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ORIGINAL ARTICLE

Comparison of short and long-time outcomes between laparoscopic and conventional open multivisceral resection for primary T4b colorectal cancer

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KEYWORDS
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Outcomes

Summary *Background:* This study aimed to compare laparoscopic multivisceral resection (LMVR) with conventional open multivisceral resection (OMVR) for primary T4b colorectal cancer (CRC) in short and long-time outcomes.
Methods: Patients receiving LMVR or OMVR for primary T4b CRC from January 2009 to June 2016 were enrolled. Patients' clinicopathological characteristics and survival data were collected and analyzed. Multivariable analysis was performed to find the factors related with survival. All statistical analysis was performed by SPSS 22.0.
Results: A total of 91 patients (LMVR 38, OMVR 53) were included in this study. Patients undergoing LMVR were associated with smaller incision length ($P < 0.001$), less blood loss ($P = 0.01$) and comparable operative time ($P = 0.071$). Patients in LMVR group also had less time to first flatus ($P = 0.025$). The results also suggested LMVR could reduce the incidence of postoperative complication. The conversion rate was 28.9%. The 3-year OS was 64.2%, 68.4% in OMVR, LMVR group respectively and the 3-year DFS was 56.6%, 52.6% in OMVR, LMVR group respectively. The Kaplan curves demonstrated that LMVR group had similar OS ($P = 0.896$) and DFS ($P = 0.806$) when compared with OMVR group. In addition, the multivariate analysis demonstrated that laparoscopic surgery was not associated with poorer survival.
Conclusion: Not all MVR for T4b CRC should be performed by open procedure, LMVR can be safe and feasible for primary T4b CRC in selected patients. It can faster the postoperative

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recovery and reduce the incidence of postoperative complication. The OS and DFS are also not inferior to open group.

1. Introduction

Colorectal cancer (CRC) has become one of the most threatening carcinomas in the world.[1] Although the multidisciplinary treatment for CRC has made great progress in the past decades, surgical resection is still the best choice for potentially radical cure.[2,3] Sometimes, besides the original tumors, surgeons need to resect extra organs for the existence of local invasion (T4b) which is defined as multivisceral resection (MVR). Traditionally, open surgery was recommended for MVR because MVR was more difficult and complex than general surgery, and open surgery might help improve the R0 resection rate.[4] However, conventional open surgery could also lead some problem including high risk of postoperative complication and slow recovery,[5,6] and patients with open surgery needed to suffer from more pain because of the long incision length.[6] These shortcomings could be overcome by laparoscopic techniques.[7]

Since the first report of laparoscopic technique in CRC surgery, it has been widely accepted and applied worldwide for its advantages which include smaller incision, less pain, and faster recovery.[5,8] At the beginning, laparoscopic surgery was associated with longer operative time and high conversion rate.[9,10] Nevertheless, with the experience accumulation in the past decades, surgeons are now more familiar and skillful in laparoscopic CRC surgery.[11] Several studies have demonstrated that laparoscopic surgery could have comparable operative time with open surgery for CRC and the conversion rate was lower.[12,13] Long-time data also suggested the laparoscopic surgery was not inferior to open surgery for survival.[14]

Thus, in recent years, surgeons began to explore the safety and feasibility of LMVR for primary CRC. Several studies have compared laparoscopic with open surgery for clinical outcomes in this issue.[4,15] However, most of them were retrospective studies and the sample size was small. Besides, the results were not consistent and the long survival outcome is still limited. Up to now, the application of laparoscopic technique in CRC surgery for MVR is still controversial. So we conducted this study to compare LMVR with OMVR for primary CRC in terms of short and long outcomes.

2. Methods

2.1. Patients

We reviewed the prospective colorectal cancer database of Department of Gastrointestinal Surgery, West China Hospital, Sichuan University retrospectively. Patients undergoing MVR for primary T4b colorectal cancer from January 2009 to June 2016 were included in this study. The inclusion criteria were as follows: 1) confirmed diagnosis of colon or rectal cancer by biopsy; 2) surgical procedure was open or laparoscopy; 3) undergoing extra organ resection besides the primary cancer because of local invasion (T4b). The exclusion criteria were: 1) benign disease such as inflammation bowel disease; 2) emergency surgery; 3) multiple cancers in gastrointestinal tract.Ethical approval was not necessary because this study was a retrospective study.

