ANTICANCER RESEARCH *41*: 5097-5106 (2021)
doi:10.21873/anticanres.15326

Can D3 Lymph Node Dissection for Patients With Colon Cancer With a Poor C-Reactive Protein/Albumin Ratio Improve Survival Outcomes?

YOSUKE ATSUMI[1], MASAKATSU NUMATA[1], KEISUKE KAZAMA[1], SHINNOSUKE KAWAHARA[1], MIHWA JU[1], KENTA IGUCHI[1], SHO SAWAZAKI[2], TORU AOYAMA[1], AYAKO TAMAGAWA[1], SUMITO SATO[1], AKIO HIGUCHI[2], NOBUHIRO SUGANO[1], TENI GODAI[3], HIROSHI TAMAGAWA[1], HIROYUKI SAEKI[2], TAKASHI OSHIMA[4], MANABU SHIOZAWA[4], NORIO YUKAWA[1] and YASUSHI RINO[1]

[1]Department of Surgery, Yokohama City University, Yokohama, Japan;
[2]Department of Surgery, Yokohama Minami Kyosai Hospital, Yokohama, Japan;
[3]Department of Surgery, Fujisawa Shounandai Hospital, Fujisawa, Japan;
[4]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan

Abstract. *Aim: D3 lymph node dissection (LND) for stage II and III colon cancer has been shown to improve prognosis, however, it generally increases surgical stress. Studies have reported that the C-reactive protein/albumin ratio (CAR) may be a useful inflammatory-nutritional biomarker to predict postoperative complications and poor prognosis for with various types of cancer. Our purposes were to assess the short- and long-term outcomes of D3 LND in patients with a high preoperative CAR (≥ 0.04). Patients and Methods: This was a retrospective cohort analysis reviewing a prospectively collected database of Yokohama City University and three affiliated hospitals. A total of 449 patients with stage II or III colon cancer with high CAR who underwent primary resection with D2 or D3 LND were identified between 2008 and 2020. The primary and secondary outcomes of interests were the 3-year recurrence-free survival and postoperative complication rates. Results: After propensity matching, 230 patients were evaluated. There was no significant difference between the D3 and D2 groups in the rate of postoperative complications overall (14.8% versus 11.3%, p=0.558), however, the incidence of anastomotic leakage tended to be greater in the D3 group (9.6% versus 2.6%, p=0.050). The long-term findings showed that there was no significant difference between the two groups (3-year recurrence-free survival rate: 77.2% versus 77.2%, p=0.880). Conclusion: D3 LND did not improve survival outcomes for patients with colon cancer with a poor CAR in this study. D2 LND may be a treatment option for patients with stage II-III colon cancer with a high preoperative CAR.*

Correspondence to: Masakatsu Numata, Department of Surgery, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. E-mail: masakatsunumata@hotmail.co.jp

Key Words: Lymph node dissection, colon cancer, C-reactive protein/albumin ratio, inflammatory-nutritional biomarker, oncological outcome.

En bloc resection of the primary lesion and its lymphatic drainage route has been shown to improve the prognosis of colorectal cancer. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the Treatment of Colorectal Cancer recommends D3 lymph node dissection (LND) for stage II and III colorectal cancer (1). On the contrary, D3 LND generally increases surgical stress represented by postoperative complications, operative time, and also increases postoperative hospital stay as compared with D2 LND (2-4); thus, the subgroup of patients who might benefit from D3 LND remains unclear.

Previous studies have reported that postoperative complications are associated with reduced long-term survival after surgery for colorectal cancer (5-8). Moreover, malnutrition and chronically systematic inflammation have been shown to play an important role in predicting postoperative complications in various types of cancer (9, 10). In particular, recent studies have reported that the C-reactive protein/albumin ratio (CAR) may be a useful inflammatory-nutritional biomarker, and a high CAR predicted postoperative complications after colorectal and gastric cancer surgery (11, 12). Therefore, there is a theoretical concern that D3 LND leads to development of more postoperative complications than D2 or less LND due to more surgical stress, which may negate the oncological benefit of D3 LND.

