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Laparoscopic approach for left-sided T4 colon cancer is a safe and feasible procedure, compared to open surgery

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Abstract

Background A laparoscopic approach can be attempted for pathologic T4 (pT4) colon cancer. Our aim was to evaluate the clinico-oncologic outcomes following laparoscopic versus open surgery for right and left-sided pT4 colon cancer.

Methods From a multicentric collaborative database, we enrolled 245 patients with right-sided colon cancer (RCC, 128 laparoscopy and 117 open) and 338 with left-sided colon cancer (LCC, 176 laparoscopy and 162 open). All patients underwent intended curative surgery for histologically proven T4 adenocarcinoma, between 2004 and 2013. The primary end-point of our analysis was the oncologic outcome, including the 5-year disease-free survival (5 year-DFS) and the 5-year overall survival (5 year-OS). The secondary end-points included the R0 resection rate and postoperative complications.

Results Our study group included 224 T4N0 and 359 T4N+ tumors. The median follow-up was 53 months. For patients with RCC, the rate of postoperative morbidities was lower for the laparoscopy than that for the open surgery group (12.5 vs. 22.2%, $p=0.044$). There was no difference in the R0 resection rate (94.5 vs. 96.6%, $p=0.425$) between the groups. The 5 year-DFS and 5 year-OS rates were lower for the laparoscopy than that in the open group (48.9% vs. 59.2%, $p=0.093$; 60.0% vs. 70.0%, $p=0.284$, respectively), but this difference was not statistically significant. Among patients with LCC, there were no differences in the rate of postoperative complication and R0 resection (15.3 vs. 21.0%, $p=0.307$; 96.0 vs. 95.7%, $p=0.875$, respectively). Both groups had comparable 5 year-DFS and 5 year-OS rates (62.7% vs. 61.1%, $p=0.552$; 72.0% vs. 71.8%, $p=0.611$, respectively).

Conclusions Laparoscopic surgery appears to be a safe procedure for patients with pT4 LCC, but requires careful consideration for patients with pT4 RCC.

Keywords Laparoscopy · Oncologic outcomes · T4 colon cancer · Tumor location

Curative resection followed by adjuvant chemotherapy currently remains the standard treatment for patients with pT4 colon cancer. Laparoscopic surgery might be attempted for the treatment of stage T4 tumor and could provide good clinical and oncologic outcomes that are comparable to the outcomes for open procedures [1–5].

However, the suitability of laparoscopy for the treatment of T4 colon cancer remains an issue of debate due to the possibility of incomplete resection and the high rate of conversion to open surgery.

In addition, T4 colon cancer requires extensive en bloc resection for curative treatment. Therefore, treatment guidelines recommend an open approach for pT4 colon cancer.

For several years, laparoscopic en bloc resection has been considered cumbersome, lengthy, and challenging for radical

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treatment. In addition, for right-sided T4 colon cancer, en bloc resection can be technically demanding, with a worse prognosis having been reported, compared to laparoscopic surgery of left-sided colon cancers [6–10].

Considering recent technical advances in laparoscopic procedures, it is not clear at this time that if a laparoscopic approach for T4 colon cancer would yield oncologic outcomes comparable to those of an open approach, irrespective of the tumor location.

Therefore, the purpose of our study was to compare the oncologic and clinical outcomes after curative treatment for pT4 colon cancer between laparoscopic and open surgery, and for right- and left-sided colon cancer.

Materials and methods

Patients

We initially recruited six centers into the study; however, the necessary data could not be collected in one of these centers, with the data from five centers ultimately being included in the analysis. All five centers are referral centers for specialized treatment of colon cancer, using multiple modalities, including surgery and chemotherapy. In this study, we retrospectively analyzed the data collected from patients who underwent curative surgical treatment for colon cancer between 2004 and 2013. Of note, these centers are located in different cities and the study was approved by the Institutional Review Board (14-I019).

