International Journal of Clinical Oncology (2021) 26:893–902
https://doi.org/10.1007/s10147-021-01870-7

ORIGINAL ARTICLE

Improved oncologic outcomes with increase of laparoscopic surgery in modified complete mesocolic excision with D3 lymph node dissection for T3/4a colon cancer: results of 1191 consecutive patients during a 10-year period: a retrospective cohort study

Tetsuro Tominaga[1] · Tomohiro Yamaguchi[1] · Toshiya Nagasaki[1] · Takashi Akiyoshi[1] · Satoshi Nagayama[1] · Yosuke Fukunaga[1] · Masashi Ueno[1] · Tsuyoshi Konishi[1,2]

Received: 7 November 2020 / Accepted: 3 January 2021 / Published online: 22 January 2021

Abstract

Background Laparoscopic modified complete mesocolic excision (mCME) with D3 lymph node dissection has been performed with increasing frequency, but the oncological safety remains unclear. This study investigated the oncological safety of laparoscopic modified CME with D3 dissection for pT3/4a M0 colon cancer.

Patients Consecutive patients with pT3/4a M0 colon cancer undergoing curative colectomy at a comprehensive cancer center between 2004 and 2013 were included. Outcomes were compared between early (2004–2008, $n=450$) and late (2009–2014, $n=741$) periods. Prognostic factors were investigated by multivariate analysis.

Results A total of 1191 patients were eligible. Median follow-up was 57 months. Laparoscopic surgeries were more common in the late period (early vs late: 53.6% vs. 91.8%, $p<0.01$). Patients in the late period showed lower blood loss (20 mL vs. 10 mL, $p<0.01$), higher number of harvested lymph nodes (18.1 vs. 21.6, $p<0.01$) and fewer patients with < 12 harvested nodes (13.6% vs. 5.8%, $p<0.01$). Postoperative complication rates were similar between periods (2.7% vs. 2.7%, $p=0.97$). Five-year relapse-free survival rate (RFS) (75.3% vs. 82.7%, $p<0.01$) and overall survival rate (OS) (86.9% vs. 91.7%, $p=0.01$) were higher in the late period. Multivariate analysis revealed laparoscopic surgery as an independent favorable prognostic factor for both RFS (hazard ratio (HR) = 0.73, 95% confidence interval (CI) 0.54–0.99, $p=0.03$) and OS (HR = 0.56, 95% CI 0.37–0.83, $p<0.01$).

Conclusion Improved oncologic outcomes and more frequent laparoscopic surgery during the 10-year period of the study were demonstrated for modified CME with D3 dissection, suggesting the safety of this procedure performed by experienced surgeons for pT3/4a M0 colon cancer.

Keywords Laparoscopic surgery · D3 dissection · Modified complete mesocolic excision

Introduction

As described by Hohenberger et al., complete mesocolic excision (CME) with central vascular ligation (CVL) is an anatomically based resection of colon cancer and locoregional lymph nodes that do not breach the visceral fascia, avoiding tumor spread outside of the mesocolon and ensuring complete lymphadenectomy [1]. Multiple studies have indicated that CME with CVL provides better oncological outcomes than standard colectomy [2]. Japanese D3 dissection is a similar surgical technique that ensures oncological sharp dissection of the embryonic plane and complete lymphadenectomy with central vascular ligation and further "D3

Supplementary Information The online version contains supplementary material available at (https://doi.org/10.1007/s10147-021-01870-7) .

✉ Tsuyoshi Konishi
tkonishi-tky@umin.ac.jp

[1] Department of Gastroenterological Surgery, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan

[2] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street Unit 1484, Houston, TX 77030, USA

lymph nodes", which are the central lymph nodes along the superior mesenteric vein or artery. This procedure is strongly recommended for T3 and deeper colon cancers by the guideline of the Japanese Society for Cancer of the Colon and Rectum (JSCCR), based on the excellent oncological outcomes from this procedure [3, 4]. With recent technical improvements in laparoscopic colectomy, D3 dissection has been performed increasingly frequently through a laparoscopic approach in Japan and other countries [5, 6]. However, the oncological safety of a laparoscopic approach for CME with D3 dissection has been controversial. Although some studies reported safe short-term and oncological outcomes [7], a recent phase III randomized controlled trial failed to show the non-inferiority of laparoscopic CME with D3 dissection compared to open CME for stage II/III colon cancer [8]. Further, subgroup analysis identified that patients with cT4a, cN2 and obesity tended to display poorer survival in the laparoscopic arm. The JSCCR guideline recommends limiting the use of laparoscopic colectomy with D3 dissection only to expert surgeons due to a lack of evidence regarding the certainty of oncological safety [3]. Although previous randomized trials have depicted laparoscopic surgery as safe and feasible compared to open surgery, no studies have successfully shown statistical noninferiority in terms of OS or RFS [9–11]. On the other hand, a recent study reported better oncological outcomes from a laparoscopic approach compared to an open approach [12, 13].

In this study, we aimed to examine the oncological safety of laparoscopic CME with D3 dissection for pT3/4a M0 colon cancer, and to examine whether increased use of a laparoscopic approach changed the outcomes in a cohort at a comprehensive cancer center.

