









**ORIGINAL ARTICLE**

# Identification of patient subgroups with unfavorable long-term outcomes associated with laparoscopic surgery in a randomized controlled trial comparing open and laparoscopic surgery for colon cancer (Japan Clinical Oncology Group Study JCOG0404)

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**Funding information**

Grant-in-Aid for Cancer Research, Grant/Award Number: 14S-3, 14S-4, 17S-3, 17S-5, 20S-3 and 20S-6; Health and Labour

**Abstract**

**Background:** Previously, we conducted a randomized controlled trial (JCOG0404) for stage II/III colon cancer patients and reported that the long-term survival after open surgery (OP) and laparoscopic surgery (LAP) were almost identical; however, JCOG0404 suggested that survival of patients after LAP with tumors located in the rectosigmoid colon, cT4 or cN2 tumors, and high body mass index (BMI) might be unfavorable.

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Sciences Research Grant for Clinical Cancer Research from the Ministry of Health, Labour and Welfare of Japan, Grant/Award Number: H15-018, H18-013, H21-017 and H24-005; the National Cancer Center Research and Development Fund, Grant/Award Number: 23-A-16, 23-A-19, 26-A-4, 29-A-3 and 2020-J-3

**Aim:** To identify the patient subgroups associated with poor long-term survival in the LAP arm compared with the OP arm.

**Methods:** Patients aged 20–75, clinical T3 or deeper lesion without involvement of other organs, clinical N0-2 and M0 were included. The patients with pathological stage IV and R2 resection were excluded from the current analysis. In each subgroup, the hazard ratio for LAP (vs. OP) in overall survival (OS) from surgery was estimated using a multivariable Cox regression model adjusted for the clinical and pathological factors.

**Results:** In total, 1025 patients (OP, 511 and LAP, 514) were included in the current analysis. Adjusted hazards ratios for OS of patients with high BMI (>25 kg/m<sup>2</sup>), pT4, and pN2 in LAP were 3.37 (95% confidence interval [CI], 1.24–9.19), 1.33 (0.73–2.41), and 1.74 (0.76–3.97), respectively. In contrast, that of rectosigmoid colon tumors was 0.98 (0.46–2.09).

**Conclusions:** Although LAP is an acceptable optional treatment for stage II/III colon cancer, the present subgroup analysis suggests that high BMI (>25 kg/m<sup>2</sup>), pT4, and pN2 except for RS were factors associated with unfavorable long-term outcomes of LAP in patients with colon cancer who underwent curative resection. (JCOG 0404: NCT00147134/UMIN-CTR: C000000105.)

#### KEYWORDS

colon cancer, laparoscopic surgery, long-term outcome, randomized controlled trial, subgroup analysis

## 1 | INTRODUCTION

In the 21st century, several randomized controlled trials on colon cancer from around the world have revealed excellent short-term and equally good long-term results following laparoscopic surgery (LAP) when compared with open surgery (OP).<sup>1–9</sup> Most of these trials showed that LAP for colon cancer has been accepted as a promising alternative to open colectomy. In Japan, the Japan Clinical Oncology Group (JCOG) conducted a randomized controlled trial to evaluate the long-term outcomes of both LAP and OP for clinical stage II/III colon cancer (JCOG0404).<sup>10</sup> Although LAP was not noninferior to OP in terms of overall survival (OS) in patients with stage II or III colon cancer, the OS in both arms was similar and better than expected; therefore, LAP was considered to be an acceptable treatment option for stage II or III colon cancer. However, long-term survival was unfavorable in the following subgroups of the LAP arm: rectosigmoid colon (RS), cT4, cN2, and high body mass index (BMI).<sup>11</sup> Despite being a randomized controlled trial, the results of the subgroup analysis might have some limitations, such as the small sample size, lower event rate, baseline imbalance between the treatment, and the influence of patients with pathological stage IV disease or R2 resection who were included in the primary analysis based on the intention-to-treat policy. In colon cancer patients undergoing laparoscopic

colectomy, identifying and evaluating risk factors for poor prognosis preoperatively could aid in providing more accurate informed consent for treatment, considering different treatment options, and identifying high-risk patients who might require special and possibly multidisciplinary treatment.

The purpose of the present study was to identify the factors associated with poor long-term survival in the LAP arm compared with the OP arm of the JCOG0404 study after adjusting for clinical and pathological factors.

