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ORIGINAL ARTICLE

Laparoscopic surgery in patients diagnosed with clinical N2 colon cancer

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Abstract

Purpose The benefits of laparoscopic surgery for colorectal cancer have been well established. Several randomized controlled trials have demonstrated similar oncological outcomes between laparoscopic and open surgery for colon cancer. However, whether or not laparoscopic surgery is acceptable in patients with clinical N2 colon cancer is unclear. Therefore, the present study aimed to evaluate the safety and oncological outcomes of laparoscopic surgery for clinical N2 colon cancer.

Methods This retrospective study assessed a prospective database and identified 262 consecutive patients with clinical N2 colon cancer who underwent either laparoscopic or open primary resection between 2000 and 2016. After propensity-score matching, 162 patients were analyzed. The primary outcome of interest was the 3-year recurrence-free survival rate, and the secondary outcome of interest was the postoperative complication rate.

Results The 3-year recurrence-free survival rate did not differ markedly between the laparoscopic and open surgery groups (77.4% vs. 76.5%, $p=0.620$). In addition, the incidence of postoperative complications did not differ markedly between the laparoscopic and open surgery groups (16.6% vs. 24.0%, $p=0.317$).

Conclusions Our findings suggest that laparoscopic surgery is safe and effective for clinical N2 colon cancer. Laparoscopic resection can be considered in patients diagnosed with clinical N2 colon cancer.

Keywords Colon cancer · Laparoscopic resection · Long-term outcomes · N2 · Clinical N2

Introduction

Complete mesocolic excision (CME) with central vascular ligation (CVL) is broadly recognized as an essential approach to improve oncological outcomes in patients with colon cancer [1]. With this approach, surgeons make an effort to achieve en bloc resection of the lymphatic drainage route as a package, without any damage.

Laparoscopic resection for colorectal cancer has become widespread, showing better short-term outcomes and reasonable long-term oncological outcomes than open surgery [2–5]. The indications for laparoscopic colorectal cancer surgery include not only early-stage tumors but also tumors invading other organs [6], node-positive disease [7], and systemic metastatic disease [8].

However, despite advancements in the procedure, laparoscopic surgery for clinically evident lymph node metastasis involving more than four nodes, which is recognized as clinical N2 (cN2) disease in the TNM staging system [9], remains a challenging procedure, as the qualities of CME and CVL can directly affect the oncological outcomes in such cases of advanced disease. Several previous studies have discussed the oncological outcomes of laparoscopic

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surgery for node-positive diseases [4, 7, 10]; however, few have focused on cN2 colon cancer.

The present study aimed to evaluate the safety and oncological outcomes of laparoscopic surgery for cN2 colon cancer.

Methods

Study design

This study used retrospectively collected data from a database that includes information on patient characteristics, preoperative assessments, operative characteristics, postoperative complications, pathological characteristics, and follow-up data. Between April 2000 and March 2016, 1822 patients underwent primary resection for colorectal cancer at Yokohama City University Hospital (Hospital A) and 3 community teaching hospitals located in Yokohama City (Hospitals B, C, and D). Of these 1822 patients, 250 with stage IV disease, 837 with cN0, 439 with cN1, 33 with non-curative resection, and 1 with multiple cancers were excluded. Thus, 262 patients with cN2 underwent the propensity-matching process. Ultimately, 162 matched patients were divided into the following 2 groups: the laparoscopic cN2 (Lap-cN2) group ($n = 54$) and the open cN2 (Open-cN2) group ($n = 108$) (Fig. 1).

The clinical lymph node evaluation

According to the TNM staging system [9], cN2 was defined as clinical lymph node metastasis involving more than four nodes. In our department, clinical lymph node metastasis refers to a lymph node size over 5 mm in the short axis detected on 5-mm-slice computed tomography (CT).