From a total of 6548 cases of colon cancer, we enrolled 583 patients who underwent curative resection for pT4 primary colon cancer with proven adenocarcinoma. The criterion for T4 was a tumor invasion beyond the adventitia or serosa layer, confirmed on pathological examination. Most resection specimens for pT4 tumor included adjacent peritoneum, additional tissue, or further structures around the main tumor. The exclusion criteria were as follows: pT1-3 colon cancers, palliative surgery, histology other than adenocarcinoma, hereditary cancer, synchronous colon cancer, or insufficient data.

Patients were classified into right-sided colon cancer (RCC) and left-sided colon cancer groups (LCC). A tumor located from the appendix to the distal transverse colon was classified as RCC, with tumors located from the splenic flexure to the recto-sigmoid colon was classified as LCC.

Of the 583 cases enrolled into the study, 303 underwent laparoscopic surgery and 280 open surgery, including 32 conversions from a laparoscopic to an open approach.

Of the 245 cases of pT4 RCC, 127 were treated with laparoscopic surgery and 118 with open surgery, including 17 conversions from laparoscopic to open surgery. Of the 338 patients with pT4 LCC, 176 were treated with laparoscopic surgery and 162 with open surgery, including 15 conversions from laparoscopic to open surgery (Fig. 1).

Adjuvant therapy and follow-up

All patients underwent standardized surgical procedures, consisting of a complete mesocolic excision and central vascular ligation. The surgical principles for the laparoscopic

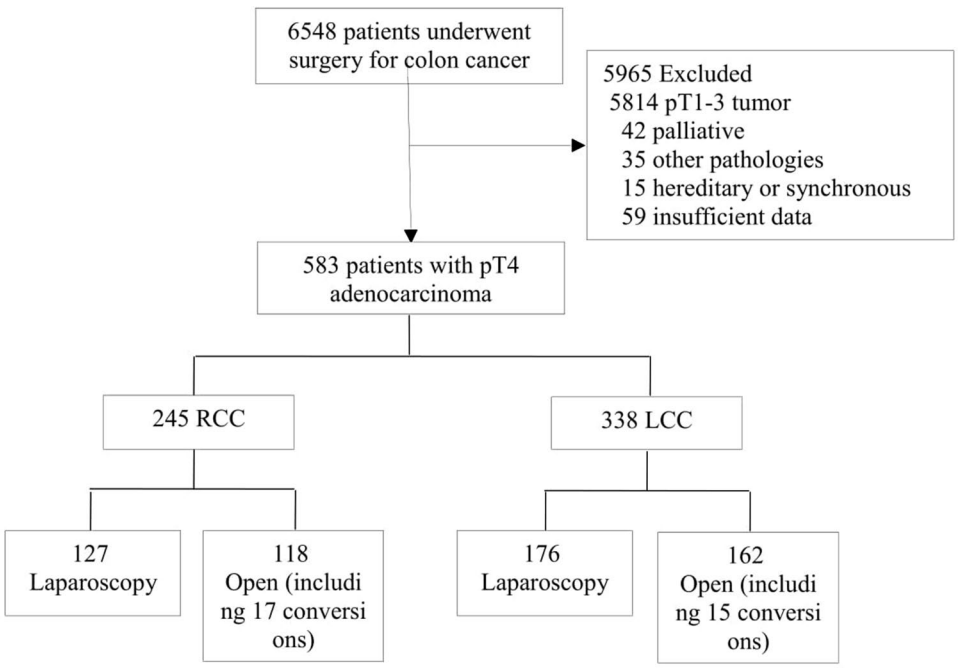

Fig. 1 Flow chart showing patients enrollment

approach were similar to those for open surgery. If resection of adjacent organs or further excision of adjacent tissues was difficult to perform through the laparoscopic approach, cases were converted to open surgery.

After recovery from surgery, adjuvant treatment was recommended to all patients with a confirmed diagnosis of pT4 cancer. The adjuvant regimen included 5-FU (fluorouracil), oral capecitabine, and FOLFOX (5-FU, leucovorin, and oxaliplatin). Among all patients, 522 (89.5%) received adjuvant chemotherapy. All patients were followed up until the last check up in the outpatient clinic or death.