2.2. Assessment parameters

Patient demographics and clinicopathological characteristics were collected, including gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) class, pretreatment carcinoembryonic antigen (CEA) level, tumor location, surgical procedure, tumor residual, neoadjuvant therapy, and adjuvant therapy. Operative parameters (including operative time, incision length, and estimated blood loss, blood transfusion, and intraoperative complication), postoperative recovery (including time to first flatus, gastric tube retaining time, time to first liquid diet, time to first soft diet, oxygen inhalation time, Catheter retaining time, and postoperative hospital days), postoperative complication, ICU staying, reoperation, mortality, and oncologic outcomes which included T stage, N stage, TNM stages, differentiation, tumor size, and retrieved lymph nodes were also recorded. All the time of postoperative recovery such as time to first flatus was recorded from the finish of surgery. Long-term endpoints were 3-year OS and DFS.

2.3. Follow-up

All patients were followed up regularly at 3, 6, 12, 24, 36, 48, and 60 months after surgery. Contrast-enhanced CT scan of the abdomen and chest were done every half year, and colonoscopy was done per year. Routine blood test and tumor biomarker were performed every time. When it was necessary, biopsy and PET-CT would be added.

2.4. Statistical analysis

Data were stored and updated in our institutional databases. Continuous variables were expressed as median (range) or mean (standard deviation), and non-parametric Mann—Whitney U test or independent-sample t test was induced for analysis. Ranked data were also analysed by non-parametric test. Categorical variables were showed as a number and analyzed by Chi-Square or Fisher's exact tests. Kaplan—Meier survival curves were used for cancer-specific outcome analysis and cox-regression was used for

multivariable analysis. A p value of 0.05 or below was deemed to be significant. All statistical analysis was performed using SPSS 22.0.

3. Results

3.1. Patient characteristics

Finally, a total of 91 patients undergoing MVR for primary CRC from January 2009 to June 2016 in our hospital were enrolled in this study. Among all the patients, 53 (male 28, female 25) were performed conventional open surgery and 38 (male 17, female 21) received laparoscopic surgery. There was no significant difference between the two groups in terms of gender (P = 0.446), age (P = 0.465), BMI (P = 0.960), ASA score (P = 0.0.947), preoperative CEA level (P = 0.926), tumor residual (P = 0.791), neoadjuvant therapy (P = 0.685), or adjuvant therapy (P = 0.811). We also found OMVR group had more tumor location on right colon (P = 0.032). In addition, 11 patients (28.9%) in LMVR group received converted surgery (Table 1).

We listed the information of resection organs in Table 2. There was no significant difference of resected organs between the two groups excepted for LMVR group had more combined resection of prostate (P = 0.011). Besides, we also found that LMVR group had significantly less abdominal organs resection that OMVR group. (P = 0.004).

As for surgical outcomes, we found LMVR group had similar operative time (P = 0 0.071) and when compared with OMVR group. However, we also observed LMVR had significantly less blood loss (P = 0.010) and smaller incision length (P < 0.001) than OMVR. Besides, blood transfusion (P = 0.137) and intraoperative complications (P = 1.000) were not significantly different between the two groups. When it came to postoperative recovery, the results demonstrated that patients undergoing LMVR were associated with faster time to first flatus (P = 0.025). In addition, the two groups were similar in time of gastric tube remaining (P = 0.058), oxygen inhalation (P = 0.050), to first liquid diet (P = 0.073) and soft diet (P = 0.745), catheter retaining (P = 0.979), and postoperative days (P = 0.609). We also observed that LMVR group had less incidence of postoperative complications thought it was not significantly different. 6 patients with open surgery were send to ICU while there were 1 patients in laparoscopic group (P = 0.256). In OMVR group, one patient got reoperation for the ostoma problem. The patients receiving reoperation in LMVR group was for abdominal washing because of the abdominal infection (Table 3).

Table 1 Patients' baseline information.