Patients and methods

This retrospective study collected data from 1510 consecutive patients with pathologically confirmed T3 and T4a colon cancer from the cecum to the rectosigmoid colon, who underwent surgery between July 2004 and December 2013 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (CIH). Exclusion criteria were synchronous malignancies ($n=29$), emergency surgery ($n=12$), appendiceal tumor ($n=15$), familial tumor (familial adenomatous polyposis or lynch syndrome) ($n=12$), inflammatory bowel disease ($n=10$), adenosquamous carcinoma, neuroendocrine tumor or signet-ring cell carcinoma ($n=6$), and D2 lymph node dissection ($n=235$). Finally, a total of 1191 patients were eligible. No patients received neoadjuvant chemotherapy or chemoradiotherapy.

Preoperative staging included total colonoscopy and contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis. Magnetic resonance imaging (MRI) and positron emission tomography (PET) were added at the discretion of the treating physician.

Postoperative complications were monitored for 30 days after surgery and were graded according to the Clavien-Dindo classification [14, 15]. Adjuvant chemotherapy was administered to patients with stage III or high-risk stage II disease after histological evaluation of surgical specimens, as recommended in national guidelines [3]. General practice for postoperative surveillance of stage I–III colon cancer was also in accordance with national guidelines, including physical examination, interval history, serum carcinoembryonic antigen (CEA) testing, and imaging (most frequently CT) of the chest, abdomen, and pelvis with intravenous contrast, at 3–6-month intervals for the first 3 years and at 6-month intervals thereafter for at least 5 years. Colonoscopy was typically performed at 1 year after surgery, then repeated every 2–3 years unless advanced adenoma was identified. Radiographic reports were reviewed, and a definitive diagnosis of recurrence was based on the appearance of new lesions on CT, MRI, and/or PET and/or histological confirmation through biopsy.

Data on patient demographics, perioperative clinical outcomes, pathological outcomes, and disease status at last follow-up were collected from the prospectively maintained database at CIH, and electronic medical records were reviewed. Informed consent was obtained in the form of an opt-out option on the hospital website. The protocols for this study were reviewed and approved by the Clinical Research Review Board of CIH (Research Registry No. 1025).

Surgical procedures

Surgical procedures for T3/4a colon cancer without distant metastasis were performed in accordance with JSCCR guidelines [3]. We performed a modified CME (mCME) using a similar surgical technique to the original approach, with some technical differences that have been described previously [1, 4, 6, 7]. After performing mobilization of the mesocolon, the supplying vessels were ligated to perform D3 lymph node dissection. The horizontal margin from the tumor was at least 10 cm from the tumor as defined by the Japanese guideline [3], which was shorter than the original CME reported by Hohenberger [1, 16]. For right colectomies, central vessel ligation and D3 dissection required complete removal of lymphatic tissue on the surface of the superior mesenteric vein (SMV). For left colectomies, the high tie of the inferior mesenteric artery (IMA) or low tie with preservation of the left colic artery and complete removal of lymphatic tissue from the root to the point of the division were performed. Both open and laparoscopic procedures were performed or supervised by attending colorectal surgeons who are board-certified and well experienced in the procedures.

Statistical analysis

Data from different groups were compared using Student's *t* test. Continuous data were expressed as mean ± standard deviation (SD). In univariate analysis, comparison of categorical variables was performed using the chi-square test or Fisher's exact test. Overall survival (OS) and relapse-free survival (RFS) were calculated using Kaplan–Meier methods, and differences were tested using the log-rank test. Cox hazard models were used to determine independent factors affecting survival. Statistical analysis was performed using JMP version 12.1.0 software (SAS Institute, Cary, NC). Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Proportion of surgical approaches and patient characteristics

A total of 1191 patients were eligible for this study. The proportion of laparoscopic approaches increased markedly during the study period, from 3.2% in 2004 to 96.5% in 2013 (Fig. 1a). The cohort was divided into an early period (2004–2008, $n = 450$) and late period (2009–2014, $n = 741$). The number of patients with comorbidity was higher in the late period (Table 1). No significant differences in sex, age, tumor location, history of abdominal surgery, or preoperative CEA level were identified.

Perioperative and pathological outcomes

Perioperative and pathological outcomes are shown in Table 2. Operative time was longer and blood loss were both lower in the late period (early vs late period: 200 min vs 185 min, $p < 0.01$; 20 mL vs 10 mL, $p < 0.01$). The late period included more pT4a tumors (16.9% vs. 23.2%, $p < 0.01$). Lymph node yield (18.1 vs. 21.6, $p < 0.01$) and the proportion of patients with < 12 lymph nodes (13.6% vs. 5.8%, $p < 0.01$) were lower in the late group. No significant differences were seen in N stage, TNM stage, or tumor size. Postoperative complication rate (Grade III or IV) (2.7% vs. 2.7%, $p = 0.97$) did not differ between groups. No mortality was encountered. Patients who received adjuvant chemotherapy with oxaliplatin were more common among Stage III patients (14.3% vs. 48.1%, $p < 0.01$). When analyzed by tumor laterality, lymph node yield was higher in the late period for both right and left colon cancer (Fig. 2a, b).