Study endpoints

The primary endpoint of analysis was oncologic outcomes, including 5-year DFS and 5-year OS, compared between laparoscopic and open surgery for pT4 RCC and pT4 LCC. The secondary endpoints were the rate of R0 resection and clinical outcomes, including postoperative complications.

Statistical analysis

Data are presented as the mean for continuous variables and as frequency (%) for categorical variables. The Chi square test and the independent *t* test were used to compare the variables between the laparoscopic and open surgery groups and the RCC and LCC groups. Survival rate was estimated by using the Kaplan–Meier method with between-group differences compared using the log-rank test. All analyzes were performed using SPSS 9 version 18.0 (Chicago, IL, USA). A two-tailed *p*-value < 0.05 was considered as statistically significant.

Results

The enrolled patients had a mean age of 61 years (range 27–93 years), including 344 men and 239 women. Our study group included 224 (38.4%) cases of T4N0 cancers and 359 (61.6%) T4N+ cancers. The mean number of retrieved and metastatic lymph nodes was 30.5 and 4.3, respectively. Over a median follow-up time of 53 months, the 5-year DFS rate was 58.6%, with a 5-year OS rate of 69.6%.

Clinical outcomes for RCC between the laparoscopic and open surgery group

There were no statistically significant differences in the clinical characteristics between the laparoscopy and open surgery groups. The laparoscopy group had a longer operative time (189 vs. 174 min), but with lesser blood loss (270 vs. 327 ml), contrast to that in the open group. Over the postoperative recovery, the laparoscopy group presented with lower rate of postoperative morbidities (12.5 vs. 22.2%), with the lower rate being specially associated to a lower rate of wound infection in the laparoscopic group (Table 1).

Oncologic outcomes in RCC between the laparoscopic and open surgery group

The tumor size was smaller in the laparoscopy group than open group (6.3 vs. 8.5 cm). Overall, 31 patients underwent combined resection (11 abdominal wall/peritoneum/retroperitoneum, 7 small bowels, 5 duodenum and/or pancreas, 4 liver and/or gallbladder, 1 stomach and 3 multiple organs). Overall, 42 patients had postoperative morbidities classified as Clavien–Dindo lesser than II ($n = 35$; 21 wound infection or dehiscence, 7 prolonged ileus, 3 minor leakage, 2 urinary retention, 1 urinary infection and 1 biliary infection), and Clavien–Dindo greater than III ($n = 7$; 3 bowel leakage, 2 bleeding, and 2 pneumonia plus multiple infections).

Despite the lower rate of combined resection in the laparoscopy group than open group (8.6 vs. 17.1%), the rate of R0 resection was similar between the two groups (94.5 vs. 96.6%; Table 2).

Patients with pT4 RCC were followed-up for a median duration of 46 months (range 5–104 months). The 5-year

Table 1 Comparison of clinical outcomes of pT4 right-sided colon cancer between the laparoscopy and open groups

Variable	Laparoscopy ($N = 127$)	Open ($N = 118$)	*p* value*
Age (years)	61.3	59.9	0.425**
Male/female	70/57	71/47	0.426
BMI (kg/m^2)	22.9	23.3	0.338
Comorbidities (%)	35 (27.6%)	35 (29.7%)	0.658
Preoperative CEA (ng/ml)	10.1	15.3	0.206**
Location			0.546
Cecum	39	36	
Ascending colon	73	65	
Transverse colon	15	17	
Operative time (min)	189	174	0.045**
Blood loss (ml)	270	327	0.034**
Length of hospital stay (days)	11.0	12.4	0.120
Postoperative morbidity (%)	16 (12.5%)	26 (22.2%)	0.044
Clavien–Dindo			
I, II	13	22	
III, IV	3	4	
Mortality within 1 month (%)	1 (0.8%)	2 (1.7%)	0.273
Adjuvant chemotherapy	115 (90.6%)	100 (84.7%)	0.167

Values are expressed as mean or number (%)

