n = 265)	OR (n = 372)	P	LR (n = 217)	OR (n = 217)	P
Age (years)	56.0 ± 5.8	55.9 ± 5.6	0.806	55.7 ± 5.8	56.0 ± 5.5	0.612
Gender (male), n (%)	161 (60.8)	208 (55.9)	0.223	128 (59.0)	126 (58.1)	0.846
Admission year			< 0.001			0.132
2009–2013	69 (26.0)	219 (58.9)		69 (31.8)	84 (38.7)	
2014–2017	196 (74.0)	153 (41.1)		148 (68.2)	133 (61.3)	
BMI (kg/m^2)	22.5 ± 2.4	21.8 ± 3.3	0.293	22.6 ± 2.5	21.6 ± 3.5	0.165
Comorbidity	66 (24.9)	112 (30.1)	0.149	56 (25.8)	66 (30.4)	0.286
Hypertension	41 (15.5)	60 (16.1)	0.823	33 (15.2)	34 (15.7)	0.894
Diabetes	16 (6.0)	30 (8.1)	0.330	13 (6.0)	20 (9.2)	0.205
Cardiac	4 (1.5)	14 (3.8)	0.091	3 (1.4)	8 (3.7)	0.127
Pneumonia	6 (2.3)	7 (1.9)	0.737	6 (2.8)	3 (1.4)	0.503*
Others	2 (0.8)	2 (0.5)	1.000*	2 (0.9)	1 (0.5)	1.000*
Tumor location, n (%)			0.001			0.380
Right-sided	37 (14.0)	98 (26.3)		34 (15.7)	41 (18.9)	
Left-sided	48 (18.1)	63 (16.9)		45 (20.7)	35 (16.1)	
Rectum	180 (67.9)	211 (56.7)		138 (63.6)	141 (65.0)	
Tumor size[a] (cm)	4.2 ± 2.7	4.5 ± 2.2	0.140	4.5 ± 2.8	4.5 ± 1.8	0.792
Preoperative CEA (ng/ml), n (%)			0.757			0.400

LR, laparoscopic resection; OR, open resection; BMI, body mass index; CEA, carcinoembryonic antigen; LNs, lymph nodes; AJCC, American Joint Cancer Committee.
*Calculated by using Fisher’s exact method.
a The largest tumor diameter
b Low: well or moderately differentiated; high: poorly differentiated, mucinous carcinoma or signet ring cell tumor.
c AJCC stage according to the American Joint Committee on Cancer 7th ed

	Before matching (n = 637)			After matching (n = 434)		
< 5	184 (69.4)	254 (68.3)		149 (68.7)	157 (72.4)	
≥ 5	81 (30.6)	118 (31.7)		68 (31.3)	60 (27.6)	
Operation time (min)	176.1 ± 62.3	171.4 ± 66.2	0.374	176.2 ± 62.0	175.3 ± 66.4	0.888
Blood loss (ml)	102.2 ± 96.6	195.6 ± 150.9	< 0.001	100.4 ± 94.8	208.0 ± 151.0	< 0.001
Length of postsurgical stay (days)	12.9 ± 7.9	13.8 ± 7.7	0.121	12.7 ± 7.9	13.4 ± 7.3	0.325
Postoperative complications, n (%)	40 (15.1)	47 (12.6)	0.373	26 (12.0)	29 (13.4)	0.665
Intra-abdominal or intraluminal bleeding	3 (1.1)	14 (3.8)	0.042	3 (1.4)	8 (3.7)	0.127
Intra-abdominal abscess	4 (1.5)	4 (1.1)	0.725*	1 (0.5)	2 (0.9)	1.000*
Cardiac	1 (0.4)	1 (0.3)	1.000*	0	1 (0.5)	1.000*
Deep vein thrombosis	0	1 (0.3)	1.000*	0	1 (0.5)	1.000*
Ileus/obstruction	6 (2.3)	5 (1.3)	0.539*	6 (2.8)	3 (1.4)	0.503*
Wound infection	10 (3.8)	4 (1.1)	0.022	8 (3.7)	3 (1.4)	0.127
Anastomotic leakage	8 (3.0)	6 (1.6)	0.233	3 (1.4)	4 (1.8)	1.000*
Pneumonia	4 (1.5)	6 (1.6)	1.000*	3 (1.4)	4 (1.8)	1.000*
Urinary infection	0	1 (0.3)	1.000*	0	1 (0.5)	1.000*
Others	4 (1.5)	5 (1.3)	1.000*	2 (0.9)	2 (0.9)	1.000*
Clavien-Dindo classification						
I-II	29 (9.9)	27 (7.3)	0.219	20 (9.2)	17 (7.8)	0.606
III-IV	11 (4.2)	20 (5.4)	0.479	6 (2.8)	12 (5.5)	0.149
Histological grade[b]			0.809			0.745

LR, laparoscopic resection; OR, open resection; BMI, body mass index; CEA, carcinoembryonic antigen; LNs, lymph nodes; AJCC, American Joint Cancer Committee.