Characteristics	OMVR (n = 53)	LMVR (n = 38)	P value
Gender			0.446
male	28	17	
female	25	21	
Age (year)	58.2 ± 1.7	60.0 ± 1.7	0.465
BMI (Kg/m^2)	22.1 ± 0.5	22.2 ± 0.6	0.960
ASA			0.947
1	0	1	
2	34	23	
3	19	14	
CEA			0.926
<5	24	18	
≥5	25	18	
Tumor location			**0.032**
Right colon	14	2	
Left colon	10	10	
Rectum	29	26	
conversion	—	11	—
Tumor residual	6	5	0.791
Neoadjuvant therapy	16	13	0.685
Adjuvant therapy	35	26	0.811

BMI, body mass index; ASA, America Society of Anesthesiologists; CEA, carcinoembryonic antigen; OMVR, open multivisceral resection; LMVR, laparoscopic multivisceral resection.
Bold values mean P< 0.05.

Table 2 combined resection organs.

Organs	OMVR (n = 53)	LMVR (n = 38)	P value
Liver wedge[a]	2	0	0.508
Gall bladder[a]	3	0	0.262
Prostate[b]	0	5	**0.011**
Seminal vesicle[b]	7	6	0.729
Uterus[b]	9	3	0.342
Vagina[b]	11	7	0.783
Ovary[b]	6	7	0.340
Uterine tube[b]	5	6	0.359
Bladder[b]	7	6	0.729
Ureter[b]	3	2	1.000
Stomach[a]	3	0	0.262
Omentum[a]	2	0	0.508
Small intestine[a]	9	3	0.342
Appendix[a]	0	2	0.172
Pancreas[a]	4	0	0.137
Spleen[a]	2	0	0.508
Coccyx[b]	3	0	0.262
Kidney[a]	3	1	0.860
Spermaduct[b]	0	1	0.418
Internal iliac vein[b]	3	1	0.860
Psoas major[b]	2	0	0.508
Pelvic plexus nerve[b]	0	2	0.172
Numbers			0.343
1	32	26	
2	15	10	
3	2	2	
4	4	0	
Location			**0.004**
Abdominal organs	28	6	
Pelvic organs	56	46	
Total organs	84	52	—

OMVR, open multivisceral resection; LMVR, laparoscopic multivisceral resection. a was defined as abdominal organ and b was defined as pelvic organ.
Bold values mean P< 0.05.

Table 3 Operative and postoperative information.

Variables	OMVR (n = 53)	LMVR (n = 38)	P value
Operative time (min)	200.0 (115–455)	170.0 (110–360)	0.071
Blood loss (ml)	100.0 (10–500)	50.0 (5–300)	**0.010**
Incision length (cm)	20.0 (13–35)	5.0 (4–25)[a]	**<0.001**
Blood transfusion	4	0	0.137
Intraoperative complication	1	1	1.000
Postoperative recovery			
Time to first flatus (day)	4.0 (1–8)	3.0 (1–10)	**0.025**
Gastric tube retaining time (day)	1.0 (0.5–28)	10.0 (0.5–6)	0.179
Time to first liquid diet (day)	4.0 (1–15)	4.0 (1–10)	0.073
Time to first soft diet (day)	6.0 (3–16)	6.0 (2.4–14)	0.847
Oxygen inhalation time (hour)	24.0 (10–792)	24.0 (10–216)	0.240
Catheter retaining time (day)	6.0 (2–20)	7.0 (1–30)	0.603
Postoperative hospital days	8.0 (4–33)	9.0 (5–63)	0.799
Complications	15	7	0.278
Wound infection	5	0	
Pulmonary infection	5	1	
Intra-abdominal infection	1	1	
Urinary retention	1	0	
Abdominal distention	0	2	
Anastomotic leakage	0	1	
Anastomotic bleeding	0	0	
Pancreatic fistula	1	0	
Chylous leakage	0	1	
Perianal abscess	0	1	
Abdominal pain	1	0	
Diarrhea	1	1	
Stoma problem	1	0	
ICU staying	6	1	0.256
Reoperation	1	1	1.000
Mortality	0	0	—

OMVR, open multivisceral resection; LMVR, laparoscopic multivisceral resection.
Bold values mean P< 0.05.
[a] Long incision like 25 cm in LMVR group was created by conversion surgery.