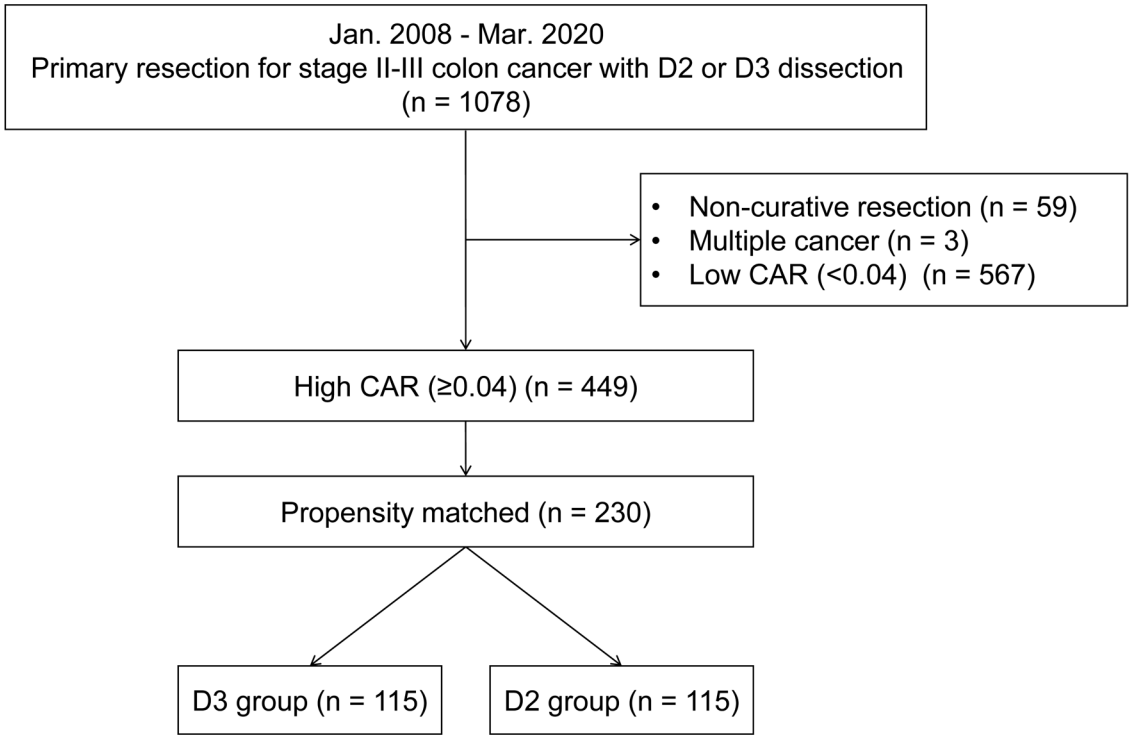

Figure 1. *Consort diagram*.

In this study, we compared the short- and long-term outcomes of D3 LND with those of D2 LND in patients with a high preoperative CAR to assess the oncological impact of D3 LND in patients with colon cancer with a poor inflammatory-nutritional status.

Patients and Methods

Study design. This study was a multicenter, retrospective cohort study reviewing a prospectively collected database of Yokohama City University and three affiliated hospitals from January 2008 to March 2020. The patients met the following inclusion criteria: (i) Histologically proven colonic or rectosigmoid cancer, (ii) pathological stage II to III disease, and (iii) complete (R0) resection of colonic cancer with D3 or D2 LND. The JSCCR classification of colorectal carcinoma (13) was used for staging. We excluded patients with R2/R1 resection, multiple cancer, or preoperative CAR less than 0.04. Subsequently, propensity matching was performed for the remaining patients (Figure 1). All study protocols were approved by the Yokohama City University Institutional Review Board (approval no. 170700003). The details of the study protocol were provided to patients through a notice board in the hospital and were also published on hospital websites. Informed consent was waived owing to the retrospective nature of the study.