*Calculated by using Fisher's exact method.

a The largest tumor diameter

b Low: well or moderately differentiated; high: poorly differentiated, mucinous carcinoma or signet ring cell tumor.

c AJCC stage according to the American Joint Committee on Cancer 7th ed

	Before matching (n = 637)			After matching (n = 434)		
Low	236 (89.1)	329 (88.4)		195 (89.9)	197 (90.8)	
High	29 (10.9)	43 (11.6)		22 (10.1)	20 (9.2)	
No. of retrieved LNs	11.2 ± 6.9	10.3 ± 7.7	0.157	10.6 ± 6.4	10.5 ± 8.2	0.927
AJCC stage[c]			0.544			0.743
I	48 (18.1)	54 (14.5)		32 (14.7)	40 (18.4)	
II	109 (41.1)	159 (42.7)		92 (42.4)	89 (41.0)	
III	79 (29.8)	109 (29.3)		66 (30.4)	60 (27.6)	
IV	29 (10.9)	50 (13.4)		27 (12.4)	28 (12.9)	
Post-op adjuvant therapy	166 (62.6)	294 (79.0)	< 0.001	151 (69.6)	149 (68.7)	0.835
LR, laparoscopic resection; OR, open resection; BMI, body mass index; CEA, carcinoembryonic antigen; LNs, lymph nodes; AJCC, American Joint Cancer Committee.						
*Calculated by using Fisher's exact method.						
a The largest tumor diameter						
b Low: well or moderately differentiated; high: poorly differentiated, mucinous carcinoma or signet ring cell tumor.						
c AJCC stage according to the American Joint Committee on Cancer 7th ed						

After PSM, there were 217 pairs of patients. No significant differences were found between the LR and OR groups in terms of age, gender, tumor location, tumor size, preoperative CEA, histological grade, number of retrieved LNs, AJCC stage, and postoperative therapy ($P > 0.05$). Although not used in PSM matching, the operation-related data, including operation time, length of postsurgical stay, and the postoperative complications, showed no significant differences between the two groups after matching (all $P > 0.05$); only the blood loss was smaller in the LR group compared with the OR group ($P < 0.001$) (Table 1).

- Survival

With a median follow-up of 46 months (range: 3-139) in the total cohort (before matching), 11 patients (3.0%) in the OR group and 14 patients (5.3%) in the LR group were lost to follow-up ($P = 0.136$).

Compared with the OR group in the total cohort, there were better survival outcomes in the LR group for 5-year OS ($P = 0.009$) and 5-year PFS ($P = 0.003$) (Fig. 2); these differences were not observed after PSM ($P = 0.458$ and $P = 0.309$) (Fig. 2). Subgroup analyses revealed no significant difference between the two groups for stages I, II, and III diseases (both before and after PSM) for 5-year OS (all $P > 0.05$) and PFS (all $P > 0.05$) (Figs. 3 and 4). For stage IV disease, the 5-year OS ($P = 0.005$) and PFS ($P = 0.018$) were significantly better in the LR group than in the OR group before PSM, but the differences were not significant after PSM ($P = 0.052$ and $P = 0.183$) (Figs. 3

and 4). No significant differences were observed between the two groups in subgroup analysis for right-sided and left-sided tumors regarding 5-year OS (all $P > 0.05$) and PFS (all $P > 0.05$) (Figs. 5 and 6). For rectal cancer, the 5-year OS ($P = 0.010$) and PFS ($P = 0.005$) were significantly better in the LR group than in the OR group before PSM, but the differences were not significant after PSM ($P = 248$ and $P = 0.137$) (Figs. 5 and 6).

- Prognostic factors

The multivariate analysis showed that high histological grade (hazard ratio [HR] = 2.262, 95%CI: 1.334–3.836, $P = 0.002$), stage III (HR = 1.744, 95%CI: 2.360-25.406, $P = 0.001$), stage IV (HR = 47.905, 95%CI: 14.430-159.033, $P < 0.001$), and adjuvant therapy (HR = 0.547, 95%CI: 0.358–0.838, $P = 0.006$) were independently associated with OS (Table 2). High preoperative CEA (HR = 1.585, 95%CI: 1.049–2.394, $P = 0.029$), high histological grade (HR = 2.128, 95%CI: 1.272–3.558, $P = 0.004$), stage III (HR = 5.562, 95%CI: 1.980-15.624, $P = 0.001$), and stage IV (HR = 26.338, 95%CI: 9.090-76.315, $P < 0.001$), were independently associated with OS (Table 2). LR was not associated with OS and PFS.

Table 2
Univariable and multivariable analyses for prognostic variables of OS and PFS using the Cox proportional hazards regression in matched cohorts (n = 434).

	n (%)	OS				PFS			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)									
< 55	177 (40.8)	1				1			
≥ 55	257 (59.2)	1.119 (0.772–1.624)	0.552			1.124 (0.787–1.606)	0.520		
Gender									
Male	254 (58.5)	1				1			
Female	180 (41.5)	0.667 (0.456–0.977)	0.038			0.820 (0.574–1.171)	0.276		
Admission year									
2009–2013	153 (35.3)	1				1			
2014–2017	281 (64.7)	1.074 (0.730–1.581)	0.717			0.995 (0.690–1.436)	0.979		
Comorbidity									
0	312 (71.9)	1				1			
≥ 1	122 (28.1)	1.065 (0.717–1.581)	0.755			1.213 (0.835–1.763)	0.311		

Factors with $P < 0.05$ were entered into the multivariable analysis with the forward method.

