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Original article

ORIGINAL ARTICLE

Survival outcomes following laparoscopic vs open surgery for non-metastatic rectal cancer: a two-center cohort study with propensity score matching

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Abstract

Background: Laparoscopic surgery for rectal cancer is commonly performed in China. However, compared with open surgery, the effectiveness of laparoscopic surgery, especially the long-term survival, has not been sufficiently proved.
Methods: Data of eligible patients with non-metastatic rectal cancer at Nanfang Hospital of Southern Medical University and Guangdong Provincial Hospital of Chinese Medicine between 2012 and 2014 were retrospectively reviewed. Long-term survival outcomes and short-term surgical safety were analysed with propensity score matching between groups.
Results: Of 430 cases collated from two institutes, 103 matched pairs were analysed after propensity score matching. The estimated blood loss during laparoscopic surgery was significantly less than that during open surgery ($P = 0.019$) and the operative time and hospital stay were shorter in the laparoscopic group (both $P < 0.001$). The post-operative complications rate was 9.7% in the laparoscopic group and 10.7% in the open group ($P = 0.818$). No significant difference was observed between the laparoscopic group and the open group in the 5-year overall survival rate (75.7% vs 80.6%, $P = 0.346$), 5-year relapse-free survival rate (74.8% vs 76.7%, $P = 0.527$), or 5-year cancer-specific survival rate (79.6% vs 87.4%, $P = 0.219$). An elevated carcinoembryonic antigen, <12 harvested lymph nodes, and perineural invasion were independent prognostic factors affecting overall survival and relapse-free survival.
Conclusions: Our findings suggest that open surgery should still be the priority recommendation, but laparoscopic surgery is also an acceptable treatment for non-metastatic rectal cancer.

Key words: laparoscopic surgery; open surgery; propensity score matching; rectal cancer

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Introduction

Colorectal cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer-related death for both sexes in China [1]. In a multidisciplinary approach that combines chemotherapy with radiotherapy for the treatment of colorectal cancer, surgery remains the major approach. The first successful use of laparoscopy in colorectal surgery was published in 1991 by Jacobs et al. [2]. Laparoscopic surgery has been performed widely in colon cancer all over the world and several randomized–controlled trials have demonstrated that laparoscopic surgery for colon cancer is safe and feasible with better short-term outcomes (including a decrease in post-operative pain, a shorter hospital stay, and earlier recovery) and equivalent long-term results compared to open surgery [3–7]. However, laparoscopic surgery for rectal cancer is more arduous than that for colon cancer, so the early clinical trials excluded rectal cancer [5–7]. Although a few clinical trials have shown the advantages of laparoscopic rectal-cancer resection compared with open surgery [8–10], both the ACOSOG Z6051 and ALaCaRT trials did not support the use of laparoscopic surgery for rectal cancer [11, 12]. It is still controversial whether laparoscopic surgery is suitable for rectal cancer, especially for low rectal cancer. Therefore, we conducted this retrospective cohort study to compare long-term survival outcomes and short-term surgical safety between laparoscopic and open surgery for non-metastatic rectal cancer in the Chinese population. Propensity score matching (PSM) was performed for the study design.

Patients and methods

Study design

All consecutive eligible patients with rectal cancer were confirmed from the Department of General Surgery of Nanfang Hospital of Southern Medical University and the Department of Proctology of Guangdong Provincial Hospital of Chinese Medicine between January 2012 and December 2014. These two centers were members of the Southern Chinese Laparoscopic Colorectal Surgery Study group. Demographic, clinical, pathologic, and imaging features together with the management and outcomes were carefully reviewed. Written informed consent was acquired from patients preceding the surgical procedures. This study was approved by the ethical committee of Nanfang Hospital and Guangdong Provincial Hospital of Chinese Medicine (No. ZE2019-052–01).

Study subjects

Inclusion criteria were patients with clinical stage I–III rectal cancer who underwent radical surgery for rectal cancer. Exclusion criteria were patients with (i) combined operations extending to the surrounding organ; (ii) multiple cancers; (iii) emergency operation; (iv) conversion to open surgery; or (v) patients who received neoadjuvant therapy.

All included cases were classified into two groups, based on the surgical approach, which was either laparoscopic or open surgery. The surgical approach was decided by the individual colorectal surgeon based on a combined assessment of clinical, endoscopic, and imaging features.