BMI body mass index, *CEA* carcinoembryonic antigen

**p* value calculated by the Chi square test

***p* value calculated by the independent *t* test

Table 2 Comparison of oncologic outcomes of pT4 right-sided colon cancer between the laparoscopy and open groups

Variable	Laparoscopy ($N=127$)	Open ($N=118$)	p value*
Tumor size (cm)	6.3	8.5	0.009**
Number of retrieved lymph nodes	33	35	0.283**
Node state (N0/N+)	45/82	44/74	0.870
Number of metastatic lymph nodes	4.8	4.9	0.937**
T4a/T4b	98/39	90/28	0.869
Lymphatic invasion (%)	91 (71.7%)	80 (67.8%)	0.609
Combined resection (%)	11 (8.6%)	20 (17.1%)	0.046
R0 resection rate (%)	120 (94.5%)	114 (96.6%)	0.425

Values are expressed as mean or number (%)

*p value calculated by the Chi square test

**p value calculated by the independent t test

DFS and OS curves for laparoscopy and open surgery are shown in Figs. 2 and 3, respectively. The 5-year DFS (48.9% vs. 59.2%, for the laparoscopy and open surgery group) and OS rate (60.0 vs. 70.0%) were lower in the laparoscopy group, but no significant statistical difference was identified between the two groups ($p=0.093$ and $p=0.284$, respectively).

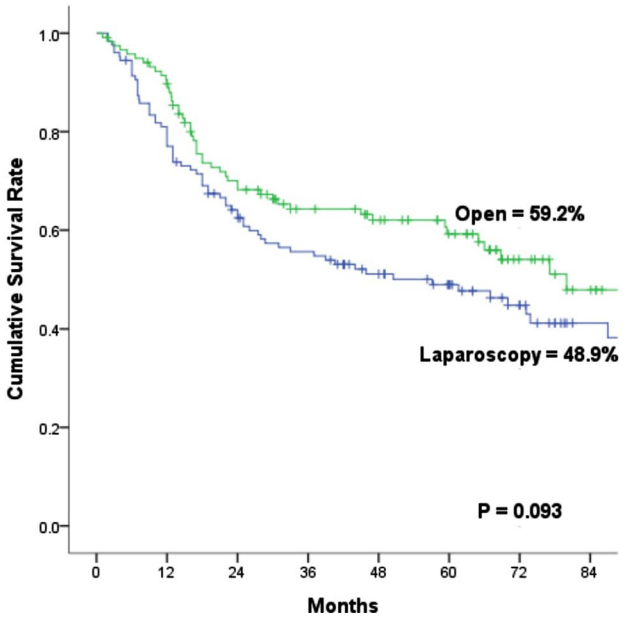

Fig. 2 Disease-free survival between the compared groups in RCC

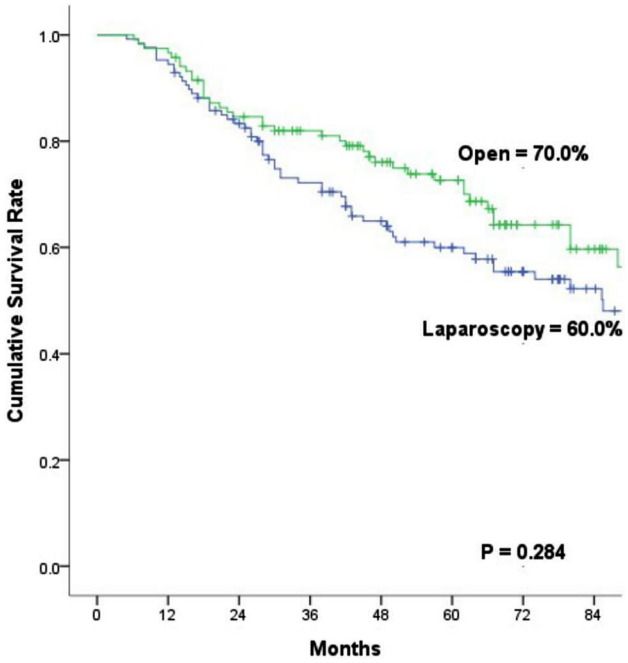

Fig. 3 Overall survival rate between the compared groups in RCC

Clinical outcomes in LCC between the laparoscopic and open surgery group

There were no statistically significant differences in clinical outcomes, including postoperative morbidities, between the laparoscopic and open surgery groups except for the longer operative time for the laparoscopy group (205 vs. 182 min; Table 3).