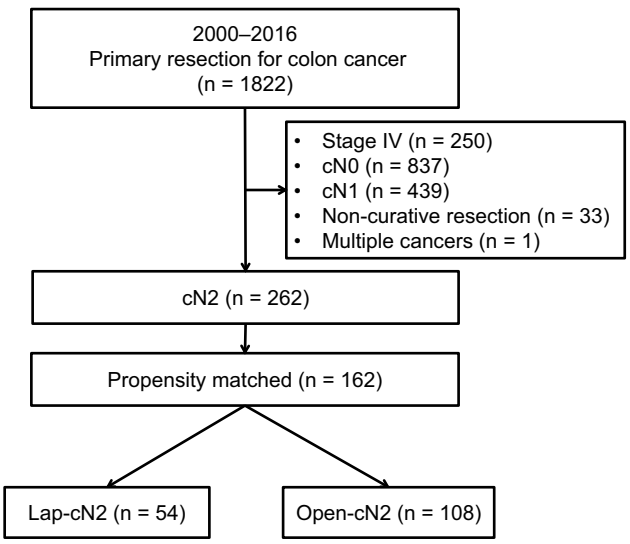

Fig. 1 Consort diagram, *Lap-cN2* laparoscopic cN2 group, *Open-cN2* open cN2 group

Indications for laparoscopic surgery

In this study, the indications for laparoscopic surgery were not standardized. Laparoscopic surgery was performed at the discretion of the surgeon after considering tumor factors, patient characteristics, and surgeon experience.

Operative procedure

Midline laparotomy was the choice for access in open colorectal resection. Colon mobilization was followed by main vessel ligation, bowel resection, and bowel anastomosis. For D3 lymph node dissection (LND), ligation was performed at the root of the main vessels, along with CME. For D2 LND, ligation was performed between the root and first branch of the main vessels.

In laparoscopic surgery, initial access to the abdomen was usually achieved via the umbilical port. Once pneumoperitoneum was established, four additional ports were placed. Vessel ligation with LND was performed, followed by colon mobilization. The pathological specimen was extracted via a 4- to 6-cm umbilical incision.

Postoperative complications

Postoperative complications were evaluated using the Clavien–Dindo classification system [11]. Grade 2–5 postoperative complications that occurred during hospitalization and/or within 30 days after surgery were prospectively recorded. Grade 1 complications were not evaluated to exclude the possibility of a description bias.

Patient follow-up

Patients were followed up at outpatient clinics. Hematological tests, including tests of serum CEA and CA19-9 levels, physical examinations, and CT examinations were performed every 6 months for 5 years after surgery.

Outcome of interest

The primary outcome of interest was the three-year recurrence-free survival (RFS) rate, and the secondary outcome of interest was the postoperative complication rate.

Propensity-score matching and statistical analyses

Propensity-score matching was performed to match patients who underwent laparoscopic or open surgery according to

their baseline characteristics. Patients in the Open-cN2 group were matched in a 2:1 ratio to patients in the Lap-cN2 group according to the following factors: American Society of Anesthesiologists (ASA) classification (1, 2/3–5), tumor location (right side/left side), sex (male/female), cT (cT1-3/4), LND extent (D2/D3), and adjuvant chemotherapy use (yes/no). Right-sided colon cancers included tumors located on the cecum, ascending colon, and transverse colon, while left-sided colon cancers included tumors located on the descending colon, sigmoid colon, and rectosigmoid colon. The significance of associations between the study groups and clinicopathological parameters was assessed using Fisher's exact test or the *t* test. The RFS curve was constructed using the Kaplan–Meier method and compared using the log-rank test.

All statistical analyses were performed using EZR [12] (Jichi Medical University, Saitama, Japan) and R software (version 3.4.3). All *p* values were two sided, and a p value < 0.05 was considered to indicate statistical significance.

All study protocols were approved by the Yokohama City University Institutional Review Board (approval no. 170,700,003). This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Instead of obtaining written informed consent, the details of the study protocol were provided to patients via a notice board in the hospitals and published on the hospital websites.

Results

Patient characteristics

The baseline characteristics of the Lap-cN2 and Open-cN2 groups are presented in Table 1. There were no significant differences between the two groups with regard to age, sex, body mass index, ASA classification, tumor location, cT, LND, and adjuvant chemotherapy. The median follow-up period was 42.8 months.

Pathological findings

The pathological findings of the Lap-cN2 and Open-cN2 groups are presented in Table 2. With regard to histology and pT, the two groups had similar findings. With regard to pN, the ratio of pN2 was significantly higher in the Lap-cN2 group than in the Open-cN2 group (53.8% vs. 26.9%, $p = 0.002$), indicating that the proportion of pathologically advanced patients was greater in the Lap-cN2 group than in the Open-cN2 group.