Data collection

Data were collected in a prospectively maintained database from clinical report forms. The demographic and clinicopathological data included age, gender, body mass index (BMI), preoperative carcinoembryonic antigen (CEA), tumor location, operative time, estimated blood loss, surgical procedure, protective ileostomy, tumor grade, tumor stage, and hospital stay. Preoperative CEA was defined as CEA measured closest to the operation time. Tumor location was divided into the following three sections: upper rectum (above 11 cm from the anal verge), middle rectum (7–11 cm from the anal verge), and lower rectum (below 7 cm from the anal verge). Surgical procedures consisted of three categories: low anterior resection, abdominoperineal

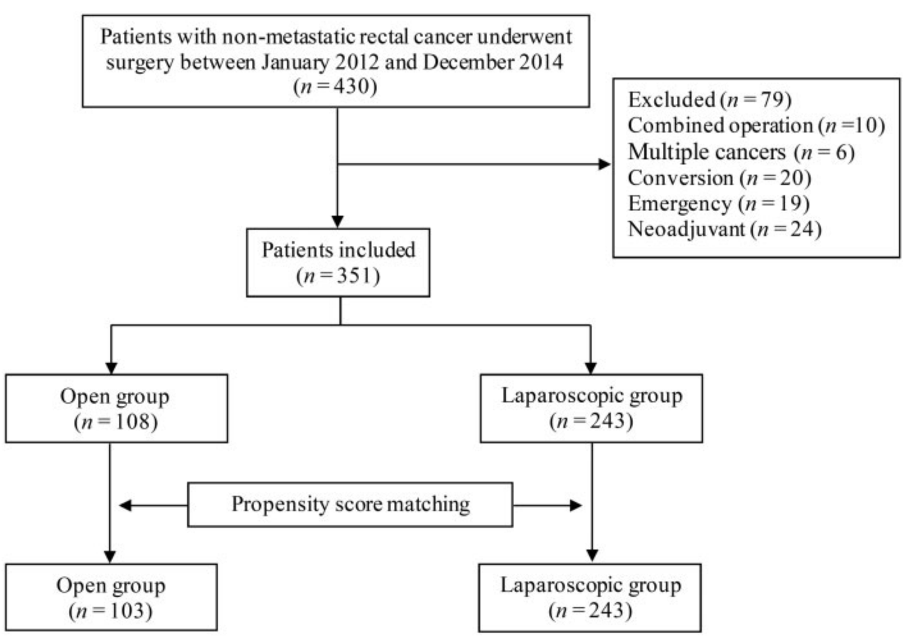

Figure 1. Flow diagram of patient disposition

Table 1. Baseline characteristics of the study population

Characteristic	Total cohort			Matched cohort		
	Laparoscopic group (*n* = 243)	Open group (*n* = 108)	P-value	Laparoscopic group (*n* = 103)	Open group (*n* = 103)	P-value
Age, years, mean ± SD	59.0 ± 13.2	62.4 ± 13.1	0.024	61.2 ± 13.0	62.0 ±13.2	0.641
Gender, *n* (%)			0.540			0.469
Male	159 (65.4)	67 (62.0)		68 (66.0)	63 (61.2)	
Female	84 (34.6)	41 (38.0)		35 (34.0)	40 (38.8)	
BMI, kg/m^2, mean ± SD	22.5 ± 3.6	21.9 ± 3.1	0.155	21.8 ± 3.9	21.9 ± 3.1	0.759
Preoperative CEA, *n* (%)			0.014			0.770
≤5 ng/mL	188 (77.4)	70 (64.8)		66 (64.1)	68 (66.0%)	
>5 ng/mL	55 (22.6)	38 (35.2)		37 (35.9)	35 (34.0%)	
Tumor location, *n* (%)			0.850			0.840
Upper rectum	109 (44.8)	45 (47.7)		40 (38.8)	42 (40.8)	
Middle rectum	101 (41.6)	48 (44.4)		46 (44.7)	47 (45.6)	
Lower rectum	33 (13.6)	15 (13.9)		17 (16.5)	14 (13.6)	
Tumor stage, *n* (%)			0.492			0.673
I	56 (23.0)	19 (17.6)		21 (20.4)	18 (17.5)	
II	94 (38.7)	43 (39.8)		36 (35.0)	42 (40.8)	
III	93 (38.3)	46 (42.6)		46 (44.6)	43 (41.7)	

SD, standard deviation; BMI, body mass index; CEA, carcinoembryonic antigen.