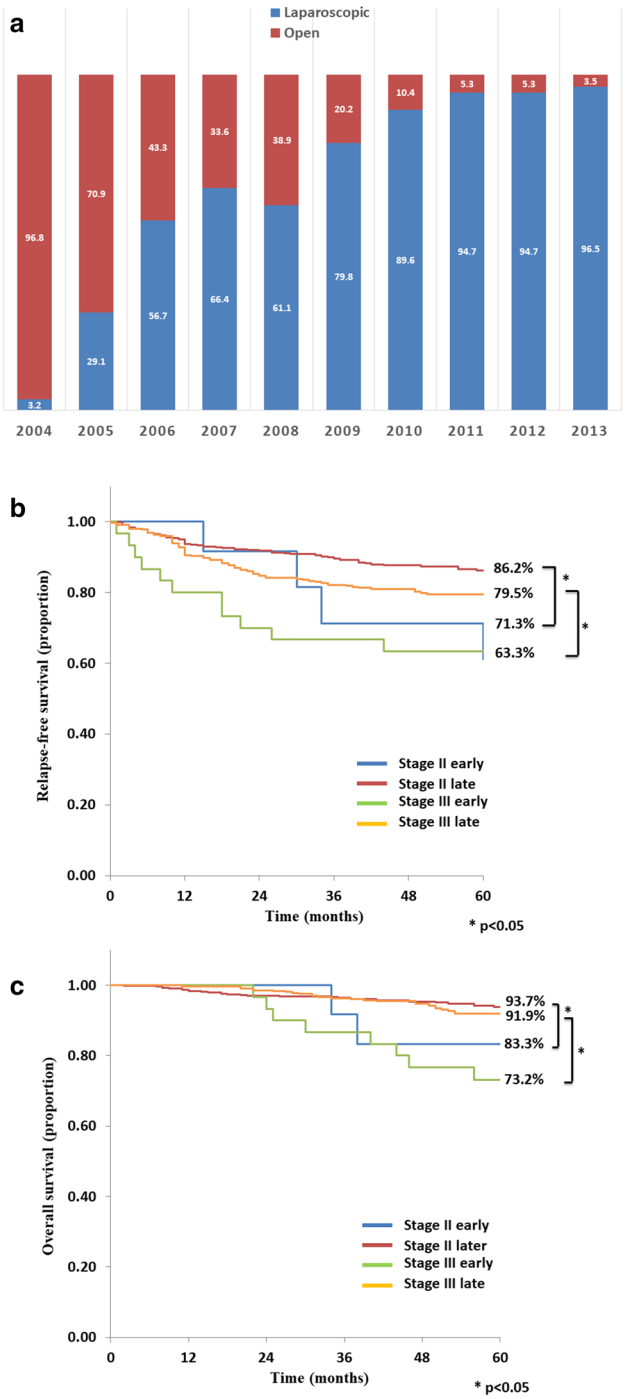

Fig. 1 **a** Proportion of laparoscopic approaches during the study period. Comparison between study periods for relapse-free survival (**b**) and overall survival (**c**) in patients with colon cancer

Oncological outcomes

Median durations of follow-up in the early and late periods were 64 and 54 months, respectively. Overall, the late period showed better RFS (75.3% vs. 82.7% at 5 years, $p < 0.01$) and OS (86.9% vs. 91.7% at 5 years, $p = 0.01$) compared to

Table 1 Clinical characteristics of patients in the early and late periods

	All cases ($n=1191$)	Early ($n=450$)	Late ($n=741$)	p values
Sex, n (%)				0.38
Male	616 (51.7)	240 (53.3)	376 (50.7)	
Female	575 (48.3)	210 (46.7)	365 (49.3)	
Age (y) (range)	65 (24–93)	66 (24–91)	65 (26–93)	0.05
Location of tumor, n (%)				0.76
Right side	449 (37.7)	177 (39.3)	272 (36.7)	
Left side	742 (62.3)	273 (60.7)	469 (63.3)	
Comorbidity, n (%)	344 (28.9)	103 (22.9)	241 (32.5)	<0.01
Previous abdominal surgery, n (%)	321 (27.0)	131 (29.1)	190 (25.6)	0.72
CEA level, n (%)				0.20
≥ 5	365 (30.6)	128 (28.4)	237 (32.0)	
<5	826 (69.8)	322 (71.6)	504 (68.0)	
Surgical approach				<0.01
Laparoscopic	921 (77.3)	241 (53.6)	680 (91.8)	
Open	270 (22.7)	209 (46.4)	61 (8.2)	

Data are presented as numbers of patients or medians (range)

CEA carcinoembryonic antigen

the early period (Fig. 3a, b). When cohorts were subdivided by stage, patients in the late period displayed better 5-year RFS (71.3% vs. 86.2% in stage II, $p<0.05$; 63.3% vs. 79.5% in stage III, $p<0.05$) and better 5-year OS (83.3% vs. 93.7% in stage II, $p<0.05$; 73.2% vs. 91.9% in stage III, $p<0.05$) (Fig. 1b, c).