C-Reactive protein/albumin ratio. The CAR was calculated by dividing the preoperative serum C-reactive protein level by the preoperative serum albumin level. A CAR of 0.04 was regarded as the optimal cutoff value according to previous studies, including reports from our group (14-19).

Definition of D3 and D2 LND. The JSCCR classification of colorectal carcinoma (13) categorizes mesenteric lymph nodes of the colon into three groups: Main lymph node (MLN), intermediate lymph node (ILN), and pericolic lymph node (PLN). Moreover, the JSCCR defines D3 LND as the removal of the MLN, ILN, and PLN, and D2 LND as the removal of the ILN and PLN. For left-sided colon cancer, the MLN is located at the root of the inferior mesenteric artery. The ILN is located between the left colic artery and the last sigmoid artery, and the PLN is located between the last sigmoid artery and the colon (Figure 2). In contrast, for right-sided colon cancer, we defined the MLN and ILN considering the superior mesenteric vein (SMV) as the important landmark according to previous reports (20-23). Additionally, the MLN is located in front of the SMV, and the ILN is located along the ileocolic, right colic, and middle colic arteries (Figure 3). Hence, when we performed D3 and D2 LND, we dissected along the left and right sides of the SMV, respectively. Japanese D3 LND is similar in concept to Western complete mesocolic excision (CME) with central vascular ligation, in which all lymphatic, vascular, and neural tissues in the drainage area of the tumor are excised as a complete mesocolic package (24).

General surgical procedure. Our standard procedures of open colorectal resection consisted of midline laparotomy, mobilization of the colon followed by ligation of the main vessels, bowel resection, and bowel anastomosis. For laparoscopic surgery, access to the abdomen was generally achieved *via* the umbilical port. After