Table 2. Operative and pathological results in matched cohorts

Variable	Laparoscopic group (*n* = 103)	Open group (*n* = 103)	P-value
Surgical procedure, *n* (%)			0.112
Low anterior resection	80 (77.6)	90 (87.4)	
Abdominoperineal resection	22 (21.4)	12 (11.6)	
Hartmann's procedure	1 (1.0)	1 (1.0)	
Protective ileostomy, *n* (%)	25 (24.3)	18 (17.5)	0.230
Operative time, min, Median (IQR)	150 (128–217)	210 (170–250)	0.000
Intraoperative blood loss, mL, Median (IQR)	50 (50–100)	100 (100–150)	0.019
Hospital stay, day, Median (IQR)	16 (13–19)	19 (17–19)	0.000
Tumor grade, *n* (%)			0.663
Well	4 (3.9)	3 (2.9)	
Moderate	85 (82.5)	90 (87.5)	
Poor/others	14 (13.6)	10 (9.7)	
Harvested lymph nodes, *n* (%)			0.129
<12	36 (35.0)	26 (25.2)	
≥12	67 (65.0)	77 (74.8)	
Lymphovascular invasion, *n* (%)	6 (5.8)	19 (18.4)	0.006
Perineural invasion, *n* (%)	4 (3.9)	8 (7.8)	0.234
Tumor deposits, *n* (%)	5 (4.9)	13 (12.6)	0.048
Post-operative complications, *n* (%)	10 (9.7)	11 (10.7)	0.818
Wound infection	0 (0)	4 (3.9)	0.121
Ileus	1 (1.0)	0 (0)	1.000
Urinary dysfunction	1 (1.0)	0 (0)	1.000
Anastomosis leakage	6 (5.8)	3 (2.9)	0.498
Intra-abdominal bleeding	1 (1.0)	1 (1.0)	1.000
Pneumonia	2 (1.9)	4 (3.9)	0.683
Cardiac event	0 (0)	2 (1.9)	0.498
Reoperation, *n* (%)	2 (1.9)	2 (1.9)	1.000
Mortality, *n* (%)	1 (1.0)	0 (0)	1.000

IQR, interquartile range.

resection, and Hartmann's procedure. Tumor grade was divided into three types: well differentiated, moderately differentiated, and poorly differentiated (including signet or mucinous adenocarcinoma). Tumor stage was based on the final pathologic report and preoperative imaging examination.

Outcome measurements

The primary endpoint of this study was overall survival (OS), relapse-free survival (RFS), and cancer-specific survival (CSS). OS was defined as the time from operation to death from any