When it came to pathological outcomes, no significant difference was found between the two group in terms of T stage (P = 0.118), N stage (P = 0.104), TNM stage (P = 0.536), differentiation degree (P = 0.093), retrieved lymph node (P = 0.184), positive CRM (P = 0.701), or R0 resection rate (P = 1.000) The tumor size of LMVR group was smaller than that of OMVR group (P = 0.004) (Table 4).

3.2. Survival outcomes

For all the patients, the median follow-up time was 34 (2–93) months. The 3-year OS was 64.2%, 68.4% in OMVR, LMVR group respectively and the 3-year DFS was 56.6%, 52.6% in OMVR, LMVR group respectively. The Kaplan curves demonstrated that LMVR group had similar OS (P = 0.896) and DFS (P = 0.806) when compared with OMVR group (Fig. 1). In addition, the multivariate analysis demonstrated that higher CEA level, open surgery, tumor residual, positive CRM and no adjuvant therapy were associated with poor OS while we also found female gender, neoadjuvant therapy and tumor residual were related with poor DFS (Table 5).

4. Discussion

Laparoscopic technique has been increasingly used for MVR in CRC.[16] After decades' development, laparoscopic techniques have been more and more mature and advanced.[17] These progress undoubtedly will promote the widely use of laparoscopic technique in CRC surgery, including MVR. However, the safety and feasibility of LMVR is still debatable and the survival outcome is lack. So we conducted this retrospective study to compare LMVR with OMVR for primary CRC in terms of short and long outcomes.

In present study, 91 patients received LMVR or OMVR for primary CRC were included. We found that patients undergoing laparoscopic surgery were associated with significantly smaller incision length and less blood loss while the operative time was similar. Besides, patients in laparoscopic group also had faster postoperative recovery and the survival outcomes were not inferior to open group.In the past, laparoscopic surgery was thought associated with longer operative duration, especially for complex resection.[18] But in our present study, we found laparoscopic surgery didn't need significantly longer operative time

Table 4 Pathological outcomes.

Variables	OMVR (n = 53)	LMVR (n = 38)	P value
T stage			
T2	2	1	0.118
T3	13	17	
T4a	8	4	
T4b	30	16	
N stage			0.104
0	33	18	
1	15	12	
2	5	8	
TNM stage			0.536
I	1	1	
II	28	16	
III	16	16	
IV	8	5	
Differentiation degree			0.093
G2	22	22	
G3	20	12	
G4	11	4	
Tumor size (cm)	6.0 (2—15)	4.0 (2.5—10)	**0.004**
Retrieved lymph node	13.0 (0—58)	11.0 (0—81)	0.241
Positive CRM	2	3	0.701
R0 resection	51	36	1.000

OMVR, open multivisceral resection; LMVR, laparoscopic multivisceral resection; CRM, circumferential resection margin.
Bold values mean P< 0.05.

when compared with open surgery. Our result was consistent with some previous studies.[15,19] We explained it that most surgery was finished by Professor Ziqiang Wang, who is a leader of CRC surgery, especially laparoscopic surgery in China, and if necessary, experienced professors of other departments will be invited to perform the surgery together. Besides, we could see that LMVR group had less resection of abdominal organs including liver, pancreas and spleen than OMVR group. That could decrease the surgical difficulty and shorten surgical process. What's more, the smaller tumor size in LMVR group could also contribute to this outcome. So the operative time was similar between the two groups. In addition, the result also demonstrated the advantages of laparoscopic technique in faster postoperative recovery, though postoperative hospital days were not significantly different. We thought hospital days could be affected by several factors including severe complications such as abdominal infection. Besides, with the improvement of nursing level and population of enhanced recovery, even patients with open surgery could have a short hospital stay.[20,21] Consistent with some previous studies, we found patients in LMVR group had less incidence of postoperative complication.[15] This might be associated with the minimal invasion in laparoscopic surgery. The less pain might help reduce the stress reaction postoperatively. Some previous studies reported that conversion could be a risk factor for the survival of CRC surgery.[10] We thought this might be greatly related with the complex disease of these patients. So accurate evaluation and careful selection before surgery are important. Base on published literature, the conversion rate of LMVR in CRC surgery ranged from 7.89% to 23.4%.[4,15,22,23] In our study, the conversion rate was 28.9% and it did not lead to any obviously adverse outcomes. We thought the conversion rate could be affected by the surgeons' learning curve, scope of local invasion and degree of abdominal adhesion We have noticed that some previous studies also classified the patients undergoing conversion surgery into the laparoscopic group.[4,22,23]