Oncologic outcomes in LCC between the laparoscopic and open surgery group

The tumor size was smaller in the laparoscopy group (6.8 vs. 8.7 cm). Although the laparoscopy group showed a higher rate of node-positive tumor, there was no difference in the mean number of metastatic nodes between the two groups. This resulted from the more patients with small number (≤ 3) of metastatic nodes in the laparoscopic group (44 in laparoscopy vs. 25 in open).

In all, 70 patients underwent combined resection (24 abdominal wall/peritoneum/retroperitoneum, 15 urinary organs, 13 gynecologic organs, 10 small bowels, and 8 multiple organs). Overall, 61 patients had postoperative morbidities classified as Clavien–Dindo lesser than II ($n=52$; 29 wound infection or dehiscence, 11 prolonged ileus, 4 urinary retention, 3 minor leakage, 2 urinary infection and 3 other infections), and Clavien–Dindo greater than III ($n=9$; 4 bowel leakage, 2 bleeding, 1 mechanical obstruction, 1 urinary injury, and 1 uncontrolled pneumonia).

Table 3 Comparison of clinical outcomes of T4 left-sided colon cancer between the laparoscopy and open groups

Variable	Laparoscopy ($N=176$)	Open ($N=162$)	p value*
Age (years)	61.5	61.5	0.972**
Male/female	108/68	95/67	0.611
BMI (kg/m^2)	23.4	22.9	0.122
Co-morbidities (%)	50 (28.4%)	56 (34.6%)	0.224
Preoperative CEA (ng/ml)	20.8	19.6	0.902**
Location			0.714
Splenic flexure	9	10	
Descending colon	32	27	
Sigmoid colon	92	83	
Rectosigmoid colon	43	42	
Operative time (min)	205	182	0.003**
Blood loss (ml)	276	310	0.135**
Length of hospital stay (days)	12.2	13.4	0.131
Postoperative morbidity (%)	27 (15.3%)	34 (21.0%)	0.307
Clavien–Dindo			
I, II	22	30	
III, IV	5	4	
Mortality within 1 month (%)	2 (1.1%)	1 (0.6%)	0.612
Adjuvant chemotherapy	157 (89.2%)	150 (92.6%)	0.282

Values are expressed as mean or number (%)

BMI body mass index, *CEA* carcinoembryonic antigen

*p value calculated by the Chi square test

**p value calculated by the independent t test

Table 4 Comparison of oncologic outcomes of T4 left-sided colon cancer between the laparoscopy and open groups

Variable	Laparoscopy ($N=176$)	Open ($N=162$)	p value*
Tumor size (cm)	6.8	8.7	0.002**
Number of retrieved lymph nodes	27	29	0.125**
Node state (N0/N+)	51/125	85/77	< 0.001
Number of metastatic lymph nodes	4.1	3.7	0.565**
T4a/T4b	128/48	123/39	0.503
Lymphatic invasion (%)	122 (69.3%)	111 (68.5%)	0.874
Combined resection (%)	29 (16.5%)	41 (25.3%)	0.045
R0 resection rate (%)	169 (96.0%)	155 (95.7%)	0.875

Values are expressed as mean or number (%)

*p value calculated by the Chi square test

**p value calculated by the independent t test

Similar to the findings in the RCC group, despite the lower rate of combined resection in the laparoscopy group than open surgery group (16.5 vs. 25.3%), the rate of R0 resection was similar between the two groups (96.0 vs. 95.7%; Table 4).