## 2 | METHODS

### 2.1 | JCOG0404 summary

Patients were recruited from 30 hospitals in Japan (Supporting information S1). Briefly, the inclusion criteria were colon carcinoma located in the cecum, ascending colon, sigmoid colon, or RS; histologically proven adenocarcinoma; clinical T3–4 without involvement of other organs, clinical N0-2 and M0; no multiple cancers; tumor size of ≤8 cm; no bowel obstruction; no history of chemotherapy and radiotherapy; no history of intestinal resection excluding appendectomy; age 20–75 years; and provision of written informed consent. The primary endpoint was OS. The secondary endpoints were

relapse-free survival (RFS), short-term clinical outcomes, incidence of adverse events, and proportion of conversion from LAP to OP.

Briefly, 1057 patients were randomly assigned to either OP ( $n = 528$ ) or LAP ( $n = 529$ ) arm. The 5-year OS was 90.4% for OP and 91.8% for LAP. Laparoscopic D3 surgery was not noninferior to OP in terms of OS for patients with stage II or III colon cancer (hazard ratio [HR], 1.06; 90% confidence interval [CI], 0.79–1.41;  $P$  for noninferiority = .073). Additionally, long-term survival in the subgroups with RS, cT4, cN2, and high BMI in the LAP arm might be unfavorable.<sup>11</sup> The 5-year RFS was 80% in the OP group and 79% in the LAP group. The HR for RFS for LAP versus OP was 1.07 (95% CI, 0.82–1.38).<sup>10,11</sup>

This trial was registered with ClinicalTrials.gov (number NCT00147134) and UMIN Clinical Trials Registry (number C000000105).

## 2.2 | Measured outcomes

In the present study, patients with pathological stage IV disease and R2 resection were excluded because these factors were considered as unrelated with the surgical approach and were thought to directly affect the long-term outcome. Among the pStage IV or R2 cases, in the OC group ( $n = 17$ ), there were 10 positive peritoneal dissemination cases, six liver metastases, two para-aortic lymph node metastases, and a case of unknown details (with duplication). In the LAP group ( $n = 15$ ), there were eight cases of positive peritoneal dissemination and seven cases of liver metastasis. Although four factors (RS, clinical T4, clinical N2, and BMI  $>25$  kg/m<sup>2</sup>) were suggested to be associated with unfavorable results in the primary analysis, we assessed the RS, higher BMI, and pathological T/N factors instead of clinical T/N factors. Because we considered that the T and N factors should be consistent with pathological findings, such as pathological stage IV and R2, which were excluded from the present study and could not be found preoperatively, the clinical T and N diagnosis do not necessarily agree with the pathological T and N diagnosis, and it is expected that the clinical diagnosis can be affected by differences between institutions. Therefore, we focused on the influence of the pathological T and N factors on prognosis, and subgroup analyses of OS and RFS were conducted for tumors located in the RS, pathological T4 (pT4), pathological N1 (pN1), N2 (pN2), and BMI  $>25$  kg/m<sup>2</sup> subgroups. We also evaluated recurrence patterns in the patient subgroups that were associated with unfavorable outcomes.

## 2.3 | Statistical analysis

OS and RFS from the time of surgery were assessed using a univariable and multivariable Cox regression model adjusted by the clinical and pathological factors for which the  $P$ -value was  $<.3$  by Fisher's exact test between the two arms. In this study, clinical and pathological factors were not always the same for T and N factors; we judged that it did not affect the model estimation and these were

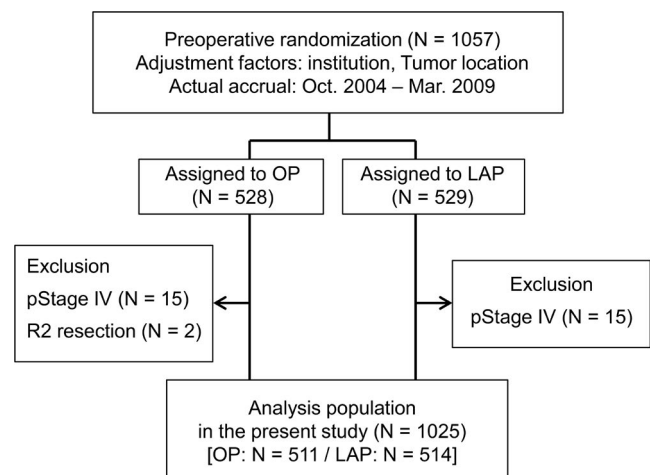
used as adjustment factors. All  $P$ -values were two-sided, and statistical analysis was performed using SAS v. 9.2 or higher (SAS Institute, Cary, NC).