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; AJCC, American Joint Cancer Committee.

a Largest tumor diameter

b Low: well or moderately differentiated; high: poorly differentiated, mucinous carcinoma or signet ring cell tumor.

c AJCC stage according to the American Joint Committee on Cancer 7th ed

	n (%)	OS				PFS			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Tumor location									
Right-sided	75 (17.3)	1				1			
Left-sided	80 (18.4)	0.815 (0.423–1.567)	0.539			0.984 (0.525–1.843)	0.959		
Rectum	279 (64.3)	1.142 (0.693–1.881)	0.603			1.271 (0.775–2.087)	0.342		
Tumor size[a] (cm)									
< 5	260 (59.9)	1				1			
≥ 5	174 (40.1)	1.564 (1.077–2.271)	0.019			1.402 (0.981–2.002)	0.064		
Pre-operative CEA (ng/ml)									
< 5	306 (70.5)	1				1		1	
≥ 5	128 (29.5)	2.345 (1.601–3.434)	< 0.001			2.390 (1.659–3.441)	< 0.001	1.585 (1.049–2.394)	0.029
Histological grade[b]									
Low	392 (90.3)	1		1		1		1	

Factors with P < 0.05 were entered into the multivariable analysis with the forward method.
OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; AJCC, American Joint Cancer Committee.
a Largest tumor diameter
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	n (%)	OS				PFS			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
High	42 (9.7)	2.158 (1.318–3.533)	0.002	2.262 (1.334–3.836)	0.002	2.111 (1.306–3.412)	0.002	2.128 (1.272–3.558)	0.004
No. of retrieved LNs									
< 12	282 (65.0)	1				1			
≥ 12	152 (35.0)	0.629 (0.415–0.952)	0.028			0.657 (0.439–0.984)	0.042		
AJCC stage									
I	72 (16.6)	1		1		1		1	
II	181 (41.7)	2.815 (0.982–8.069)	0.054	2.561 (0.760–8.628)	0.129	2.060 (0.855–4.962)	0.107	2.009 (0.696–5.801)	0.197
III	126 (29.0)	8.670 (3.105–24.208)	< 0.001	1.744 (2.360-25.406)	0.001	6.171 (2.637–14.444)	< 0.001	5.562 (1.980-15.624)	0.001
IV	55 (12.7)	57.358 (20.214-162.756)	< 0.001	47.905 (14.430-159.033)	< 0.001	32.941 (13.801–78.630)	< 0.001	26.338 (9.090-76.315)	< 0.001
Post-op adjuvant therapy									
No	134 (30.9)	1		1		1			
Yes	300 (69.1)	0.570 (0.394–0.824)	0.003	0.547 (0.358–0.838)	0.006	0.628 (0.440–0.897)	0.011		

Factors with P < 0.05 were entered into the multivariable analysis with the forward method.

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; AJCC, American Joint Cancer Committee.

a Largest tumor diameter

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	n (%)	OS				PFS			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Mode of operation									
Open	217 (50.0)	1				1			
Laparoscopic	217 (50.0)	0.872 (0.606–1.255)	0.460			0.835 (0.589–1.185)	0.312		

Factors with P < 0.05 were entered into the multivariable analysis with the forward method.

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; AJCC, American Joint Cancer Committee.

a Largest tumor diameter

b Low: well or moderately differentiated; high: poorly differentiated, mucinous carcinoma or signet ring cell tumor.

c AJCC stage according to the American Joint Committee on Cancer 7th ed

Discussion

The incidence of CRC peaks at 74–80 years of age, and patients with a genetic condition have a young-onset. The prognosis of middle-aged patients with CRC treated by LR is unclear. This study aimed to evaluate the survival outcomes of LR compared with OR for patients with CRC and 45–65 years of age. The results suggest that in middle-aged patients with CRC, OR and LR have similar survival outcomes and complications.

In this study of middle-aged patients with CRC, there were no differences in OS and DFS in all patients after matching with age, gender, BMI, tumor location, AJCC stage, and admission year. LR has become an accepted therapeutic option for CRC patients, providing similar OS and DFS compared with OR in stages I-III disease (22–29), supporting the present results. Previous studies in patients with CRC (irrespective of age, but most studies included older patients) showed that LR was at least comparable to OR, as shown by two meta-analyses (7, 30), supporting the present study. Jayne et al. (23) reported that LR maximized the short-term outcomes compared with OR without comprising the long-term outcomes. Long-term results by Green et al. (31) also support the use of LR for CRC. On the other hand, Fabio et al. (32) reported that the 5-year cancer-related survival after LR was significantly higher than that after OR. Similar results were reported by Law et al. (33). Park et al. (34) reported that similar outcomes between LR and OR in T4 tumors, but a tendency for better outcomes with LR in tumors < 4 cm. Hence, contradictory results can be observed in the literature. Middle-age patients are fitter for surgery and have fewer comorbidities than older patients, which could explain why there were no differences between LR and OR in the present study. LR is known to minimize the surgical stress and systemic inflammatory response after surgery (8), which is conducive to reduce complications and improve recovery. Hypotheses have been proposed to explain this beneficial oncological role of LR in the treatment of CRC. One possible reason is that the numbers of LNs harvested by laparoscopy were higher than by OR (32, 33), but in the present study, the mean number of LNs harvested was not different between the two groups. Still, the number of harvested LNs was small but supported by previous studies (35–39).