Prognostic factors for 5-year RFS and OS are shown in Table 3. Univariate analysis showed that elevated CEA, open surgery, combined resection, lymphovascular invasion, LN yield < 12, lymph node metastasis, early study period and pT4 were significantly associated with lower 5-year-RFS. Multivariate analysis revealed laparoscopic surgery (hazard ratio (HR) 0.67; 95% confidence interval (CI) 0.50–0.91, $p=0.01$) as an independent prognostic factor along with lymphovascular invasion (HR 1.56; 95% CI 1.08–2.26, $p=0.01$), LN yield < 12 (HR 1.56; 95% CI 1.08–2.26, $p=0.01$) and lymph node metastasis (HR 1.41; 95% CI 1.06–1.87, $p=0.01$), and pT4 (HR 2.25; 95% CI 1.70–2.99, $p<0.01$). In univariate analysis for OS, age > 75 years, male sex, open surgery, longer operation time, combined resection, poor histological grade, lymphovascular invasion, lymph node metastasis, postoperative complications, early study period and T4 were associated with lower 5-year OS. Multivariate analysis revealed laparoscopic surgery (HR 0.56; 95% CI 0.37–0.83, $p<0.01$) as an independent prognostic factor along with age > 75 years (HR 2.57; 95% CI 0.80–3.67, $p<0.001$), male (HR 1.61; 95% CI 1.13–2.29, $p=0.007$), longer operation time (HR 1.57; 95% CI 1.03–2.39, $p=0.03$), poor histological grade (HR 2.57; 95% CI 1.56–4.24, $p<0.001$), and pT4 (HR 1.78; 95% CI 1.21–2.63, $p=0.003$). Repeat analyses using cancer-specific survival showed similar results for comparison of the early and late periods and multivariate analysis (Supple Fig. 1a, b, Supple Table 1). Overall, recurrences occurred at a median of 18.4 months (range 2–67 months). The most common site of recurrence was the liver, followed by lung and peritoneal dissemination. No differences in site of recurrence were seen between laparoscopic and open procedures or between the early and late periods (Table 4).

Discussion

In the present study, a cohort of consecutive patients with pT3/4a M0 colon cancer who underwent mCME with D3 dissection was analyzed. With the increased use of laparoscopic approaches, patients in the late period (2009–2013) exhibited better survival outcomes compared to the early period (2004–2008). After multivariate analyses, laparoscopic surgery remained as a prognostic factor associated with better RFS and OS The improvement in outcomes we observed in the 2009–2013 period relative to the 2004–2008 period likely results from multiple factors, including better staging by enhanced imaging using multidetector-row helical CT and liver MRI, increased use of oxaliplatin-based regimens in adjuvant chemotherapy and a better understanding of the CME concept with greater lymph node yield for curative resection. With these bundled together, improved oncologic outcomes with an evident increase in laparoscopic approach would justify this approach for mCME with D3 dissection in pT3/4a M0 colon cancer.

Table 2 Pathological and perioperative characteristics of patients between early and late periods

	All cases ($n=1191$)	Early ($n=450$)	Late ($n=741$)	p values
T stage, *n* (%)				< 0.01
T3	943 (79.2)	374 (83.1)	569 (76.8)	
T4a	248 (20.8)	76 (16.9)	172 (23.2)	
N stage, *n* (%)				0.40
N0	677 (56.8)	246 (54.7)	431 (58.2)	
N1	361 (30.3)	140 (31.1)	221 (29.8)	
N2	153 (12.9)	64 (14.2)	89 (12.0)	
TNM stage (AJCC 7th ed)				0.21
II	678 (56.9)	246 (54.7)	432 (58.3)	
III	513 (43.1)	204 (45.3)	309 (41.7)	
Tumor size, mean ± SD, cm	4.8 ± 2.1	4.8 ± 2.0	4.7 ± 2.1	0.09
Resection margin, mean ± SD, cm				
Proximal	12.0 ± 8.9	12.1 ± 8.9	12.1 ± 9.0	0.13
Distal	10.2 ± 4.8	10.1 ± 4.9	10.1 ± 4.7	0.60
Operation time, median, range, min	120 (45–570)	185 (60–570)	200 (71–555)	< 0.01
Blood loss, median, range, mL	15 (0–2320)	20 (0–2320)	10 (10–1150)	< 0.01
No of retrieved lymph nodes,	20.3 ± 7.8	18.1 ± 6.5	21.6 ± 8.2	< 0.01
Cases with < 12 LNs, *n* (%)	104 (8.7)	61 (13.6)	43 (5.8)	< 0.01
Lymphovascular invasion, *n* (%)	931 (78.2)	387 (86.0)	544 (73.4)	< 0.01
Histological type, *n* (%)				< 0.01
Well	426 (35.8)	203 (45.1)	223 (30.0)	
Mod	686 (57.6)	212 (47.1)	474 (64.0)	
Poor	79 (6.6)	35 (7.8)	44 (6.0)	
Combined resection, *n* (%)	82 (6.9)	47 (10.4)	35 (4.7)	< 0.01
Postoperative complications, *n* (%)	32 (2.7)	12 (2.7)	20 (2.7)	0.97
Adjuvant chemotherapy, yes, n (%)	434 (36.4)	157 (34.9)	277 (37.4)	0.38
Chemo, regmens, *n* (%)				
Stage II				0.67
FU	60	9	51	
With oxaliplatin	18	2	16	
Stage III				< 0.01
FU	234	125	109	
With oxaliplatin	122	21	101	

Data are presented as numbers of patients or medians (range)

LN lymph node, *FU* fluorouracil

Adequate lymph node evaluation is central to the prognosis of colon cancer patients, possibly serving as a surrogate marker for surgical quality [17–19]. Several guidelines have shown < 12 harvested lymph nodes as a predictor of poor prognosis, and have recommended postoperative adjuvant chemotherapy for Stage II patients [3, 20]. Modified CME plus CVL and Japanese D3 apply the same concept of surgical resection of the embryological plane and true central ligation of the supplying artery [1, 2]. Hohenberger et al. reported an average of 32 harvested lymph nodes in CME and discussed the number of harvested lymph nodes as an indicator of CME quality [1]. Multiple studies have investigated the benefits of laparoscopic CME or Japanese D3 [7, 12, 21]. Although some studies have reported fewer harvested lymph nodes in laparoscopic surgery compared to open surgery [22], recent studies have reported similar lymph node yields between these two approaches [7, 8]. In the present study, more lymph nodes were harvested from patients in the late period than in the early period, regardless of the use of a laparoscopic or open approach (Fig. 2), resulting in fewer patients with < 12 harvested lymph nodes. Multivariate analysis revealed laparoscopic surgery and number of harvested lymph nodes as independently associated with better RFS. Such data suggest that the increased use of a laparoscopic approach in the latter period was accompanied by a better quality of CME consequently improving oncologic outcomes.