## 3 | RESULTS

Of the 1057 patients, 30 presented with pathological stage IV disease and two with R2 resection. Following the exclusion of these patients, the final number of patients analyzed was 1025 (LAP, 514 and OP, 511; Figure 1). No significant differences in patient characteristics were observed between the two groups (Table 1). In the RS (OP 136, LAP 119), BMI  $\geq 25$  (OP 121, LAP 133), pT4 (OP 87, LAP 92), pN1 (OP 144, LAP 167), and pN2 (OP 58, LAP 65) subgroups, the  $P$ -values of some factors were  $<.3$  by Fisher's exact test, as shown in Table 2.

The adjusted HRs (95% CI) of the four important clinicopathological factors for OS and RFS in the multivariable Cox regression models are shown in Tables 3 and 4. Adjusted HRs for OS of patients with high BMI ( $>25$ ), pT4, and pN2 in LAP were 3.37 (95% CI, 1.24–9.19), 1.33 (0.73–2.41), and 1.74 (0.76–3.97), respectively. For RFS, adjusted HRs of high BMI ( $>25$ ), pT4, and pN2 in LAP were 2.95 (95% CI, 1.53–5.69), 1.36 (0.85–2.18), and 1.32 (0.73–2.39), respectively. In the RS subgroup, there was a significant difference between pathological stage ( $P = .004$ ) and venous invasion ( $P = .022$ ), and when adjusted with clinicopathological features, there was no difference in HRs in RS. The adjusted HRs were 0.98 (0.46–2.09) in OS and 1.04 (0.59–1.84) in RFS; therefore, the long-term survival of the patients with tumors in RS was not unfavorable after LAP. The present study showed that patients with high BMI, pT4, or pN2 who underwent LAP tended to show worse survival compared with those in the OP group, even after adjustment for the clinicopathological factors. Among these three subgroups, high BMI in LAP was the strongest factor reflecting worse survival compared to those who underwent OP.

Tables 5–7 show the recurrence patterns in patients in the pT4, pN2, and higher BMI subgroups who underwent OP and LAP. In the



**FIGURE 1** CONSORT diagram. OP, open surgery; LAP, laparoscopic surgery

**TABLE 1** Patient characteristics

(OP 511, LAP 514)	OP	LAP
Clinical factors		
Sex		
Male	304	275
Female	207	239
Age (years)		
Median	64	64
Range	33–75	28–75
Tumor location		
C, A, or S	376	397
RS	135	117
Body mass index (kg/m <sup>2</sup> )		
<20	82	84
≥20, <25	308	297
≥25	121	133
Clinical T factor		
cT3	396	401
cT4	115	113
Clinical N factor		
cN0	357	327
cN1	121	152
cN2	33	35
Clinical stage		
II	357	327
III	154	187
Comorbidity or past history		
Absence	375	390
Presence	136	124
Pathological factors		
Pathological T factor		
pT3 or less	424	422
pT4	87	92
Pathological N factor		
pN0	309	282
pN1	144	167
pN2	58	65
Pathological stage		
II or less	309	282
III	202	232
Venous invasion		
v 0–1	407	386
v 2–3	104	128
Lymphatic invasion		
ly 0–1	411	410
ly 2–3	100	104

Abbreviations: LAP, laparoscopic surgery; OP, open surgery.

pathological T4 subgroup, peritoneum and locoregional recurrence in LAP were higher than those in OP, whereas liver and lymph node recurrences in OP were higher than those in LAP (Table 5). In the pathological N2 subgroup, peritoneum recurrence in LAP was higher than that in OP, whereas lung and lymph node recurrences in OP were higher than those in LAP (Table 6). In the BMI  $\geq 25$  kg/m<sup>2</sup> subgroup, lymph node recurrences and others in LAP were higher than those in OP, whereas lung recurrence in OP was higher than that in LAP (Table 7). As a result of scrutiny, no characteristic recurrence of the LAP group was found. All cases of lymph node recurrence were sigmoid colon or RS cases. Recurrence of para-aortic lymph nodes occurred in one of the OP group and four of the six in the LAP group. One patient in the LAP group showed cervical lymph node recurrence, and the remaining one lymph node recurrence was associated with adrenal metastasis, but the location of the lymph nodes was unknown. The recurrence of "others" in the LAP group were the adrenal glands in two cases and the ovary in one case. Both cases of adrenal recurrence also had lymph node recurrence. The proportion and site of recurrence in the patients in the pT4, pN2, and the higher BMI subgroups showed no apparent differences between OP and LAP (Tables 5–7).