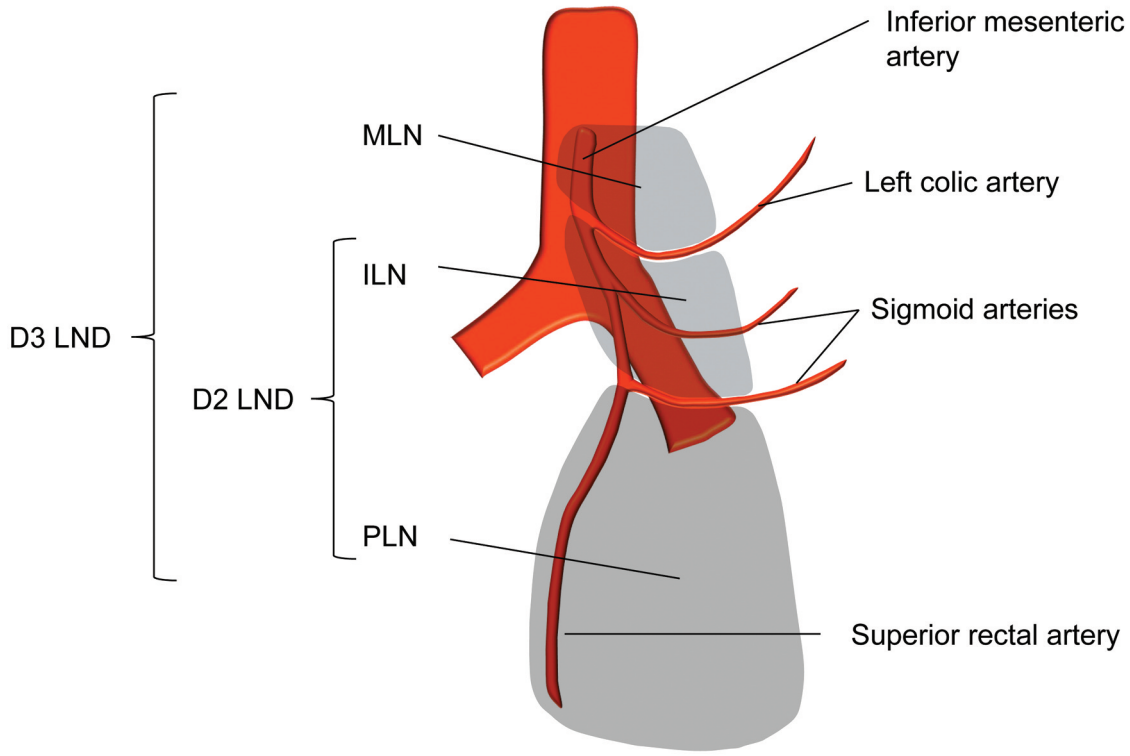

Figure 2. *Schematic diagram of mesenteric lymph nodes and the extent of lymph node dissection (LND) for left-sided colonic cancer. ILN: Intermediate lymph node; MLN: Main lymph node; PLN: perirectal lymph node.*

the pneumoperitoneum was performed, a five-port system was established. Artery ligation with lymph node dissection was performed before mobilization of the colon. The specimen was removed *via* a 4-6 cm umbilical incision.

Definition of postoperative complications. Postoperative surgical complications of grade 3-5 according to the Clavien–Dindo classification (25) were retrospectively determined from the patient's records.

Follow-up. Patients were followed up at outpatient clinics. Hematological tests and physical examinations were performed every 3 months for 5 years. The serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were checked every 3 months for 5 years. Patients underwent a computed tomographic examination every 6 months until 5 years after surgery.

Outcome of interest. The primary outcome of interest in this study was the 3-year recurrence-free survival (RFS), and the secondary outcome was the postoperative complication rate. The RFS was defined as the period between surgery and recurrence or death, whichever came first.

Propensity score matching and statistical analysis. Propensity score matching was used to match the patients who underwent D3 or D2 LND based on their baseline characteristics. Each patient in the D3 group was matched to a patient in the D2 group according to the following factors: Age, sex, American Society of Anesthesiologists (ASA) classification (1-2/3-4), tumor location (right/left side), pathological stage (II/III), surgical approach (laparoscopy/open), and adjuvant chemotherapy (yes/no). Right-sided colon cancer included tumors located in the cecum, ascending colon, and transverse colon, while left-sided colon cancer included tumors located in the descending, sigmoid, and rectosigmoid colon. The significance of correlations between the extent of LND and clinicopathological parameters was determined using Fisher's exact test or the chi-squared test. The RFS curves were calculated using the Kaplan–Meier method and compared using the log-rank test.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Australia). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (26). All p-values are two sided, and a value of $p<0.05$ was considered to indicate significance.

Results

Patients. Figure 1 shows the Consort diagram for the present study. A total of 1,078 patients who underwent primary resection for stage II or III colon cancer with D2 or D3 dissection were identified. Patients were excluded according to the following criteria: non-curative resection in 59,