In the present study, LR showed an advantage over OR in stage IV CRC before PSM, but the differences were lost after PSM. The present study is supported (at least before PSM) by Day et al. (40), who reported 665 resections (457 LR and 208 OR) for CRC, and the 5-year OS for non-stage IV disease in the LR group was significantly better than in the open group (79.4% vs. 74.0%, P = 0.03). The role of LR in stage IV CRC patients with unresectable metastases has not been sufficiently evaluated. The National Comprehensive Cancer Network (NCCN) guidelines recommend that asymptomatic patients with metastatic CRC should receive chemotherapy and that patients with symptomatic or curable metastatic disease should be considered for surgery (41). Verheijen et al. (42) reported that short-term outcomes after laparoscopic surgery for stage IV colorectal cancer in selected patients are equivalent to those for stage I. Previous studies reported that LR for stage IV CRC had equivalent long-term outcomes to OR (43, 44), supporting the present study after PSM, but Hida et al. (45) reported that the OS after LR was better than that after OR, but no difference was apparent in the multivariable analysis.

The surgical approach was not independently associated with better OS and PFS in the multivariable analyses. These results are in contradiction with studies in elderly patients (46, 47), but results in middle-aged patients are scarce, and the comorbidities probably play roles in this discrepancy. One study suggests that LR achieved similar outcomes among elderly and middle-aged patients with rectal cancer (48). The present study is supported by the literature because it is known that middle-aged patients have specific risk factors (14, 15) and better prognosis because of better access to treatments and fewer comorbidities (16).

In this study, LR showed an advantage over OR in rectal cancer before PSM, but the differences disappeared after PSM. In rectal cancer, some studies revealed that LR and OR have similar effects on long-term survival (49, 50). On the other hand, Nonaka et al. (51) reported that DFS was better in the LR group than in the OR group. Ng et al. (52) reported a trend toward a lower recurrence rate at 10 years after LR than after OR among patients with stage III rectal cancer (P = 0.078). These points will have to be examined in future studies because the numbers of stage IV and rectal cancer patients were small in this study.

The complications were similar between LR and OR in this study, except for less blood loss with LR, supported by the general principle of LR (4–8) and by a previous meta-analysis (53) and a cohort study (54). A recent study showed that LR and OR was safe both in elderly and non-elderly patients (55). This lack of difference in complications might play a role in the lack of difference in survival. The conversion rate was 3%, similar to that of a previous study (2%) (29).

There are some limitations that are inherent to retrospective studies (such as missing data and various biases), but the present study used the PSM approach, which allows for more robust analysis by reducing confounders (56), but without completely mitigating all sources of bias of non-randomized studies. This is particularly useful when a randomized controlled trial is not possible due to practical, medical, or ethical issues. Moreover, this study was based on a single-institution series, and the generalizability of the results might be limited. Performing a prospective observational study at multiple centers would be needed to confirm the conclusions of this study. In addition, the patients who received neoadjuvant chemotherapy (n = 121 in the present study) were excluded because of the possibility that the neoadjuvant therapy affected staging (41) and prognosis (57). Finally, the proportion of patients with rectal cancer was high, but it is in line with previous studies in the Chinese population (58, 59). Additional studies should be performed in this population of patients.

Conclusions

In conclusion, LR in patients with CRC and aged 45–65 years have similar OS and PFS compared with OR. Complications are similar, except for less blood loss with LR.

Abbreviations

LR	laparoscopic resection
OR	open resection
OS	overall survival
BMI	body mass index
PFS	progression-free survival
CRC	Colorectal cancer
TME	Total mesorectal excision
AJCC	American Joint Committee on Cancer
FAP	familial adenomatous polyposis

Declarations

Ethics approval and consent to participate

Studies involving human subjects (including research on identifiable human material and data) must have been performed with the appropriate participants’ informed consent in compliance with the Helsinki Declaration. This study was approved by the ethics committee of Mianyang Central Hospital, and the need for individual consent was waived by the committee because of the retrospective nature of this study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this manuscript and its supplemental files.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

BF and SJY carried out the studies, participated in collecting data, and drafted the manuscript. WLR, DZG, XCH and LGQ performed the statistical analysis and participated in its design. ZX, LW, WD and XYJB participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Figures