#### 4 | DISCUSSION

The present study revealed that high BMI ( $>25$  kg/m<sup>2</sup>), pT4, and pN2 might be factors associated with unfavorable long-term outcomes of LAP compared with OP for colon cancer with curative resection. However, tumors located in RS were not associated with this outcome. LAP might not be recommended for patients with high BMI, and careful postoperative follow-up is recommended for patients with pT4 and pN2.

In 2017, Fung et al<sup>12</sup> conducted a meta-analysis to assess the long-term outcomes of laparoscopic colorectal cancer resections in obese patients compared to nonobese patients. Obese patients were defined as having a BMI  $\geq 30$  kg/m<sup>2</sup>. The 5-year disease-free survival (DFS) and OS were similar in the obese and nonobese groups.<sup>12</sup> Several reports supported the feasibility of long-term outcomes in obese patients with colon cancer in laparoscopic cancer resection compared to open resection. However, several studies reported that laparoscopic surgery for colon cancer is technically more demanding in obese patients than in nonobese patients, and special care was required because of the increased risk of developing postoperative complications.<sup>13,14</sup> BMI is commonly used as an objective measure of body fat with the global cutoff point for obesity (BMI  $\geq 30.0$  kg/m<sup>2</sup>) set by the World Health Organization.<sup>15</sup> In the present study, however, the proportion of obese patients with a BMI  $\geq 30.0$  kg/m<sup>2</sup> was only 2.3%. Although the average BMI is lower in the Asian population compared to non-Asian populations, the incidence of visceral adiposity is higher in Asians.<sup>16</sup> Because of the inappropriateness of this cutoff point, the International Obesity Task Force has proposed a

TABLE 2 Patient characteristics in each subgroup

	Rectosigmoid		Pathological T4		Pathological N1		Pathological N2		BMI ≥25	
	OP (136)	LAP (119)	OP (87)	LAP (92)	OP (144)	LAP (167)	OP (58)	LAP (65)	OP (121)	LAP (133)
Clinical factors										
Sex										
Male	103	69	46	50	76	90	31	36	78	84
Female	33	50	41	42	68	77	27	29	43	49
		<b>.003</b>			<b>0.882</b>		<b>0.909</b>		<b>0.858</b>	<b>0.896</b>
Age (years)										
≤64	82	75	39	46	87	99	26	43	65	77
≥65	54	44	48	46	57	68	32	22	56	56
		<b>0.700</b>			<b>0.550</b>		<b>0.908</b>		<b>.019</b>	<b>0.529</b>
Tumor location										
C, A or S	0	0	62	72	110	119	44	49	86	103
RS	136	119	25	20	34	48	14	16	35	30
		-			<b>0.305</b>		<b>0.366</b>		<b>1.000</b>	<b>.254</b>
Body mass index (kg/m <sup>2</sup> )										
<20	17	25	14	20	24	31	9	6	0	0
≥20, <25	84	64	56	53	88	88	36	42	0	0
≥25	35	30	17	19	32	48	13	17	121	133
		<b>.178</b>			<b>0.536</b>		<b>0.305</b>		<b>0.575</b>	<b>0</b>
Clinical T factor										
cT3	102	94	43	60	107	133	39	44	98	106
cT4	34	25	44	32	37	34	19	21	23	27
		<b>0.462</b>			<b>.036</b>		<b>.281</b>		<b>1.000</b>	<b>0.875</b>
Clinical stage										
II	96	73	47	51	87	93	29	26	79	88
III	40	46	40	41	57	74	29	39	42	45
		<b>.144</b>			<b>0.881</b>		<b>0.422</b>		<b>.282</b>	<b>0.895</b>
Comorbidity or past history										
Absence	70	55	40	52	63	82	26	31	46	60
Presence	66	64	47	40	81	85	32	34	75	73
		<b>0.452</b>			<b>.180</b>		<b>0.364</b>		<b>0.857</b>	<b>0.308</b>
Pathological factors										
Pathological T factor										
pT3 or less	111	99	0	0	110	121	33	43	104	114
pT4	25	20	87	92	34	46	25	22	17	19
		<b>0.869</b>			<b>0.439</b>		<b>0.354</b>		<b>1.000</b>	<b>1.000</b>
Pathological stage										
II or less	88	55	28	24	0	0	0	0	76	68
III	48	64	59	68	144	167	58	65	45	65
		<b>.004</b>			<b>0.412</b>		<b>0.076</b>		<b>.076</b>	<b>.076</b>