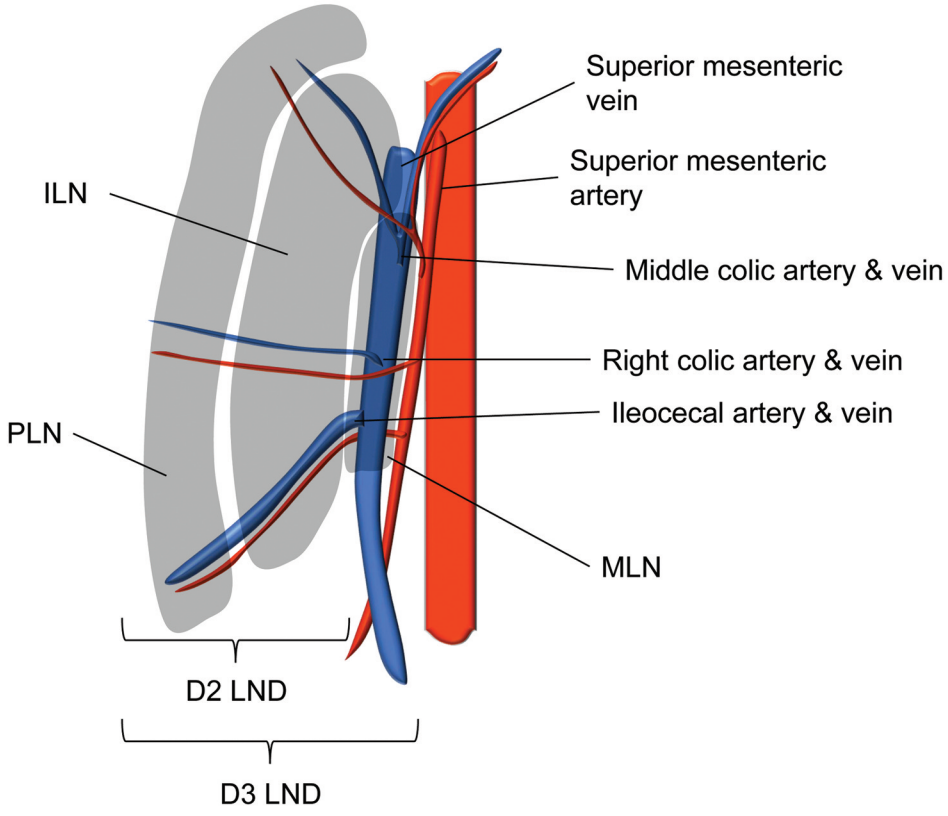

Figure 3. *Schematic diagram of the mesenteric lymph nodes and the extent of lymph node dissection (LND) for right-sided colonic cancer. ILN: Intermediate lymph node; MLN: main lymph node; PLN: perirectal lymph node.*

multiple cancer in three, and low CAR (<0.04) in 567. One-to-one propensity score matching was performed for the remaining 449 patients. Finally, 230 matched patients were divided into two groups according to the LND performed: the D3 and D2 groups (Figure 1). The characteristics of the patients in the D3 and D2 groups are presented in Table I. There were no significant differences between the two groups in terms of age, sex, body mass index, ASA classification, preoperative CAR level, tumor location, surgical approach, pathological stage, and adjuvant chemotherapy. The median follow-up period of the matched patients was 33.4 months.

Short-term outcomes. Table II summarizes the short-term outcomes of the patients. There was no significant difference in the operative time (185.5 *vs*. 171.0 min, p=0.115) and the amount of blood lost (107.5 *vs*. 100.0 ml, p=0.637) between the D3 and D2 groups. The number of lymph nodes harvested was significantly higher for the D3 group than for the D2 group (22 *vs*. 16, p<0.001). There was no significant difference between the two groups in the rate of postoperative complications overall (14.8% *vs*. 11.3%, p=0.558); however, the incidence of anastomotic leakage tended to be greater in the D3 group (9.6% *vs*. 2.6%, p=0.050). The mortality rate did not differ significantly between the two groups (0.9% *vs*. 1.7%, p<0.99).

Long-term outcomes. During the study period, 20 patients (17.4%) in each of the D3 and D2 groups developed recurrence. The results of the RFS analysis were similar and showed no significant difference between the two groups (3-year RFS rate: 77.2% *vs*. 77.2%, p=0.880) (Figure 4). Comparison of the distribution of the sites of recurrence showed no significant difference between the two groups (Table III). The major sites of recurrence in the D3 group in order of frequency were the liver, extra-regional lymph nodes, and locally, while those in the D2 group were the liver and peritoneum, followed by the extra-regional lymph nodes, lung, and locally.

Discussion

In this study, we evaluated the oncological impact of D3 LND in patients with colonic cancer with poor preoperative