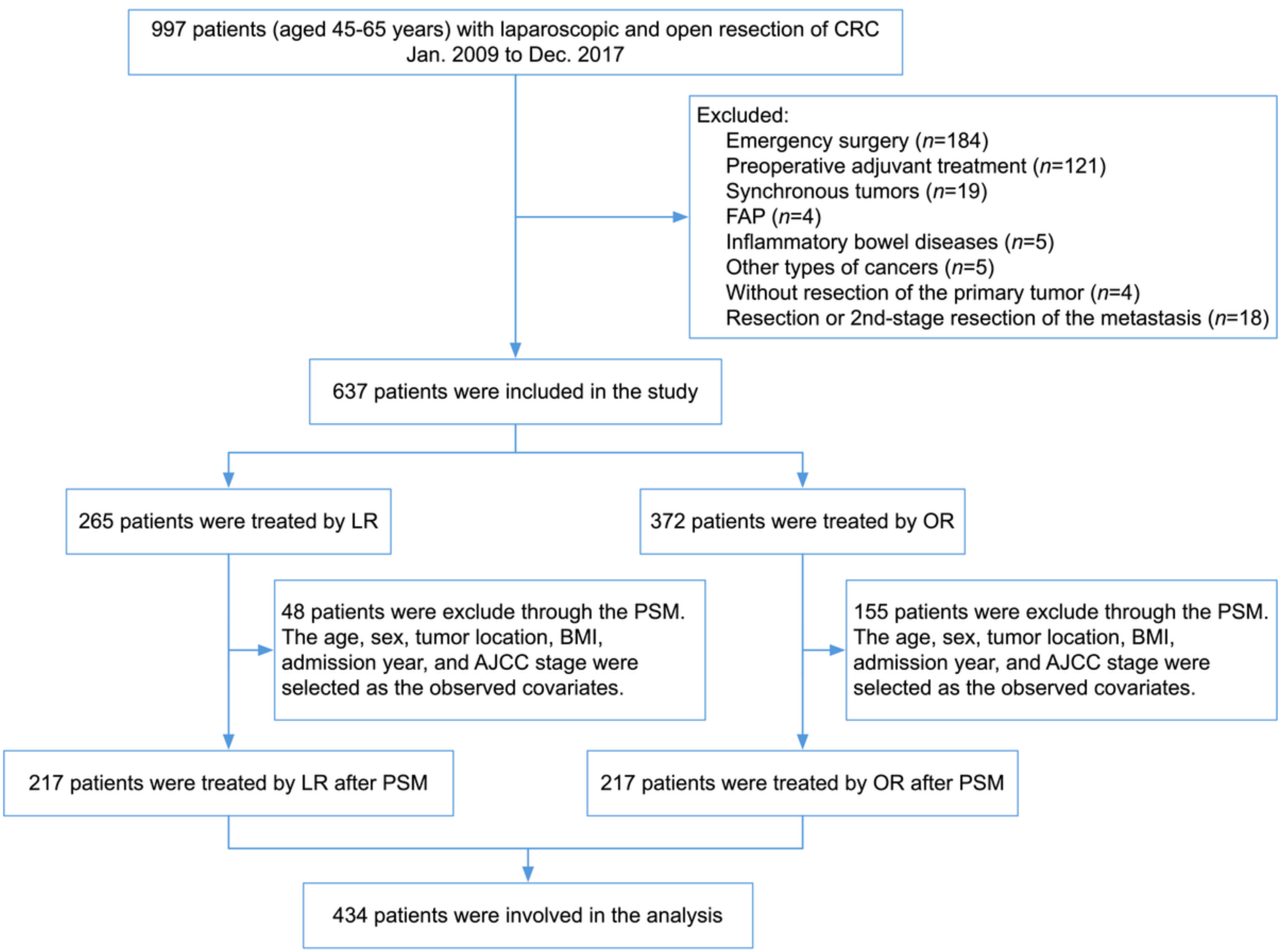

Figure 1

Enrollment flowchart. Propensity score matching (PSM) was done using age, gender, body mass index (BMI), tumor location, AJCC stage, and admission year.