(Continues)

TABLE 2 (Continued)

	Rectosigmoid		Pathological T4		Pathological N1		Pathological N2		BMI $\geq 25$		
	OP (136)	LAP (119)	OP (87)	LAP (92)	OP (144)	LAP (167)	OP (58)	LAP (65)	OP (121)	LAP (133)	
Venous invasion											
v 0-1	109	80	62	57	108	123	42	47	90	103	0.659
v 2-3	27	39	25	35	36	44	16	18	31	30	
Lymphatic invasion											
ly 0-1	113	97	58	61	108	121	30	36	95	114	.142
ly 2-3	23	22	29	31	36	46	28	29	26	19	

Bold entries indicates P value  $< .3$ . OS and RFS were assessed using a univariable and multivariable Cox regression model adjusted by the clinical and pathological factors for which the P-value was  $< .3$  by Fisher's exact test between the two arms. The adjusted HRs (95% CI) of the four important clinicopathological factors for OS and RFS in the multivariable Cox regression models are shown in Tables 3 and 4.

lower cutoff BMI value for obesity in Asians of  $\geq 25.0 \text{ kg/m}^2$ ,<sup>15-17</sup> which we used in the present study. Our results showed that LAP for colon cancer patients with high BMI ( $\geq 25.0 \text{ kg/m}^2$ ) should be performed with caution, and careful postoperative follow-up is recommended. Although the photographs of the operation field after lymph node dissection were submitted from all patients for quality control and quality assurance in the JCOG0404 study, the process for the lymph node dissection related to complete mesocolon excision (CME) was not evaluated. We speculated that there might be a possibility of difficulty with performing CME in obese patients. This might be the reason why the local recurrence was slightly higher in the LAP group; however, lymph node recurrence in high BMI patients was not regional lymph node recurrence but distant lymph node recurrence in both the OP and LAP group. The reason why patients with high BMI had a poor long-term prognosis for LAP we could not elaborate on from these results. These findings might not provide concrete evidence of the superiority of OP over LAP for obese colon cancer patients because of the small number of patients. Thus, a multicenter, retrospective, large-scale study initiated by more than 50 member institutions of the JSLCS (Japan Society of Laparoscopic Colorectal Surgery) is currently being conducted to compare the short- and long-term outcomes of colorectal cancer patients with high BMI ( $\geq 25.0 \text{ kg/m}^2$ ) undergoing LAP or OP (trial number: UMIN000033529).

In 2004, Leung et al reported that in patients participating in a prospective randomized trial, laparoscopic resection of rectosigmoid carcinoma did not jeopardize survival or disease control.<sup>18</sup> After adjustment for patient characteristics including sex, BMI, clinical stage, pathological stage, and venous invasion in the RS group, the adjusted HRs of tumor location of RS for LAP versus OP were almost similar in terms of both OS and RFS. Therefore, we concluded that the long-term survival of the patients in the RS subgroup was not unfavorable after LAP.

In colon cancer, T4 stage is considered a contraindication for LAP. In some studies, stage T4 was regarded as a risk factor that may lead to poor oncologic outcomes for LAP in comparison to OP.<sup>8,19,20</sup> However, other comparative analyses claimed that patients with T4 colon cancer achieved similar outcomes for both LAP and OP.<sup>21-25</sup> As shown in Table 5, the recurrence pattern in pT4 cases showed that the LAP group did not present with significantly increased rates of peritoneal dissemination or local recurrence compared to the open group. Each approach might favorably or unfavorably affect the recurrence pattern such as in liver, peritoneum, lung, and lymph node, which could not be explained individually because of the small number of recurrences. Presently, because it is generally accepted that the potential risk of the recurrence of peritoneal dissemination is high in patients with T4 disease, it is important to avoid touching the tumor during surgery as much as possible.