Table 1 Baseline characteristics ($n = 162$)

Parameter	Lap-cN2 ($n = 54$)	Open-cN2 ($n = 108$)	*p* value
Age, years	71 (39–87)	70 (27–98)	0.774
Sex			0.865
Male	32 (59.2%)	66 (61.1%)	
Female	22 (40.8%)	42 (38.9%)	
Body mass index	22.5 (14.0–33.6)	22.3 (16.8–34.9)	0.627
ASA classification			0.609
Class 1–2	49 (90.7%)	94 (87.0%)	
Class 3	5 (9.3%)	14 (13.0%)	
Tumor location			0.868
Right-sided	25 (46.2%)	53 (49.0%)	
Left-sided	29 (53.8%)	55 (51.0%)	
cT			0.309
cT1	2 (3.7%)	0 (1.8%)	
cT2	10 (18.5%)	5 (4.6%)	
cT3	21 (38.8%)	52 (48.1%)	
cT4a	19 (35.1%)	43 (39.8%)	
cT4b	2 (3.7%)	6 (5.5%)	
LND			0.312
D2	9 (16.6%)	26 (25.0%)	
D3	45 (83.4%)I	82 (75.0%)	
Adjuvant chemotherapy			0.591
Yes	28 (51.8%)	53 (49.1%)	
No	26 (48.2%)	55 (50.9%)	

Continuous variables are presented as medians with ranges

Discrete variables are presented as numbers with percentages

ASA American Society of Anesthesiologists, *LND* Lymph node dissection

Short-term outcomes

The short-term outcomes of the patients are summarized in Table 3. The operation time was longer and the amount of blood loss was lower in the Lap-cN2 group than in the Open-cN2 group (operation time: 202 min vs. 156 min, $p = 0.005$; blood loss: 10 mL vs. 100 mL, $p = 0.003$). With regard to postoperative complications, there was no marked difference between the Lap-cN2 and Open-cN2 groups (16.6% vs. 24.0%, $p = 0.317$), and mortality was not noted. In contrast, the postoperative hospital stay was significantly shorter in the Lap-cN2 group than in the Open-cN2 group (9 days vs. 13 days, $p = 0.005$).

Survival outcome

Considering the median follow-up period of the cohort (42.8 months) and the loss of some patients to follow-up after recurrence owing to hospital transfer, the 3-year RFS was set as the primary outcome of interest in this study.

Table 2 Pathological findings ($n = 162$)

Parameter	Lap-cN2 ($n = 54$)	Open-cN2 ($n = 108$)	p value
Histology			1.000
Tubular	51 (94.4%)	99 (91.7%)	
Poorly differentiated	1 (1.9%)	3 (2.8%)	
Mucinous	2 (3.7%)	6 (5.5%)	
pT			0.567
pT1	2 (3.7%)	2 (1.8%)	
pT2	12 (22.2%)	21 (19.4%)	
pT3	24 (44.4%)	44 (40.7%)	
pT4a	18 (33.4%)	39 (36.1%)	
pT4b	0 (0.0%)	2 (1.8%)	
pN			0.002
pN0	12 (22.2%)	48 (44.4%)	
pN1	13 (24.0%)	31 (28.7%)	
pN2	29 (53.8%)	29 (26.9%)	
pStage			0.437
I	5 (9.2%)	10 (9.2%)	
II	7 (12.9%)	38 (35.1%)	
III	42 (77.7%)	60 (55.5%)	

Continuous variables are presented as medians with ranges

Discrete variables are presented as numbers with percentages

pT pathological T factor, *pN* pathological N factor

The RFS analysis showed a similar curve in the Lap-cN2 and Open-cN2 groups, with no significant difference in the 3-year RFS rate between the groups (77.4% vs. 76.5%, log-rank $p = 0.620$) (Fig. 2).