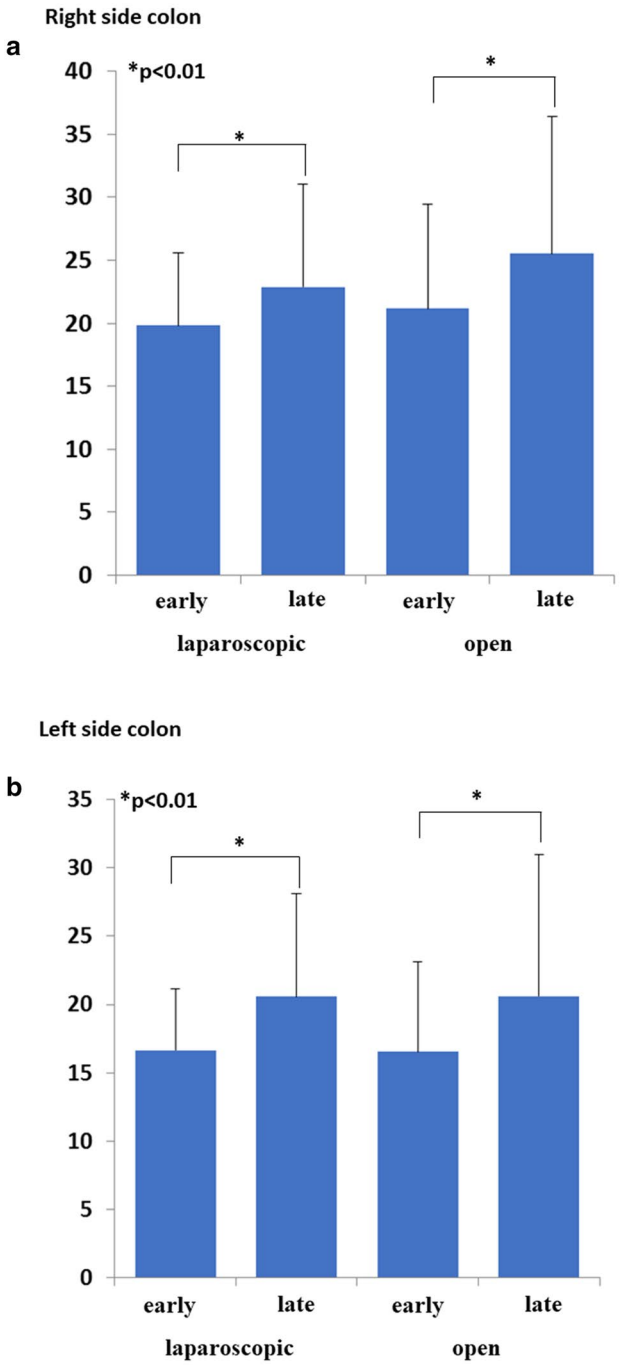

Fig. 2 Comparison of number of dissected lymph nodes between laparoscopic and open surgeries