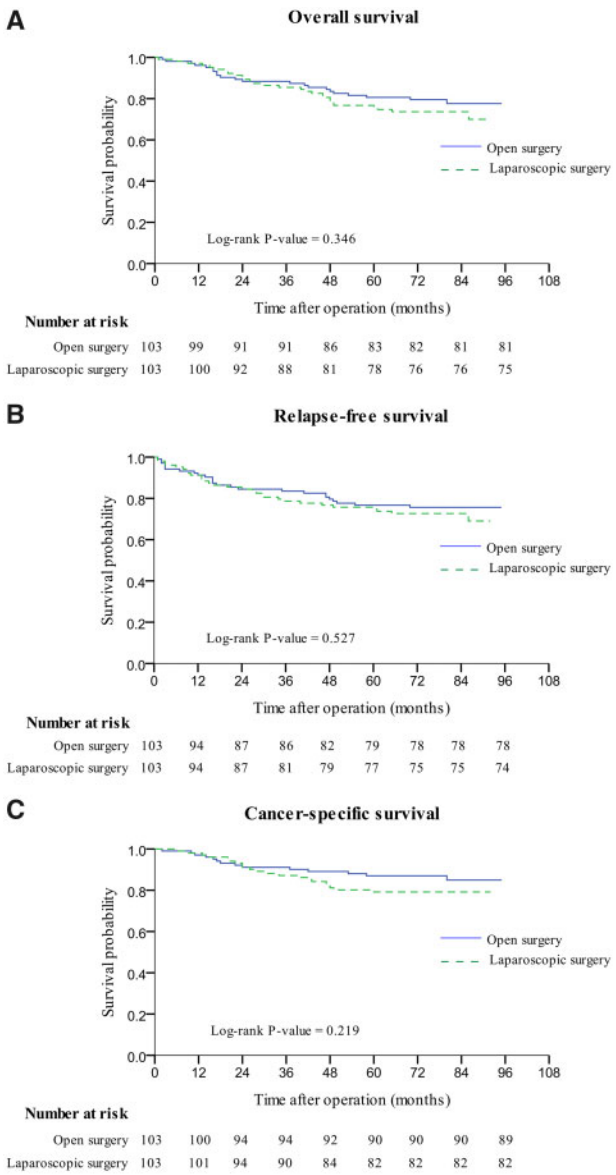

Figure 2. Survival curve after laparoscopic surgery vs open surgery in matched cohorts

cause or the last follow-up. RFS was defined as the time from operation to identified recurrence or any cause of death. CSS was defined as the time from operation to death due to rectal cancer. The last follow-up was January 2020.

The secondary endpoints were operative time, estimated blood loss, hospital stay, reoperation, post-operative complications, and mortality. Post-operative complications were defined as wound infection, ileus, urinary dysfunction, anastomotic leakage, intra-abdominal bleeding, pneumonia, and cardiac events. Intra-abdominal bleeding was defined in this study as bleeding requiring transfusion or reoperation. All complications within 30 days after surgery were recorded. Post-operative mortality was traditionally defined as any death occurring within 30 days after surgery.

Statistical analysis

Data are presented as mean ± standard deviation or median with interquartile range (IQR) for quantitative variables with paranormal distribution and numbers with percentages for categorical variables. Quantitative variables were compared using the Student's *t*-test or Mann–Whitney *U* test. Categorical variables were analysed using the Chi-square test or Fisher's exact test. The estimates of the differences in age, gender, BMI, preoperative CEA level, tumor location, and tumor stage between the two groups were performed using PSM [13, 14].

Survival rates were calculated by using the Kaplan–Meier method and comparisons between groups were performed with the log-rank test. To identify the prognostic factors, univariate and multivariate analyses were performed using the Cox proportional hazards regression model and the results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Only factors with $P < 0.10$ in the univariate analysis were evaluated in subsequent multivariate analysis using forward stepwise selection for OS and RFS. A $P < 0.05$ was regarded as statistically significant. All statistical analyses were carried out with IBM® SPSS® Statistics version 23.0.

Results

Baseline characteristics

Between 1 January 2012 and 31 December 2014, 430 eligible patients were collected from 2 hospitals in China. Of 430 patients, 79 cases were excluded. Among the remaining 351 cases, 69% (243/351) underwent laparoscopic surgery and 31% (108/351) underwent open surgery. After PSM of 1:1, 103 pairs of patients were successfully matched (Figure 1). Baseline characteristics are outlined in Table 1. Before PSM, there were differences in age and preoperative CEA between the two groups. After PSM, all variables were well balanced.

Short-term surgical outcomes

The perioperative and pathological results in matched cohorts are presented in Table 2. The estimated blood loss during laparoscopic surgery was significantly less than that during open surgery ($P = 0.019$). In the laparoscopic group, the operative time and hospital stay were shorter than in the open group ($P < 0.001$). The incidence of post-operative complications was 9.7% in the laparoscopic group and 10.7% in the open group ($P = 0.818$). In the open group, the most common complications were wound infection (3.9%) and pneumonia (3.9%), followed by anastomosis leakage (2.9%), whereas, in the laparoscopic group, the most common complication was anastomosis leakage (5.8%), followed by pneumonia (1.9%).

Long-term survival outcomes

In the matched cohorts, the median follow-up period was 76.0 months in the laparoscopic group (IQR 67.0–86.0 months) and 80.0 months in the open group (IQR 74.0–85.0 months). During the follow-up, 50 patients died, among whom 35 died from rectal cancer and 39 had locoregional recurrence or distant metastasis. No significant difference was observed between the laparoscopic group and the open group in 5-year OS (75.7% vs 80.6%, $P = 0.346$), 5-year RFS (74.8% vs 76.7%, $P = 0.527$), or 5-year CSS (79.6% vs 87.4%, $P = 0.219$) (Figure 2).