Table I. *Patient characteristics (n=230).*

Parameter		D3 (n=115)	D2 (n=115)	*p*-Value
Age, years	Median (range)	75 (33-98)	77 (43-96)	0.341
Gender, n (%)	Male	70 (60.9%)	66 (57.4%)	0.688
	Female	45 (39.1%)	49 (42.6%)	
BMI, kg/m^2	Median (range)	21.9 (13.9-38.5)	21.5 (14.6-38.1)	0.429
ASA classification, n (%)	Class 1 or 2	70 (60.9%)	73 (63.5%)	0.786
	Class 3 or 4	45 (39.1%)	42 (36.5%)	
Preoperative albumin, g/dl	Median (range)	3.7 (1.8-5.0)	3.6 (1.6-4.4)	
Preoperative CRP, mg/l	Median (range)	0.55 (0.17-12.09)	0.50 (0.15-23.05)	**0.040**
Preoperative CAR	Median (range)	0.15 (0.04-5.47)	0.13 (0.04-6.23)	0.367
Tumor location, n (%)	Right side	58 (50.4%)	64 (55.7%)	0.778
	Left side	57 (49.6%)	51 (44.3%)	0.509
Approach, n (%)	Open	83 (72.2%)	89 (77.4%)	
	Laparoscopic	32 (27.8%)	26 (22.6%)	0.448
pStage, n (%)	II	70 (60.9%)	61 (53.0%)	
	III	45 (39.1%)	54 (47.0%)	0.287
Adjuvant chemotherapy, n (%)	Yes	20 (17.4%)	23 (20.0%)	
	Oral 5-FU-based	17 (14.8%)	22 (19.1%)	0.735
	Oxaliplatin-based	3 (2.6%)	1 (0.9%)	

ASA: American Society of Anesthesiologists; BMI: body mass index; CAR: C-reactive protein-to-albumin ratio; CRP: C-reactive protein; 5-FU: 5-fluorouracil. Statistically significant *p*-values are shown in bold.

inflammatory-nutritional status and demonstrated that D3 LND did not improve long-term outcomes for these patients.

Systematic LND is one of the most important prognostic factors in the treatment of colonic cancer (27, 28). As described previously, D3 LND is recommended for all patients with stage II or III colonic cancer in Japan. In addition, in Western countries, CME with central vascular ligation, which is similar in concept to Japanese D3 LND, has been recently reported to improve oncological outcomes for the entire cohort of patients with stage I-III colonic cancer (24, 29). However, it is still unclear whether CME/D3 LND improves long-term outcomes in patients with colonic cancer with poor inflammatory-nutritional status (9-12), who have high postoperative morbidity rates. To the best of our knowledge, this is the first study to investigate the efficacy and safety of D3 LND for such patients.

It has been reported that poor status by inflammatory-nutritional biomarkers, including CAR, as well as neutrophil-lymphocyte ratio, prognostic nutritional index, and controlling nutritional status, are associated with high postoperative morbidity rates (11, 12, 30-34). Among these, CAR was introduced as a simple and easy complication prediction system by Fairclough *et al*. in 2009, and has been adopted as a predictive marker of postoperative complications for colorectal and gastric cancer surgery (11, 12). Moreover, we showed in a previous research that preoperative CAR can be used a risk factor for overall survival (OS) in patients who underwent surgery for colorectal cancer and a useful tool for devising treatment strategies (35). Thus, we chose CAR as a representative inflammatory-nutritional biomarker in this research.

Firstly, regarding the short-term outcome, there was no significant difference between the two groups in the rate of postoperative complications overall in this study. Moreover, a previous multicenter randomized clinical trial comparing short-term outcomes of 56 patients who underwent D3 LND and 43 who underwent D2 LND showed that there was no significant difference between the two groups in the 30-day postoperative morbidity rate (36). Moreover, Bertelsen *et al*. reported that the rate of postoperative complications did not differ between CME and non-CME groups in a retrospective study of 198 patients (37). Our results were consistent with those of previous studies. Our study also showed that the incidence of anastomotic leakage tended to be greater in the D3 group. Contrary to this, most previous studies comparing CME *versus* non-CME, including one randomized clinical trial, reported that there was no significant difference between the groups in the incidence of anastomotic leakage (36-39). Although the cause of this discrepancy is unclear, it might be due to the fact that patients with rectosigmoid colonic cancer (13.0% *vs*. 9.6%, $p=0.533$) and those who needed combined resection of surrounding organs (6.1% *vs*. 3.5%, $p=0.539$) were more common in the D3 group, although not significantly.