Patients with pT4 LCC were followed-up with a median duration of 56 months (range 2–105 months). The 5-year DFS and OS curves for laparoscopy and open surgery are shown in Figs. 4 and 5, respectively. The 5-year DFS (62.7% and 61.1% for the laparoscopy and open surgery group, respectively, $p=0.552$) and OS rate (72.0 and 71.8%, $p=0.611$) were comparable between the two groups.

Discussion

Laparoscopic surgery can be used for T4 tumor, but it is still controversial whether it is suitable for patients with T4 colon cancer, due to the possibility of incomplete resection and frequent need for conversion to open surgery.

In this study, the rate of postoperative morbidity was lower in the laparoscopy than open surgery group (12.5 vs. 22.2%, respectively) in patients with RCC. The most common morbidities in the open surgery group were wound-related infection or disruption, as previously reported [11]. The rate of severe complications was similar between the groups.

One of the concerns with laparoscopy for T4 colon cancer is incomplete tumor resection which is associated with a worse prognosis. In our study group, a more than 90% curative resection rate was achieved in both the laparoscopy and open surgery groups.

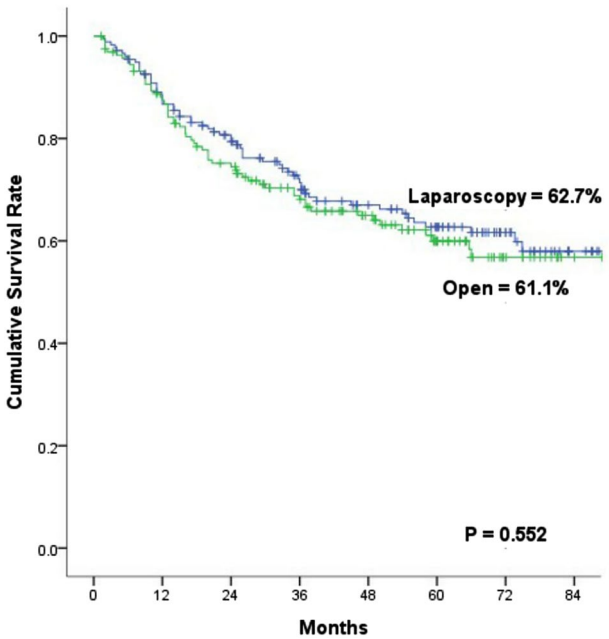

Fig. 4 Disease-free survival between the compared groups in LCC

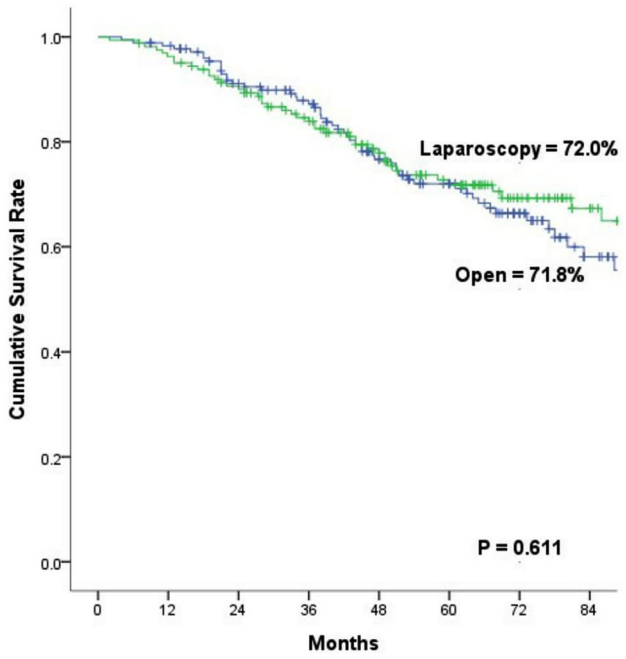

Fig. 5 Overall survival rate between the compared groups in LCC

The conversion rate from laparoscopy to open surgery was 11.7% in the RCC group and 9.7% in the LCC group. The major reason for conversion was the size of the tumor, which required extended incision and fixed invasion of the adjacent organ. It has been reported that patients who underwent conversion had adverse oncologic outcomes [12, 13], a finding which was confirmed in our study, with a low survival rate among the 32 cases of conversion (5-DFS, 18.7%, and 5-OS, 33.2%). However, the conversion rate was relatively low overall. Of note, conversion is more likely to be required in cases of severe or advanced cancer, as the surgeons who performed a laparoscopy approach were highly experienced, having performed at least 500 laparoscopic major procedures. Thus, we could not conclude if adverse oncologic outcomes associated with conversion from laparoscopic to open surgery was due to multiple biases in the retrospective setting (limitation of this study), or the conversion itself. Further prospective research needed to address this issue.

With regard to oncologic outcomes, our findings indicate that laparoscopy could be a safe approach for patients with pT4 LCC, regardless of the lower combined resection and conversion rates.

Laparoscopy for pT4 LCC was associated with better outcomes than open surgery for patients with N+ disease (5-DFS, 63.3% and 5-OS, 67.8% vs. 5-DFS, 51.1% and 5-OS, 57.7%), but with poorer outcomes among patients with N0 disease (5-DFS, 62.1% and 5-OS, 79.3% vs. 5-DFS, 75.1% and 5-OS, 92.1%). This finding could be resulted from intrinsic biases in retrospective design and other possible risk factors that could influence survival were not considered. Despite unbalanced node status, it was not conclusive that the oncologic outcomes are different between the laparoscopy and open surgery in the LCC.