Previous reports showed that the results of the N1 plus N2 subgroup and stage III subgroup were the same in terms of long-term outcomes following the LAP approach. In a meta-analysis comprising the Barcelona,<sup>1</sup> Clinical Outcomes of Surgical Therapy

Factors (N of OP, N of LAP)	HR before adjustment	HR adjusted by clinical factors	HR adjusted by clinicopathological factors
Rectosigmoid colon (OP 136, LAP 119)	1.34 (0.66–2.75)	1.33 (0.64–2.76)	0.98 (0.46–2.09)
Pathological T4 (OP 87, LAP 92)	1.35 (0.75–2.45)	1.29 (0.71–2.35)	1.33 (0.73–2.41)
Pathological N1 (OP 144, LAP 167)	0.79 (0.43–1.44)	0.79 (0.43–1.45)	0.79 (0.43–1.45)
Pathological N2 (OP 58, LAP 65)	1.97 (0.90–4.33)	1.74 (0.76–3.97)	1.74 (0.76–3.97)
BMI $\geq 25$ kg/m <sup>2</sup> (OP 121, LAP 133)	3.55 (1.32–9.57)	3.80 (1.40–10.26)	3.37 (1.24–9.19)

TABLE 3 Overall survival

TABLE 4 Relapse-free survival

Factors (N of OP, N of LAP)	HR before adjustment	HR adjusted by clinical factors	HR adjusted by clinicopathological factors
Rectosigmoid colon (OP 136, LAP 119)	1.25 (0.74–2.12)	1.35 (0.79–2.32)	1.04 (0.59–1.84)
Pathological T4 (OP 87, LAP 92)	1.44 (0.90–2.28)	1.39 (0.87–2.22)	1.36 (0.85–2.18)
Pathological N1 (OP 144, LAP 167)	0.96 (0.61–1.51)	0.98 (0.62–1.54)	0.98 (0.62–1.54)
Pathological N2 (OP 58, LAP 65)	1.47 (0.83–2.59)	1.32 (0.73–2.39)	1.32 (0.73–2.39)
BMI $\geq 25$ kg/m <sup>2</sup> (OP 121, LAP 133)	2.64 (1.39–5.00)	3.03 (1.59–5.77)	2.95 (1.53–5.69)

Abbreviations: BMI, body mass index; HR, hazard ratio; LAP, laparoscopic surgery; OP, open surgery.

Recurrence	OP n = 27	LAP n = 40	Total n = 67
Liver	9 (33.3%)	11 (27.5%)	20
Peritoneum	4 (14.8%)	9 (22.5%)	13
Lung	9 (33.3%)	15 (37.5%)	24
Locoregional	3 (11.1%)	7 (17.5%)	10
Lymph node	6 (22.2%)	4 (10.0%)	10
Laparotomy wound, port site	0 (0%)	0 (0%)	0
Other	1 (3.7%)	2 (5.0%)	3

TABLE 5 Recurrence patterns in the laparoscopic (LAP) and open (OP) group patients in the pathological T4 subgroup (n = 179)

Note: Number (percentage) of patients with disease recurrence is shown. There is some duplication of patients.

(COST),<sup>3</sup> Colon Cancer Laparoscopic or Open Resection (COLOR),<sup>5</sup> and Conventional versus Laparoscopic-Assisted Surgery in Patients With Colorectal Cancer (CLASICC) trials,<sup>6</sup> 31.3% of patients presented with stage III disease. No significant differences in OS were observed between the two treatments in stage III patients. Likewise, no significant difference in DFS was noted between the randomized procedures in stage III patients.<sup>26</sup> Our analysis showed that, although the long-term outcomes of LAP were equivalent for colon cancer in the pN1 subgroup, they were unfavorable for colon cancer in the pN2 subgroup when compared with OP. In the pN2 subgroup, the incidence of lymph node metastatic recurrence, local recurrence, or

recurrence of peritoneal dissemination was not significantly higher in those who underwent LAP versus OP. Thus, based on these results, it is not possible to conclude the superiority of OP over LAP for pN2 colon cancer. However, it is important to presume complete mesocolic excision with central vascular ligation during surgery.

LAP for clinical T4 or N2 colon cancer should be performed with caution, but it is difficult to accurately predict pathological T4 and pathological N2 before and during surgery. Therefore, when the pathological diagnosis is T4 or N2, strong adjuvant chemotherapy or careful postoperative follow-up is recommended to be considered.