Secondly, regarding the long-term outcome, this study showed that D3 LND did not improve RFS for patients with preoperative poor inflammatory-nutritional status. The reason for this is unclear; however, considering the results of this

Table II. *Short-term outcomes (at discharge) of study patients (n=230).*

Parameter		D3 (n=115)	D2 (n=115)	*p*-Value
Operative time, min	Median (range)	185.5 (83-432)	171.0 (57-529)	0.115
Blood loss, ml	Median (range)	107.5 (5-1,410)	100.0 (1-1,339)	0.637
Harvested lymph nodes, n	Median (range)	22 (4-81)	16 (3-77)	**<0.001**
Complications, n (%)	CD grade ≥3	17 (14.8%)	13 (11.3%)	0.558
Surgical	Overall	32 (27.8%)	28 (24.3%)	0.653
	Wound infection	9 (7.8%)	5 (4.3%)	0.409
	Ileus	12 (10.4%)	19 (16.5%)	0.246
	Anastomotic leakage	11 (9.6%)	3 (2.6%)	0.050
	Abdominal abscess	2 (1.7%)	3 (2.6%)	>0.99
	Lymphorrhea	2 (1.7%)	0 (0.0%)	0.498
Non-surgical	Overall	8 (7.0%)	10 (8.7%)	0.807
	Pneumonia	2 (1.7%)	3 (2.6%)	>0.99
	Brain infarction	2 (1.7%)	1 (0.9%)	>0.99
	Gastric ulcer	2 (1.7%)	0 (0.0%)	0.498
	Cholecystitis	2 (1.7%)	0 (0.9%)	>0.99
	Heart failure	0 (0.0%)	1 (0.9%)	>0.99
	PTE	0 (0.0%)	2 (1.7%)	0.498
	Urinary tract infection	0 (0.0%)	2 (1.7%)	0.498
POS, days	Median (range)	12 (6-206)	13 (6-85)	0.246
Mortality, n (%)	Overall	1 (0.9%)	2 (1.7%)	>0.99
Cause	Anastomotic leakage	0 (0.0%)	1 (0.9%)	>0.99
	Brain infarction	1 (0.9%)	0 (0.0%)	>0.99
	Heart failure	0 (0.0%)	1 (0.9%)	>0.99

CD: Clavien–Dindo classification; PE: pulmonary thromboembolism; POS: postoperative hospital stay. Statistically significant *p*-values are shown in bold.

study, anastomotic leakage and greater general surgical stress (40, 41) in the D3 group might have negatively affected the long-term prognosis. Previous studies reported that CME surgery improved the 5-year survival rate of patients with colonic cancer by 5.1-22.6% compared with non-CME surgery (29, 42, 43). Moreover, postoperative anastomotic leakage worsens long-term prognosis, and previous studies reported that there was an 11.1-19.7% reduction of the 5-year survival rate in patients with anastomotic leakage as compared with those without it (44-47). The mechanism by which anastomotic leakage negatively influences long-term outcomes remains controversial. However, studies reported that viable cancer cells running out of the bowel lumen can lead to local recurrence (48, 49), and the systemic inflammatory response might enhance tumor spread and metastasis in the event of anastomotic leakage (50, 51). The concept of general surgical stress was first propounded in the Estimation of Physiologic Ability and Surgical Stress score (41) and the surgical Apgar score (52). Both scores include intraoperative factors, such as blood loss and operative time, and are associated with not only short-term but also long-term outcomes in various cancer surgeries (41, 53-58). These findings are biologically plausible; as illustrated in Figure 2 and Figure 3, D3 LND requires a greater dissection area than D2 LND, which somewhat leads to greater general surgical stress in consequence, although there were no marked differences in terms of operative time and blood loss between the two groups in the present cohort. Considering the results of these previous studies and ours, one of the reasons for D3 LND not leading to an improvement of prognosis in patients with high CAR might be a higher postoperative anastomotic leakage rate and greater general surgical stress canceling out the positive impact on survival.