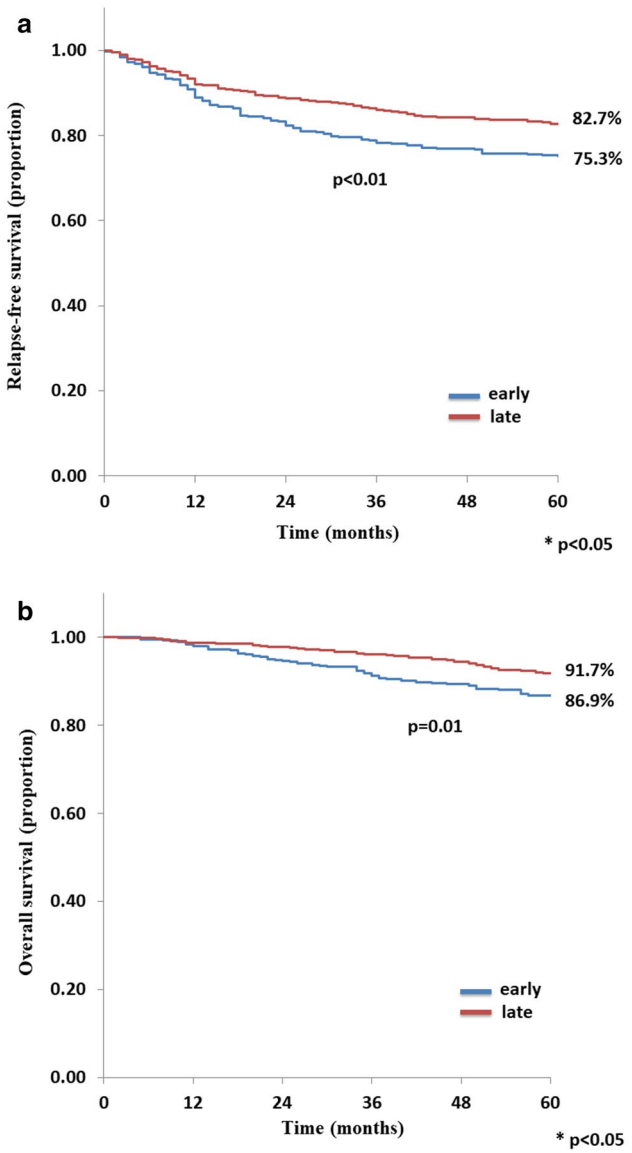

Fig. 3 Comparison between study periods for relapse-free survival (**a**) and overall survival (**b**) by TNM stage

The JSCCR guideline recommended that the use of laparoscopic surgery for D3 resection should be limited to experts, due to technical difficulties and a lack of sufficient evidence for this procedure [3]. A subgroup analysis of the JCOG 0404 randomized trial, which compared laparoscopic and open D3 dissection for cStage II–III colon cancer, revealed some differences in short-term outcomes between high- and low-volume centers [8]. In Japan, a board-certification system called the Japanese Endoscopic Surgical Skill Qualification System (JESSQS) has been established to assess the skill of laparoscopic surgeons [23]. For JESSQS accreditation, two expert referee surgeons evaluate unedited videos of laparoscopic colectomy from the applicant in a double-blinded fashion, and the pass rate in the field of colorectal surgery is below 30% each year. In the present study, all open and laparoscopic procedures were performed or supervised by board-certificate surgeons [24]. Interestingly, improved oncologic outcomes in laparoscopic D3 dissection compared to open surgery have also been reported from a large center in Korea [12, 13]. The laparoscopic approach to colon cancer

Table 3 **a** Uni- and multivariate analyses for prediction of relapse-free survival, **b** Uni- and multivariate analyses for prediction of overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
(a)						
Age ≥ 75 years	1.28	0.96–1.70	0.08			
Sex (male vs female)	1.29	0.99–1.65	0.05			
Comorbidity (yes vs no)	1.20	0.94–1.62	0.11			
CEA ≥ 5 ng/ml	1.41	1.09–1.83	< 0.01	1.23	0.94–1.60	0.11
Laparoscopic surgery (yes vs no)	0.53	0.41–0.69	< 0.01	0.67	0.50–0.91	0.01
Blood transfusion (yes vs no)	0.99	0.24–4.04	0.99			
Operation time ≥ 250 min	1.00	0.71–1.41	0.99			
Blood loss ≥ 20 ml	1.23	0.96–1.58	0.09			
Combined resection (yes vs no)	1.60	1.07–2.41	0.02	1.35	0.94–1.94	0.09
Tumor location (right vs left)	0.88	0.68–1.14	0.36			
Tumor size (≥ 50 mm)	1.01	0.79–1.30	0.88			
Histological type (poor vs well/mod)	1.42	0.91–2.23	0.11			
Lymphovascular invasion (yes vs no)	1.97	1.46–2.65	< 0.01	1.56	1.08–2.26	0.01
Retrieved lymph nodes (< 12 vs ≥ 12)	1.73	1.20–2.48	< 0.01	1.63	1.12–2.37	< 0.01
Stage II vs stage III	1.95	1.51–2.51	< 0.01	1.41	1.06–1.87	0.01
Adjuvant chemotherapy, absent	1.00					
5-FU	1.10	0.83–1.45	0.48			
With oxaliplatin	1.01	0.90–2.08	0.68			
Postoperative complications (yes vs no)	1.20	0.59–2.43	0.60			
Period of operation (late vs early)	0.66	0.51–0.85	< 0.01	0.80	0.57–1.03	0.08
T3 vs T4a	2.59	1.99–3.36	< 0.01	2.25	1.70–2.99	< 0.01
(b)						
Age ≥ 75 years	2.37	1.66–3.37	< 0.01	2.57	1.80–3.67	< 0.01
Sex (male vs female)	1.44	1.02–2.03	0.03	1.61	1.13–2.29	< 0.01
Comorbidity (yes vs no)	2.04	1.44–2.89	< 0.01			
CEA ≥ 5 ng/ml	1.30	0.92–1.86	0.13			
Laparoscopic surgery (yes vs no)	0.47	0.33–0.68	< 0.01	0.56	0.37–0.83	< 0.01
Blood transfusion (yes vs no)	2.35	0.74–7.40	0.14			
Operation time ≥ 250 min	1.64	1.09–2.48	0.01	1.57	1.03–2.39	0.03
Blood loss ≥ 20 ml	1.37	0.97–1.93	0.06			
Combined resection (yes vs no)	1.95	1.26–3.01	< 0.01	1.42	0.90–2.23	0.12
Tumor location (right vs left)	1.25	0.89–1.76	0.19			
Tumor size (≥ 50 mm)	0.85	0.60–1.20	0.36			
Histological type (poor vs well/mod)	2.86	1.74–4.67	< 0.01	2.57	1.56–4.24	< 0.01
Lymphovascular invasion (yes vs no)	1.89	1.22–2.95	< 0.01	1.56	0.91–2.67	0.10
Retrieved lymph nodes (< 12 vs ≥ 12)	1.54	0.94–2.54	0.08			
Stage II vs stage III	1.88	1.32–2.66	< 0.01	1.42	0.97–2.10	0.06
Adjuvant chemotherapy, absent						
5-FU	0.85	0.57–1.26	0.43			
With oxaliplatin	1.12	0.68–1.85	0.63			
Postoperative complications (yes vs no)	2.28	1.06–4.89	0.03	2.01	0.90–4.65	0.08
Period of operation (early vs late)	0.60	0.42–0.87	< 0.01	0.72	0.48–1.07	0.11
T3 vs T4a	2.10	1.47–3.01	< 0.01	1.78	1.21–2.63	< 0.01