Discussion

The surgical treatment of colon cancer has drastically changed with the emergence of laparoscopic surgery in the last decade. Sufficient evidence supports the safety and feasibility of minimally invasive approaches for colon cancer [2, 3, 13]. At the beginning of the laparoscopic era, studies mainly focused on the oncological outcomes of laparoscopic surgery for early cancer and revealed similar oncological results between laparoscopic resection and open resection [14–16]. Later studies assessed the use of laparoscopic resection for locally advanced cancer. A large-scale randomized controlled Japanese study investigated the long-term outcomes of laparoscopic surgery and open surgery for clinical stage II/III colon cancer (JCOG0404) and revealed a worse survival trend for cN2 or cT4 with laparoscopic surgery than with open surgery in a subgroup analysis [4]. In particular, patients with a high risk of recurrence had a potential for poor survival outcomes following laparoscopic surgery. However, more recent studies have indicated the

Table 3 Short-term outcomes ($n = 162$)

Parameter	Lap-cN2 ($n = 54$)	Open-cN2 ($n = 108$)	p value
Operation time (min)	202 (85–359)	156 (73–405)	0.005
Blood loss (mL)	10 (0–1410)	100 (10–2900)	0.003
Conversion	2 (3.7%)	–	–
Complications (CD ≥ Grade 2)	9 (16.6%)	26 (24.0%)	0.317
Wound dehiscence	0 (0.0%)	2 (1.8%)	
Ileus	4 (7.4%)	12 (11.1%)	
Anastomotic leakage	4 (7.4%)	5 (4.6%)	
Abdominal abscess	0 (0.0%)	1 (0.9%)	
Anastomotic bleeding	0 (0.0%)	1 (0.9%)	
Pneumonia	0 (0.0%)	1 (0.9%)	
Brain infarction	1 (1.8%)	0 (0.0%)	
Gastric ulcer	0 (0.0%)	1 (0.9%)	
Delirium	0 (0.0%)	1 (0.9%)	
Enteritis	1 (1.8%)	1 (0.9%)	
Rash	0 (0.0%)	1 (0.9%)	
Bed sore	0 (0.0%)	1 (0.9%)	
Mortality	0 (0.0%)	0 (0.0%)	–
POS (days)	9 (6–40)	13 (6–96)	0.005
Harvested lymph nodes	29 (7–52)	26 (2–47)	0.847

Continuous variables are presented as medians with ranges

Discrete variables are presented as numbers with percentages

CD Clavien–Dindo classification, *POS* Postoperative hospital stay

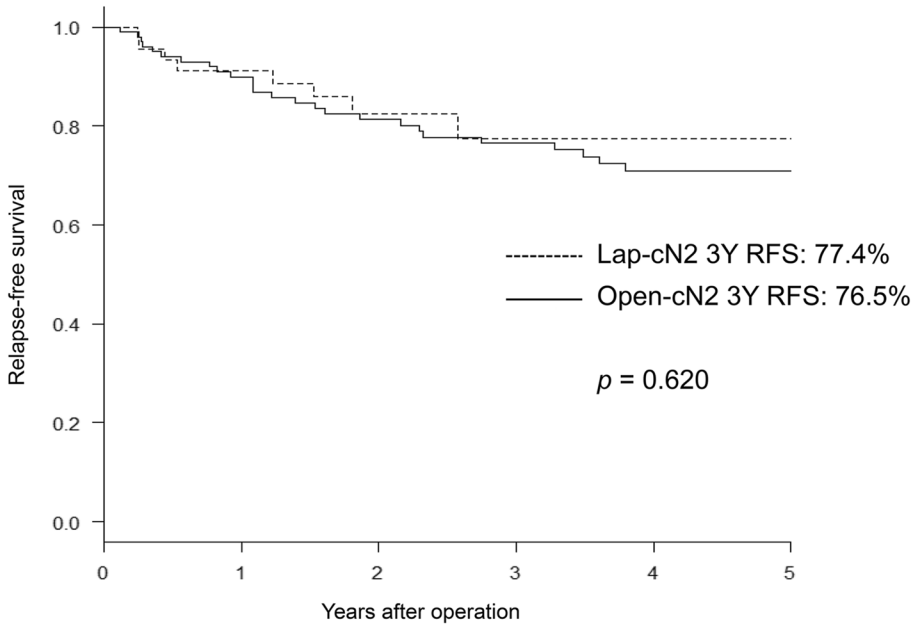

Fig. 2 Recurrence-free survival rates in the Lap-cN2 and Open-cN2 groups. *Lap-cN2* laparoscopic cN2 group, *Open-cN2* open cN2 group, *3Y RFS* 3-year recurrence-free survival

safety and feasibility of laparoscopic surgery for T4 disease [17, 18].