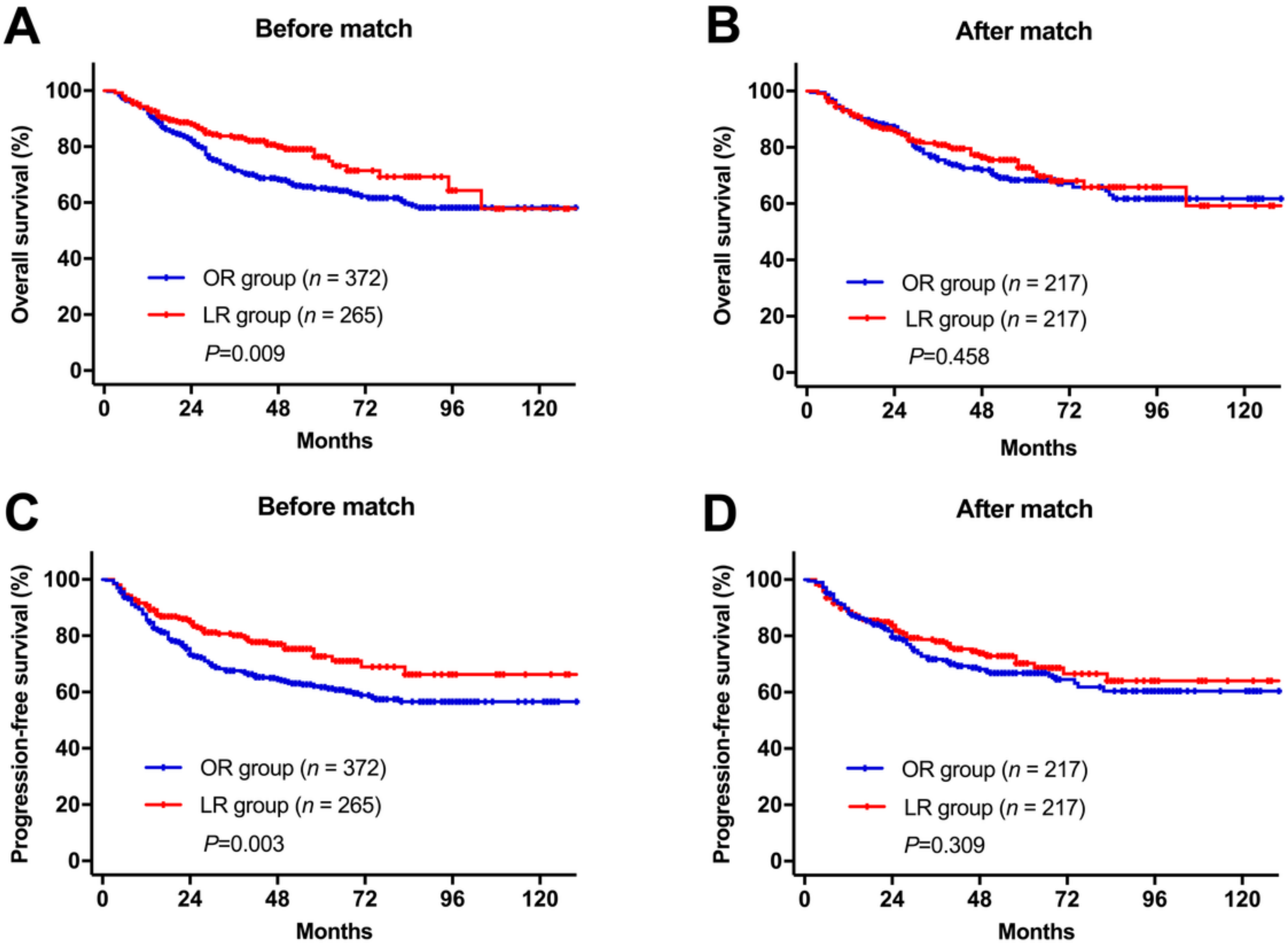

Figure 2

The overall survival (OS) and progression-free survival (PFS) curves of the two groups before and after propensity score matching (PSM). The survival in the laparoscopic resection (LR) group was significantly better than that of the open resection (OR) group in OS and PFS before PSM (A and C), but not after PSM (B and D).

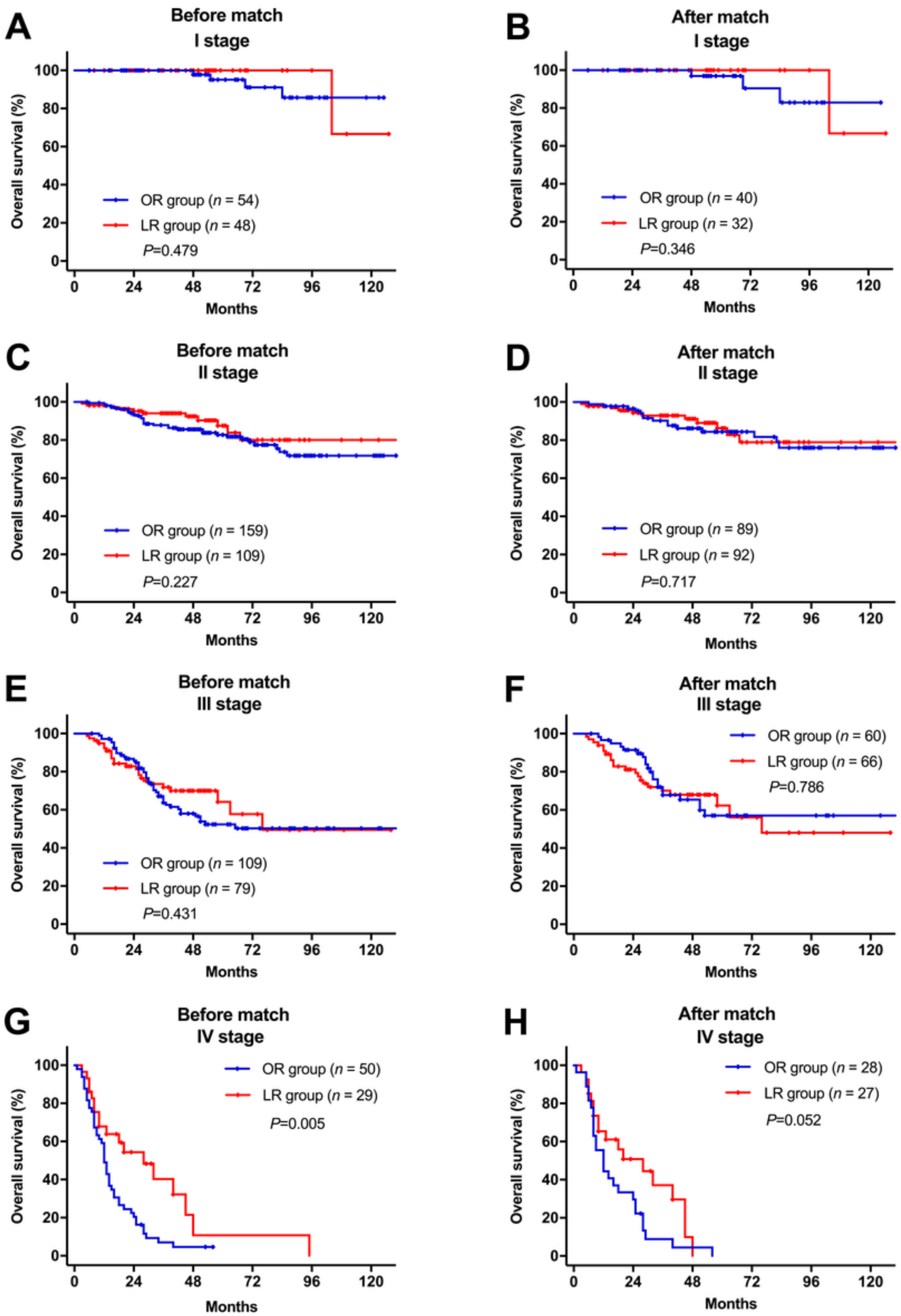

Figure 3

The overall survival (OS) curves of the two groups according to cancer stage before and after propensity score matching (PSM). The laparoscopic resection (LR) group was significantly better than the open resection (OR) group in OS (G; P=0.005) in stage IV disease before PSM but not after (H). There were no differences between LR and OR for stage I-III cancer (A-F; all P>0.05).