In fact, some previous studies have compared laparoscopic with open surgery in combined liver resection for primary CRC with synchronous liver metastasis.[24,25] However, multivisceral resection for M1 and T4b were totally

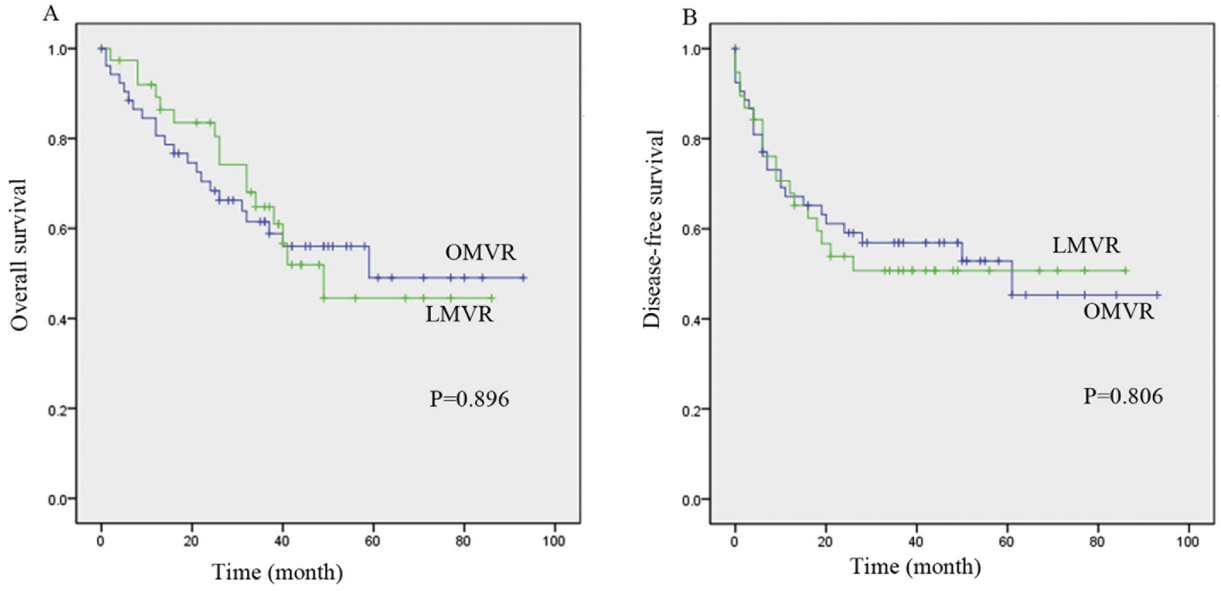

Figure 1 LMVR versus OMVR for OS (A), DFS (B).LMVR, laparoscopic multivisceral resection; OMVR, open multivisceral resection; OS, overall survival; DFS, disease-free survival.

Table 5 Univariated and multivariate analysis for OS and DFS.