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen, *5-FU* 5-fluorouracil

Table. 4 **a** Comparison of recurrence pattern between laparoscopic and open procedure, **b** comparison of recurrence pattern between the early and late period

	T4a			T3		
	Laparoscopic	Open	*p* value	Laparoscopic	Open	*p* value
(a)						
5-year RFS rate (%)	65.4	51.5		87.0	75.5	
5-year OS rate (%)	83.8	78.6		94.4	84.0	
Recurrence, *n* (%)	58	24		55	42	
Liver	24 (41.4)	6 (25.0)	0.16	24 (43.6)	26 (61.9)	0.07
Lung	11 (19.0)	6 (25.0)	0.53	15 (27.3)	7 (16.7)	0.21
Peritoneal dissemination	7 (12.1)	7 (29.2)	0.06	3 (5.5)	5 (11.9)	0.25
Ovary	5 (8.6)	1 (4.2)	0.480	2 (3.6)	0 (0)	0.21
Lymph node	8 (13.8)	2 (8.3)	0.49	8 (14.5)	8 (19.0)	0.55
Local	0 (0)	0 (0)	1.00	1 (1.8)	4 (9.5)	0.16
Others	9 (15.5)	3 (12.5)	0.72	6 (10.9)	1 (2.4)	0.13
	T4a			T3		
	Early	Late	*p* value	Early	Late	*p* value
(b)						
5-year RFS rate (%)	55.7	65.8		81.5	83.2	
5-year OS rate (%)	76.2	85.8		89.2	90.3	
Recurrence, *n* (%)	31	51		45	51	
Liver	10 (32.3)	20 (39.2)	0.91	22 (48.9)	28 (54.9)	0.83
Lung	5 (16.1)	12 (23.5)	0.81	8 (17.8)	14 (27.4)	0.77
Peritoneal dissemination	6 (19.3)	8 (15.7)	0.70	4 (8.9)	4 (7.8)	0.72
Ovary	2 (6.5)	4 (7.8)	0.81	1 (2.2)	1 (1.9)	0.50
Lymph node	5 (16.1)	5 (9.8)	0.07	6 (13.3)	10 (19.6)	0.09
Local	0 (0)	0 (0)	1.00	4 (8.9)	1 (2.0)	0.18
Others	3 (9.7)	9 (17.6)	0.51	0 (0)	7 (13.7)	0.12

RFS relapse-free survival, *OS* overall survival

by an experienced surgeon might contribute to improved oncological outcomes.

A subgroup analysis of the JCOG0404 randomized trial for OS suggested poorer survival from the laparoscopic approach among patients with cT4 and/or cN2 disease [8]. The authors speculated that pneumoperitoneum and manipulations with forceps during the operation might have affected long-term outcomes. Some studies have also indicated unfavorable effects of pneumoperitoneum and instrumental manipulation during laparoscopic surgery causing peritoneal dissemination [25, 26]. Several randomized trials have also demonstrated a higher incidence of perineal dissemination in laparoscopic surgery compared to open surgery [27–29]. The present study did not identify any significant differences in sites of recurrence (including peritoneal dissemination) between laparoscopic and open procedures. We pay careful attention to avoiding manipulation of tissues around the tumor during laparoscopic surgery, to prevent microscopic dissemination. A recent study from a large center also demonstrated the oncological safety of laparoscopic surgery in cT4 colon cancer [30, 31].

Strengths of the present study include the relatively large cohort of patients who underwent a standardized resection procedure. Other strengths have included the availability of granular clinical and demographic information. However, the study was subject to the selection bias inherent in observational retrospective studies. In the present study, difficult procedures or advanced disease were more likely treated with open surgery particularly in the early period. Although we tried to minimize such selection bias by multivariate analyses, the results need careful interpretation as we cannot eliminate the effects of confounding factors. Data from a specialty institution in Japan, where patients are generally fit and non-obese, have the potential for limited applicability. Survival outcomes in this study resembled those of a previous Japanese RCT (5-year OS, 91.8%) [8]. Further external validation with contemporary data is thus needed. Improved outcomes in the late period could have resulted from a shorter follow-up compared to an early period. However, the

median follow-up of 54 months in the late period would still cover the majority of recurrences. Despite such limitations, our findings support the oncological safety of a laparoscopic approach for D3 dissection in pT3/4a colon cancer. Further studies are needed to reveal the benefits of a minimally invasive approach in this procedure compared to open surgery.

In summary, a cohort of patients with pT3/4a M0 colon cancer who underwent CME with D3 dissection at a single cancer center demonstrated improved oncological outcomes with an evident increase in the laparoscopic approach during the 10-year period from 2004 to 2013. Improvements in outcome are encouraging and likely reflect advances in surgical techniques along with the spectrum of care, including staging and adjuvant chemotherapy. Laparoscopic modified CME appears oncologically safe and feasible under a bundle of modern improvements in cancer care, and future prospective studies investigating the true benefits of this specific procedure are warranted.