**TABLE 6** Recurrence patterns in the laparoscopic (LAP) and open (OP) group patients in the pathological N2 subgroup (n = 123)

Recurrence	OP n = 18	LAP n = 29	Total n = 47
Liver	7 (38.9%)	11 (37.9%)	18
Peritoneum	2 (11.1%)	5 (17.2%)	7
Lung	6 (33.3%)	8 (27.6%)	14
Locoregional	2 (11.1%)	3 (10.3%)	5
Lymph node	6 (33.3%)	7 (24.1%)	13
Laparotomy wound, port site	0 (0%)	0 (0%)	0
Others	0 (0%)	0 (0%)	0

Note: Number (percentage) of patients with disease recurrence is shown. There is some duplication of patients.

**TABLE 7** Recurrence patterns in the laparoscopic (LAP) and open (OP) group patients with BMI  $\geq 25$  kg/m<sup>2</sup> (n = 254)

Recurrence	OP n = 12	LAP n = 30	Total n = 42
Liver	5 (41.7%)	12 (40.0%)	17
Peritoneum	1 (8.3%)	2 (6.7%)	3
Lung	6 (50.0%)	11 (36.7%)	17
Locoregional	1 (8.3%)	3 (10.0%)	4
Lymph node	1 (8.3%)	5 (16.7%)	6
Laparotomy wound, port site	0 (0%)	0 (0%)	0
Others	0 (0%)	3 (10.0%)	3

Note: Number (percentage) of patients with disease recurrence is shown. There is some duplication of patients.

There are a few limitations to this study. First, this study was an exploratory subgroup analysis of data from a randomized controlled trial. Second, the number of patients with higher BMI, N positivity, RS-located tumor, and T4 were insufficient to obtain concrete evidence. Especially for higher BMI, the number of obese patients was especially small. Therefore, comparability might not be maintained, even though the multivariable analysis showed a significantly different HR compared with that of the univariable analysis. Thus, additional investigation will be necessary to precisely identify the patient subgroups with poor prognosis in the LAP group.

In conclusion, the present subgroup analysis suggested that pT4, pN2, and high BMI were factors associated with unfavorable long-term outcomes in LAP compared with OP for colon cancer patients who underwent curative resection. However, the presence of tumors in the RS was not associated with unfavorable outcomes. Therefore, LAP might need to be carefully indicated for patients with high BMI, and patients with pT4 and pN2 might need careful postoperative follow-up after LAP.

#### ACKNOWLEDGMENTS

We thank all of the participating patients and their families; the investigators, research nurses, study coordinators, and operations staff; and the members of the JCOG Data Center and JCOG Operations Office for their support in data management (Harumi Kaba, Ayaka

Nakano), and overseeing the study management (Haruhiko Fukuda). We thank Dr Satoshi Ikeda for reviewing the article.

#### DISCLOSURE

**Funding:** This study was supported in part by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19, 26-A-4, 29-A-3, 2020-J-3), Grant-in-Aid for Cancer Research (14S-3, 14S-4, 17S-3, 17S-5, 20S-3 and 20S-6), and Health and Labour Sciences Research Grant for Clinical Cancer Research (HI5-018, H18-013, H21-017, H24-005) from the Ministry of Health, Labour and Welfare of Japan.

**Conflict of Interest:** Author Y.K. (Yusuke Kinugasa) was supported by donations and lecture fees from Johnson & Johnson and Medtronic. All other authors declare no conflicts of interest for this article.

**Author Contributions:** MI, SY, MI, YM, YK and SK contributed to the study design. SS, TA, MI, SY, MI, YK, HE, YM, YK, HB, MY, MI, KN, DS, and YK contributed to data collection, data analysis, and interpretation. HK and MW contributed to data management, statistical analysis, and data interpretation. All the authors contributed to writing or reviewing the report and approved the final version.

**Ethical Statement:** The protocol for this research project was approved by the Ethics Committee of the institution (#2018-0027), and it conforms to the provisions of the Declaration of Helsinki.



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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Saito S, Akagi T, Katayama H, et al. Identification of patient subgroups with unfavorable long-term outcomes associated with laparoscopic surgery in a randomized controlled trial comparing open and laparoscopic surgery for colon cancer (Japan Clinical Oncology Group Study JCOG0404). *Ann Gastroenterol Surg*. 2021;5:804–812. <https://doi.org/10.1002/ags3.12475>