Variables	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Gender:female/male	**0.450 (0.230, 0.881)**	**0.020**	0.377 (0.162, 0.878)	0.024	**0.375 (0.195, 0.722)**	**0.003**	**0.321 (0.145, 0.707)**	**0.005**
Age≥65 years	1.794 (0.940, 3.423)	0.076	2.109 (0.917, 4.853)	0.079	1.492 (0.799, 2.785)	0.209		
CEA≥5	1.734 (0.902, 3.336)	0.099	**2.678 (1.159, 6.187)**	**0.021**	1.713 (0.917,3.200)	0.091	**2.204 (1.020, 4.765)**	**0.044**
Neoadjuvant therapy	**1.985 (1.038, 3.794)**	**0.038**	2.160 (0.951, 4.905)	0.066	1.532 (0.820,2.862)	0.181	1.300 (0.616, 2.734)	0.491
Rectum/colon	0.682 (0.344, 1.353)	0.274			0.739 (0.388,1.408)	0.358		
Open/laparoscopy	0.958 (0.502, 1.827)	0.896	**0.369 (0.171, 0.797)**	**0.011**	1.079 (0.585,1.990)	0.808	0.630 (0.313, 1.267)	0.195
Tumor residual	**6.915 (3.241,14.751)**	**<0.001**	**35.315 (8.555,145.770)**	**<0.001**	**8.902 (4.177,18.973)**	**<0.001**	**51.606 (12.995,204.936)**	**<0.001**
Tumor size≥5 cm	0.966 (0.504, 1.853)	0.918			0.920 (0.496, 1.705)	0.791		
pT4b stage	1.439 (0.755, 2.743)	0.269			1.186 (0.646, 2.179)	0.582		
N0/N+	**3.386(1.719, 6.671)**	**<0.001**	1.390 (0.424, 4.556)	0.586	**2.858(1.524, 5.361)**	**0.001**	0.877 (0.260, 2.964)	0.833
Retrieved LN ≥ 12	0.963 (0.508, 1.826)	0.907			1.037 (0.565, 1.903)	0.908		
G1+G2/G3+G4	1.342 (0.708, 2.544)	0.368			1.310 (0.713, 2.409)	0.384		
Tumor stage								
I,II/III, IV	**4.502 (2.114, 9.591)**	**<0.001**	1.791 (0.454, 7.066)	0.405	**3.536 (1.800, 6.945)**	**<0.001**	1.847 (0.497, 6.869)	0.360
R0 resection	**15.097 (4.707, 48.419)**	**<0.001**	0.498 (0.089, 2.796)	0.428	**358.806(10.972, 13565.697)**	**0.001**	1.239 (0.183, 8.372)	0.826
Positive CRM	2.658 (0.936, 7.547)	0.066	**5.622 (1.674, 18.881)**	**0.005**	2.090 (0.742, 5.884)	0.163	2.759 (0.896, 8.493)	0.077
Organs numbers>1	1.129 (0.589, 2.166)	0.715			0.909 (0.483, 1.709)	0.766		
Adjuvant therapy	**0.454 (0.239, 0.863)**	**0.016**	**0.344 (0.165, 0.720)**	**0.005**	0.574 (0.309, 1.065)	0.079	0.540 (0.275, 1.061)	0.074

OS, overall survival; DFS, disease-free survival; CEA, arcinoembryonic antigen; HR, hazard ratio; CI, confidence intervals; LN, lymph node.
Bold values mean P< 0.05.

different including the surgical procedure and difficulty. For local invasion, combined organ resection could help achieve higher R0 resection rate and improve the prognosis.[22] In the past, almost all MVR was performed by open procedure because surgeons afraid LMVR could decrease the quality of resection.[15] In our study, the R0 resection rate and positive CRM was not significantly different between the two groups. That might be related with experience accumulation and the similar resection principle. In the multivariate analysis, the results demonstrated that LMVR could be an protective factor for OS. We thought this outcome could be associated with the potential selection bias including LMVR group had less invasion to abdominal organs.Some limitations of this study have to be mentioned. Firstly, the sample size of this study was still not large enough. Secondly, this was a retrospective study and there existed some selection bias including OMVR group had more right colon cancer, more resection of abdominal organs and larger tumor size though we have performed multivariate analysis. So a prospective randomized study is still needed to compare laparoscopic with open surgery for MVR in the future.

In conclusion, not all MVR for T4b CRC should be performed by open procedure, LMVR can be safe and feasible for primary T4b CRC in selected patients. It can faster the postoperative recovery and reduce the incidence of postoperative complication. The OS and DFS are also not inferior to open group.

Conflict of interest

None declared.

Disclosure statement

No competing financial interests exist.

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