Subgroup analyses for OS were conducted for gender, age, BMI, tumor location, and tumor stage. Compared with open surgery, male patients or those with an intermediate BMI (>20 to 25) who underwent laparoscopic surgery tended to show worse OS (Figure 3).

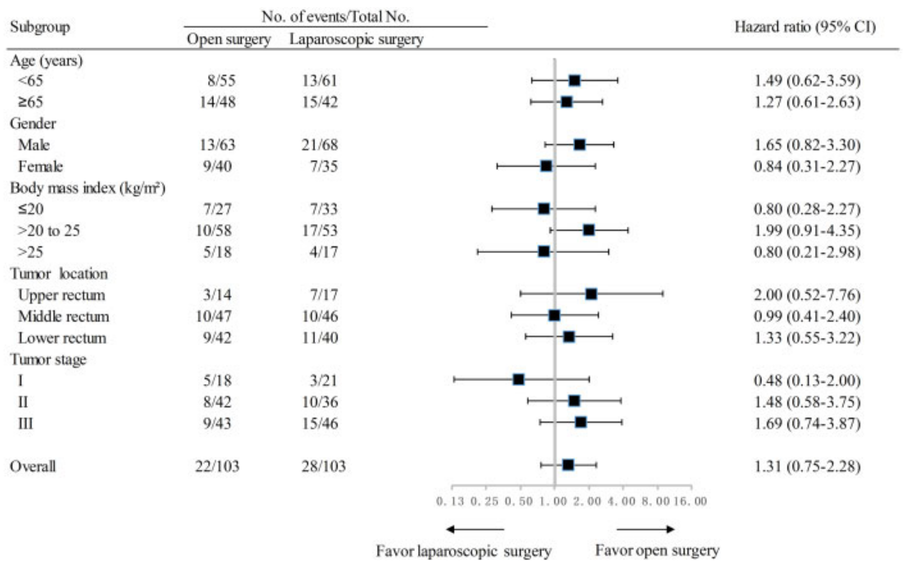

Figure 3. Subgroup analysis of overall survival in matched cohorts

Table 3. Multivariate analysis for OS and RFS in matched cohorts

Variable	OS			RFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Preoperative CEA (>5 vs ≤5 ng/mL)	2.43	1.38–4.29	0.002	2.27	1.31–3.93	0.003
Number of harvested lymph nodes (≥12 vs <12)	0.48	0.27–0.85	0.011	0.53	0.30–0.92	0.024
Perineural invasion (yes vs no)	2.88	1.29–6.43	0.010	3.23	1.51–6.91	0.002

OS, overall survival; RFS, relapse-free survival; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

Prognostic factors for long-term survival

Prognostic factors affecting survival are presented in Table 3. Univariate analyses revealed that an elevated CEA (>5 ng/mL), <12 harvested lymph nodes, perineural invasion, and tumor deposits were associated with poor OS, and that an elevated CEA, <12 harvested lymph nodes, perineural invasion, and lymphovascular invasion were associated with poor RFS (data not shown). The surgical approach (laparoscopic vs open) was not associated with OS (HR 1.31, 95% CI 0.75–2.28) and RFS (HR 1.19, 95% CI 0.70–2.03). Multivariate analyses testified that an elevated CEA, <12 harvested lymph nodes, and perineural invasion were independent factors affecting OS and RFS (Table 3).

Discussion

Laparoscopic surgery for rectal cancer is commonly performed in many countries. Nevertheless, the evidence for laparoscopic surgery for rectal cancer is insufficient. This study focused on the long-term survival outcomes and surgical safety of patients who underwent laparoscopic or open surgery for non-metastatic rectal cancer in the Chinese population. In this two-center study, PSM was performed to make selection balance between patients treated with laparoscopic and open surgery. The six factors of age, gender, BMI, preoperative CEA level, tumor location, and tumor stage were used as described in the protocol. The baseline characteristics were ideally balanced between the laparoscopic and open groups.

Some studies have reported similar post-operative complications and mortality between laparoscopic surgery and open surgery for rectal cancer [8, 15] and other studies have reported fewer post-operative complications after laparoscopic surgery than after open surgery [16, 17]. In our study, there were no significant differences in post-operative complications including wound infection, ileus, urinary-tract infection, anastomosis leakage, intra-abdominal bleeding, pneumonia, and cardiac event between the two groups. The longer operative time is often considered a disadvantage of laparoscopic surgery according to some previous reports [15, 18]. In contrast, our study showed that the operative time of laparoscopic surgery was shorter than that of open surgery. The CLASICC trial and COLOR II trial both showed that hospital stay was significantly shorter in the laparoscopic group [8, 19]. Similarly, our study also showed that the hospital stay for laparoscopic surgery was shorter than for open surgery.