Therefore, although the long-term survival result was not poor with laparoscopic surgery, the laparoscopic approach for pT4 RCC was not as effective in achieving good outcomes as open surgery.

Differences in the clinical, pathological, and genetic features of RCC and LCC have been suggested, with poorer survival outcomes for RCC than LCC, especially among patients with the regional or advanced stages. Findings were comparable among our study group, with lower survival in RCC than that in the LCC group (5-year DFS; 53.9% vs. 61.4%, $p = 0.008$ and 5-year OS; 66.1% vs. 71.9%, $p = 0.038$).

T4 colon cancer is likely to be infiltrative and can spread to adjacent organs. Infiltration to adjacent organs with RCC might be associated with a greater difficulty in achieving radical resection compared to LCC. As such, it might be more difficult to achieve complete resection for pT4 RCC using the standard principles of laparoscopic approach. Although a good R0 resection rate was achieved in the laparoscopy group in our study, missing or hidden micro-metastases can exist without pathologic detection.

A T4 invasion has been identified as a major histopathological indicator of poor prognosis in stage II and stage III cancer [14]. T4 colon cancers have a significantly higher risk of peritoneal carcinomatosis, with this being the only metastatic site in some patients [15, 16].

In our data, the systemic and non-resectable recurrence rate was higher in the RCC (99/245, 40.4%) than LCC (106//338, 31.4%) group. This could be one of the possible adverse long-term oncologic outcomes for patients with pT4 RCC, and laparoscopy should be cautiously considered to ensure oncologic safety.

However, which of these biologic differences based on the tumor location translate into a significant impact on prognosis is still unclear. The behavior of T4 tumors located in the right-sided colon, in patients who have undergone a curative resection has not been fully addressed and further studies are necessary [17–20].

Moreover, although laparoscopic surgery is widely used, for patients with pT4 colon cancer, there is a lack of evidence to assess the safety and efficacy of laparoscopy and a randomized trial would be warranted to provide this information.

Overall, our study findings indicate that laparoscopic surgery can provide a safe alternative to open surgery for the treatment of pT4 LCC, offering oncologic outcomes that are comparable to those for open surgery.

Compliance with ethical standards

Disclosures Jung Ho Park, Hyoung-Chul Park, Sung Chan Park, Dae Kyung Sohn, Jae Hwan Oh, Sung-Bum Kang, Seung Chul Heo, Min Jung Kim, Ji Won Park, Seung-Yong Jeong, and Kyu Joo Park have no conflicts of interest or financial ties to disclose.

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