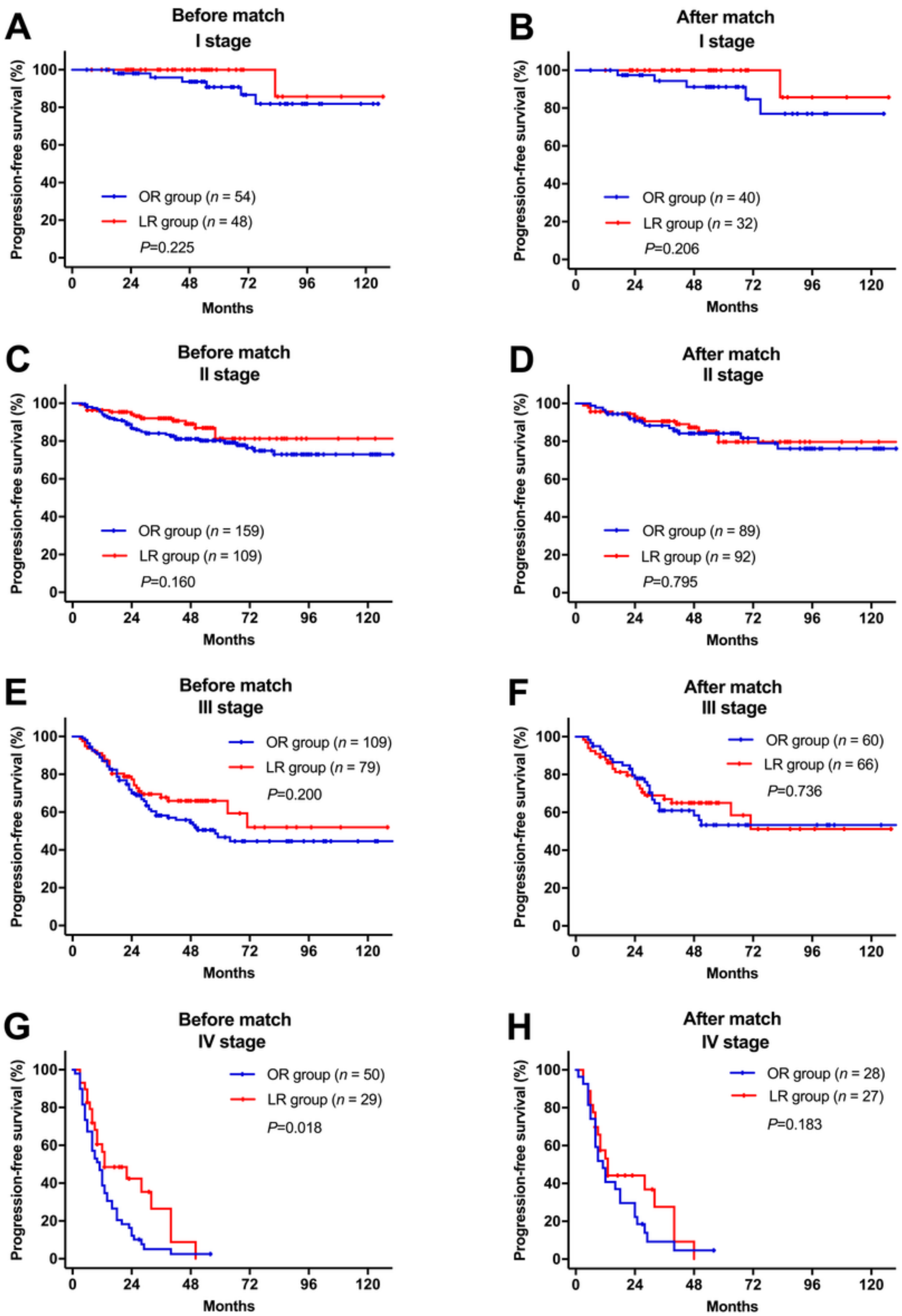

Figure 4

The progression-free survival (PFS) curves of the two groups according to cancer stage before and after propensity score matching (PSM). The laparoscopic resection (LR) group was significantly better than the open resection (OR) group in PFS (G; P=0.018) in stage IV disease before PSM but not after (H). There were no differences between LR and OR for stage I-III cancer (A-F; all P>0.05).