Table III. *Site of recurrence (n=40).*

	Extent of lymph node dissection, n (%)		
Site	D3 (n=20)	D2 (n=20)	*p*-Value
Liver	8 (40.0%)	10 (50.0%)	0.75
Extra-regional lymph node	5 (25.0%)	2 (10.0%)	0.41
Local	4 (20.0%)	2 (10.0%)	0.66
Lung	3 (15.0%)	2 (10.0%)	1.0
Peritoneum	3 (15.0%)	3 (15.0%)	1.0
Bone	0 (0.0%)	1 (5.0%)	1.0
Ureter	0 (0.0%)	1 (5.0%)	1.0

There are some limitations associated with this study. Firstly, selection bias may be present due to its retrospective,

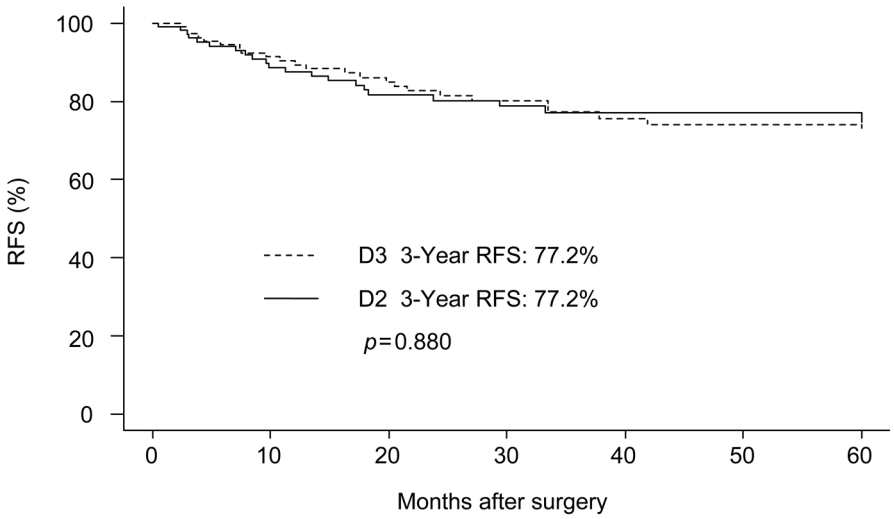

Figure 4. *Recurrence-free survival (RFS) curves for the D3 and D2 lymph node dissection groups.*

non-randomized design. However, the propensity matching method allowed a balanced cohort and result. Secondly, the present study is also limited by the small sample size. We cannot deny the possibility that our findings were observed by chance. Further prospective investigations with larger sample sizes are needed to confirm our results. Thirdly, we were unable to evaluate the OS rate and 5-year RFS owing to the relatively short follow-up periods. One of the reasons for this may be that patients with high preoperative CAR often had poor ASA performance score and were unable to attend the hospital regularly after surgery. However, despite these limitations, our finding was significant for establishing the optimal surgical strategy for patients with high preoperative CAR and colonic cancer.

In conclusion, D3 LND did not improve survival outcomes for patients with colon cancer with a poor CAR in this study. D2 LND resection may be a treatment option for patients with stage II-III colon cancer and a high preoperative CAR. Further investigation is needed to clarify the impact of D3 and D2 LND on OS in such patients.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

All Authors contributed to the study conception and design. Data collection was performed by Yosuke Atsumi, Masakatsu Numata, Keisuke Kazama, Shinnosuke Kawahara, Mihwa Ju, Kenta Iguchi, Sho Sawazaki, Toru Aoyama, Ayako Tamagawa, Sumito Sato, Akio Higuchi, Nobuhiro Sugano, Teni Godai, Hiroshi Tamagawa, Hiroyuki Saeki, Takashi Oshima, Manabu Shiozawa, Norio Yukawa, and Yasushi Rino. statistical analysis was performed by Yosuke Atsumi. The first draft of the article was written by Yosuke Atsumi, and all Authors commented on previous versions of the article. All Authors read and approved the final article.

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Received May 21, 2021
Revised August 7, 2021
Accepted August 24, 2021