With regard to long-term survival, no large-scale clinical trials have demonstrated a statistically significant difference between laparoscopic and open surgery for rectal cancer. The COLOR II trial indicated no statistically significant differences in DFS and OS between laparoscopic and open surgeries [15]. In the COREAN study, DFS in laparoscopic surgery is non-inferior compared to that in open surgery for mid or low rectal cancer [20]. Consistently with previous studies, OS, RFS, and CSS did not differ in both groups in our study. Interestingly, subgroup analyses for OS showed that male and intermediate BMI (>20 to 25 kg/m^2) subgroups were associated with unfavorable outcomes in the laparoscopic-surgery group vs the open-surgery group. Chinese male populations have a narrow pelvis, which might affect the visualization of and access to the deep pelvic anatomy during laparoscopic surgery. Kitano *et al.* [21] found that laparoscopic surgery might affect long-term outcomes in the high-BMI (>25 kg/m^2) subgroup. In the current study, the BMI subgroup unfavorable for laparoscopic surgery that we identified was intermediate BMI, not high BMI. It might be due to lower BMI in the Chinese population compared to that in the Western population and the small proportion (17%) of patients with high BMI in our cohort. Further evaluation will be needed to determine which subgroups of patients require additional attention when undergoing laparoscopic surgery.

We evaluated several possible prognostic factors that may influence survival in patients with rectal cancer, including tumor location, tumor stage, tumor grade, surgical approach, preoperative CEA level, lymphovascular invasion, perineural invasion, and tumor deposits [22–25]. As expected, our study showed that perineural invasion was the significant prognostic factor affecting OS and RFS. Perineural invasion refers to the invasion of cancer cells into any of the layers of the nerve sheath. A higher grade of perineural invasion was related to local recurrence and metastasis in distant organs such as the liver, lung, and peritoneum [26]. All patients in this study underwent radical surgery with lymph-node dissection. A minimum of 12 harvested lymph nodes is recommended to ensure adequate staging and oncologic resection for colorectal cancer [27]. The more lymph nodes harvested, the better the prognosis [28, 29]. In this study, the average number of harvested lymph nodes was 15 ± 7. We found that patients with $\geq$12 harvested lymph nodes had better OS and RFS than those with <12 harvested lymph nodes. Several studies have shown that elevated preoperative CEA was a poor prognostic factor in colorectal cancer [30–32]. In our study, we also found that patients with an elevated preoperative CEA had poorer OS and RFS.

Our study has several limitations. First, a selection bias existed due to its retrospective design. To reduce this, the two groups were matched carefully using PSM. Second, the statistical power is insufficient because the number of patients enrolled may not be sufficient after matching. Third, data about adjuvant therapy after surgery were not collected, which might be different between both groups and thus have influenced survival outcomes. Fourth, the exclusion of converted cases may introduce a bias in favor of laparoscopic surgery. Finally, the bowel-recovery data could not be exactly assessed due to the lack of records in this retrospective study. Therefore, further research with a large population is still awaited.

Conclusion

In conclusion, our study revealed the benefit of laparoscopic surgery on short-term outcomes including less blood loss, shorter operative time, and shorter hospital stay. We did not find any differences in post-operative complications. Laparoscopic surgery was similar to open surgery in terms of OS, RFS, and CSS for patients. However, male patients and those with an intermediate BMI in the laparoscopic group tended to show worse OS than those in the open group. Findings from this study suggest that open surgery should still be the priority recommendation, but laparoscopic surgery is also an acceptable treatment for non-metastatic rectal cancer in the Chinese population.

Authors' contributions

K.L.T., H.J.D., Z.Q.C., and T.Y.M. collected and analysed the data. K.L.T., H.L., and R.S.X. performed statistical analysis. K.L.T. and H.J.D. drafted the manuscript. G.X.L. and X.H.F. performed the procedure, conceived of and designed the study, and critically revised all the intellectual content of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare that there is no conflict of interests in this study.

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