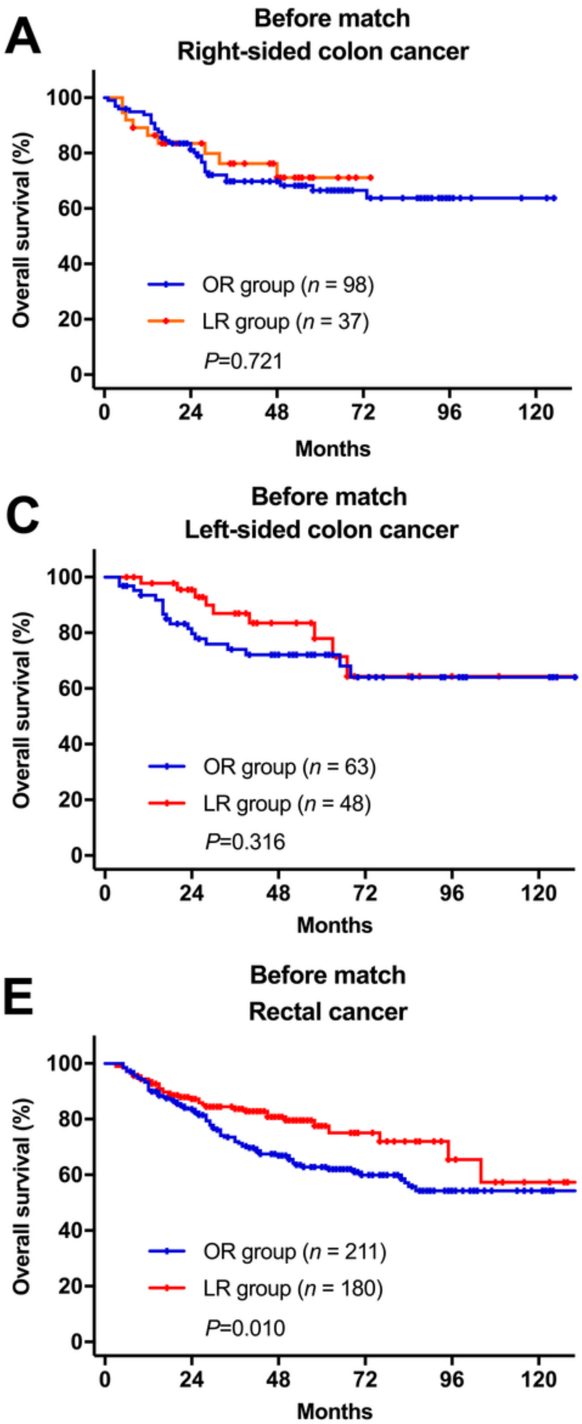

Figure 5

The overall survival (OS) curves of the two groups according to cancer location before and after propensity score matching (PSM). The laparoscopic resection (LR) group was significantly better than the open resection (OR) group in OS (E; P=0.010) in rectal cancer before PSM but not after (F). There were no significant differences for right- (A and B) and left-sided colon cancer (C and D).

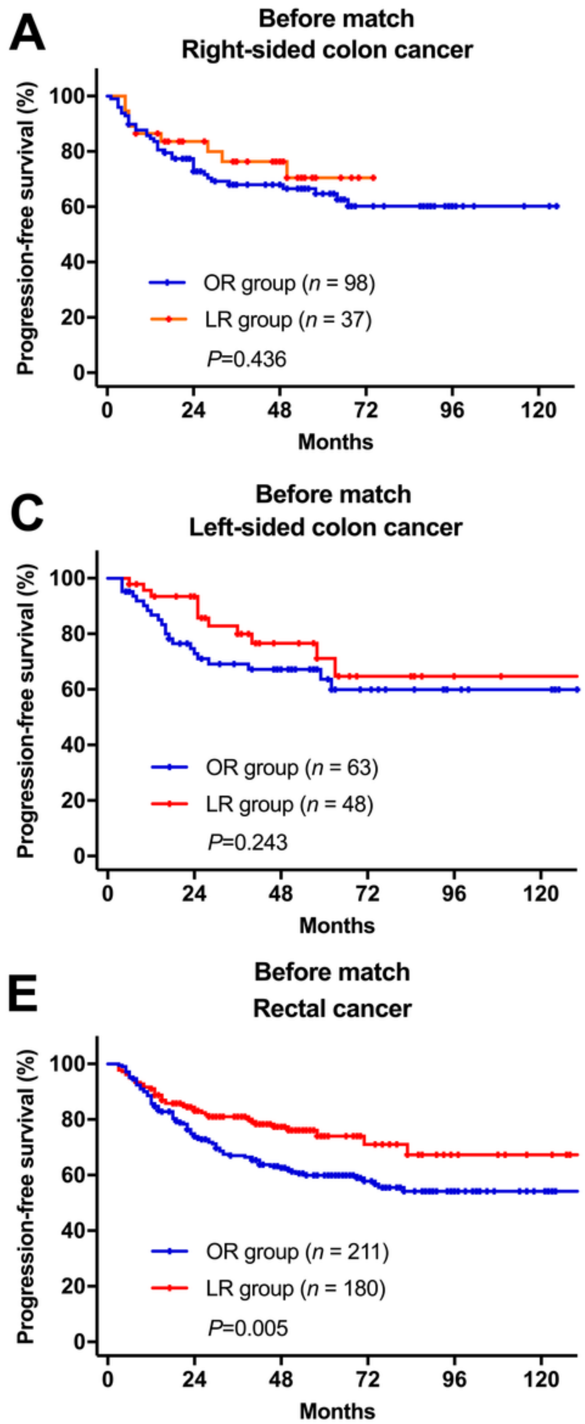

Figure 6

The progression-free survival (PFS) curves of the two groups according to cancer location before and after propensity score matching (PSM). The laparoscopic resection (LR) group was significantly better than the open resection (OR) group in OS (E; P=0.005) in rectal cancer before PSM but not after (F). There were no significant differences for right- (A and B) and left-sided colon cancer (C and D).