Acknowledgements We would like to thank FORTE Science Communications (www.forte-science.co.jp) for English language editing.

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

References

1. Hohenberger W, Weber K, Matzel K et al (2009) Standardized surgery for colonic cancer: complete mesocolic excision and central ligation–technical notes and outcome. Colorectal Dis 11:354–364
2. West NP, Morris EJ, Rotimi O et al (2008) Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol 9:857–865
3. Watanabe T, Itabashi M, Shimada Y et al (2015) Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol 20:207–239
4. Nagasaki T, Akiyoshi T, Fujimoto Y et al (2015) Prognostic impact of distribution of lymph node metastases in stage III colon cancer. World J Surg 39:3008–3015
5. Ishiguro M, Higashi T, Watanabe T et al (2014) Changes in colorectal cancer care in japan before and after guideline publication: a nationwide survey about D3 lymph node dissection and adjuvant chemotherapy. J Am Coll Surg 218:969–977
6. Xie D, Yu C, Gao C et al (2017) An optimal approach for laparoscopic D3 lymphadenectomy plus complete mesocolic excision (D3+CME) for right-side colon cancer. Ann Surg Oncol 24:1312–1313
7. Bae SU, Saklani AP, Lim DR et al (2014) Laparoscopic-assisted versus open complete mesocolic excision and central vascular ligation for right-sided colon cancer. Ann Surg Oncol 21:2288–2294
8. Kitano S, Inomata M, Mizusawa J et al (2017) Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 2:261–268
9. Green BL, Marshall HC, Collinson F et al (2013) CLASICC trial Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 100:75–82
10. Buunen M, Veldkamp R, Hop WC et al (2009) COLOR2 Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 10:44–52
11. Bagshaw PF, Allardyce RA, Frampton CM et al (2012) ALCCaS trilLong-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study trial. Adv Surg 256:915–919
12. Cho MS, Baek SJ, Hur H et al (2015) Modified complete mesocolic excision with central vascular ligation for the treatment of right-sided colon cancer: long-term outcomes and prognostic factors. Ann Surg 261:708–715
13. Shin JK, Kim HC, Lee WY et al (2018) Laparoscopic modified mesocolic excision with central vascular ligation in right-sided colon cancer showes better short- and long-term outcomes compared with the open approach in propensity score analysis. Surg Endosc 32:2721–2731
14. Clavien PA, Barkun J, Oliveira ML et al (2009) The Clavien-Dindo classification of surgical complications: 5-year experience. Ann Surg 250:187–196
15. Dindo D, Demartines N, Clavien N (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
16. Nicholas PW, Kobayashi H, Takahashi K et al (2012) Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol 30:1763–1769
17. Chang GJ, Rodriguez-Bigas MA, Skibber JM et al (2007) Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 99:433–441
18. Le Voyer TE, Sigurdson ER, Hanlon AL et al (2003) Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 21:2912–2919
19. Zurleni T, Cassiano A, Gjoni E et al (2018) Surgical and oncological outcomes after complete mesocolic excision in right-sided colon cancer compared with conventional surgery: a retrospective, single-institution study. Int J Colorectal Dis 33:1–8
20. Schmoll HJ, Van Cutsem E, Stein A et al (2012) ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 23:2479–2516
21. Kitano S, Kitajima M, Konishi F et al (2006) A multicenter study on laparoscopic surgery for colorectal cancer in Japan. Surg Endosc 20:1348–1352
22. Hasegawa H, Okabayashi K, Watanabe M et al (2014) What is the effect of laparoscopic colectomy on pattern of colon cancer recurrence? A propensity score and competing risk analysis compared with open colectomy. Ann Surg Oncol 2:2627–2635
23. Mori T, Kimura T, Kitajima M (2010) Skill accreditation system for laparoscopic gastroenterologic surgeons in Japan. Minim Invasive Ther Allied Technol MITAT 19:18–23
24. Akiyoshi T, Kuroyanagi H, Ueno M et al (2011) Learning curve for standardized laparoscopic surgery for colorectal cancer under supervision: a single-center experience. Surg Endosc 25:1409–1414
25. Brundell SM, Tucker K, Texler M et al (2002) Variables in the spread of tumor cells to trocars and port sites during operative laparoscopy. Surg Endosc 16:1413–1419
26. Takeuchi M, Inomata M, Fujii K et al (2004) Increased peritoneal dissemination after laparotomy versus pneumoperitoneum in a mouse cecal cancer model. Surg Endosc 18:1795–1799

27. Lacy AM, Garcia-Valdecasas JC, Delgado S et al (2002) Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 359:2224–2229
28. Martel G, Boushey RP (2006) Laparoscopic colon surgery: past, present and future. Surg Clin N Am 86:867–897
29. Nelson H, Sargent DJ, Wieand HS et al (2004) A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 350:2050–2059
30. Elnahas A, Sunil S, Jackson TD et al (2016) Laparoscopic versus open surgery for T4 colon cancer: evaluation of margin status. Surg Endosc 30:1491–1496
31. Kim IY, Kim BR, Kim YW (2016) The short-term and oncologic outcomes of laparoscopic versus open surgery for T4 colon cancer. Surg Endosc 30:1508–1518