Some studies have assessed the use of laparoscopic surgery for N2 disease in subgroup analyses but not in the main analysis [4, 7]. Consistent with the findings in the JCOG0404 study, Shida et al. concluded that cN2 patients had a higher risk of recurrence after laparoscopic surgery than after open surgery [7]. As the RFS following laparoscopic surgery was worse for cN2 than for cN0 or cN1 disease [10], the indication of laparoscopic surgery for cN2 disease remains controversial.

Our short-term results support the safety of laparoscopic surgery for cN2 disease. The oncological outcome was the main outcome of interest in this study. To our knowledge, this is the first study focusing on cN2 disease to show a similar long-term survival after laparoscopic and open surgery. Our long-term results were almost identical in the laparoscopic and open surgery groups, despite a higher rate of pN2 patients in the laparoscopic group.

A previous study showed that a good surgical plane along with the embryonic plane improved oncological outcomes, especially in colon cancer patients with node-positive disease [19]. A technique that avoids any breach of the visceral layer, which might cause inadvertent exfoliation of tumor cells into the peritoneal cavity, is strictly demanding, especially in patients with N2 disease. The laparoscope, which has a telescopic video camera, usually provides surgeons with a magnified and better view of internal organs than the view afforded with the traditional open procedure [14]. Our hypothesis is that precise laparoscopic surgery with a magnified view might have favorable oncological effects in patients with cN2 disease. This might explain our results.

The limitations of the present study should be considered when interpreting the results. The retrospective, non-randomized design of this study was associated with selection bias. To eliminate selection bias as much as possible and balance the cohort, propensity-score matching was performed. However, two major biases remained between the two groups. The first bias is that the pathological findings indicated a higher pN2 rate in the Lap-cN2 group than in the Open-cN2 group. This difference might be attributed to the improvement in the diagnosis of lymph node metastasis on CT, and laparoscopic surgery was more often performed during the late study period than during the early period. The second bias involves adjuvant chemotherapy. Although the rate of adjuvant chemotherapy among all patients was similar in the 2 groups (51.8% vs. 49.1%, $p = 0.591$), the rate of adjuvant chemotherapy for pathological node-positive disease was higher in the Open-cN2 group than in the Lap-cN2 group (88.3% vs. 66.7%, $p = 0.012$). The indication of adjuvant therapy was the same in the Open-cN2 and Lap-cN2 groups, i.e. pathological node-positive disease, with consideration of the patient age, organ function, clinical course after the operation, and patient preference. As these factors did not differ markedly between the two groups, the reason for the difference in the rate of adjuvant chemotherapy for pathological node-positive disease was unclear. Although these two biases indicated that the Open-cN2 group had an advantage with regard to Lap-cN2, the RFS curve was similar between the Lap-cN2 and Open-cN2 groups. As we were attempting to determine whether or not it is acceptable to consider laparoscopic resection in patients with cN2 colon cancer, we selected patients according to the presence of cN2 disease and not pN2 disease. A randomized, controlled

study is needed to address these limitations. However, despite the above-mentioned limitations, our findings support the use of laparoscopic surgery for cN2 colon cancer.

In conclusion, our findings suggest that laparoscopic surgery is safe and effective for cN2 colon cancer. Laparoscopic resection can be considered in patients diagnosed with cN2 colon cancer.

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Compliance with ethical standards

Conflict of interest Drs. Masakatsu Numata, Sho Sawazaki, Toru Aoyama, Hiroshi Tamagawa, Tsutomu Sato, Hiroyuki Saeki, Yusuke Saigusa, Masataka Taguri, Hiroyuki Mushiake, Takashi Oshima, Norio Yukawa, Manabu Shiozawa, Munetaka Masuda, and Yasushi Rino have no conflicts of interest or financial ties to disclose.

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