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ORIGINAL ARTICLE

D3 lymph node dissection reduces recurrence after primary resection for elderly patients with colon cancer

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Abstract

Purpose The favorable oncological impact of D3 lymph node dissection after colon cancer surgery has been described previously. However, D3 lymph node dissection is potentially more invasive than conventional D2 lymph node dissection. The oncological merit of D3 lymph node dissection in elderly patients with colon cancer remains unclear. This study aimed to clarify the oncological outcome after D3 lymph node dissection in patients with colon cancer aged > 75 years.

Methods This is a retrospective cohort analysis using propensity matching method. The study was conducted at a university hospital and two community teaching hospitals in a large urban city. A total of 378 consecutive patients with pathological stage II and stage III colon cancer who underwent primary resection with either D2 or D3 lymph node dissection were retrospectively identified on a prospective database between 2000 and 2015. The primary and secondary outcomes of interests were recurrence-free survival and postoperative complication rate, respectively.

Results After propensity matching, 232 patients were analyzed. The long-term findings showed that the elderly who underwent D3 lymph node dissection had significantly better recurrence-free survival than those who underwent D2 lymph node dissection ($p = 0.01$). The incidence of postoperative complication was almost similar between the two groups.

Conclusions D3 lymph node dissection provides better recurrence-free survival than D2 lymph node dissection after primary resection for elderly patients with pathological stage II and stage III colon cancer.

Keywords Lymph node dissection · Colon cancer · Elderly · Oncological outcome

Introduction

En bloc resection of the primary lesion and its lymphatic drainage route is essential in the treatment of colon cancer. As the number of retrieved lymph node has significant influence on the oncological outcome after primary resection [1, 2], the extent of lymph node dissection (LND) has become of interest for many colorectal surgeons. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the Treatment of Colorectal Cancer [3] recommend D2 LND and D3 LND for early stage disease and for stages II and III colorectal cancer, respectively; thus, Japanese colorectal surgeons are familiar with D3 LND. In Western countries, complete mesocolic excision (CME) with central vessel ligation (CVL), which is similar in concept to D3 LND, is now broadly recognized as an essential approach to improve oncological outcomes compared with conventional D2 resection [4].

The elderly population, that is, individuals aged > 75 years, continues to increase worldwide. In general, elderly patients are more frail [5] and have shorter remaining lifespan than young patients. Moreover, elderly patients are characterized by loss of physiological reserve, decreased ability to maintain homeostasis, and increased vulnerability to morbidity and

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mortality following surgery [6–9]. Thus, the clinical benefit of D3 LND for elderly patients should be assessed.

This study aimed to evaluate the safety and oncological impact of D3 LND in patients with colon cancer aged > 75 years.

Materials and methods

Study design

A prospective colorectal database that contains information on patient characteristics, preoperative assessment, operative characteristics, postoperative complications, pathological characteristics, and follow-up data was used for analysis. From April 2000 to March 2015, a total of 1876 patients underwent primary resection for colorectal cancer at Yokohama City University Hospital (hospital A) and two community teaching hospitals located at Yokohama City (hospitals B and C). Among the patients diagnosed with pathological stages II–III colon cancer who underwent primary resection with D3 or D2 LND, those who did not achieve curative resection or were < 75 years old were excluded. Subsequently, propensity matching was performed for the remaining patients (Fig. 1). All study protocols were approved by the Yokohama City University Institutional Review Board (Approval No. 170700003).

Definition of D3 and D2 LND

The JSCCR classification of colorectal carcinoma [10] categorizes mesenteric LNs of the colon into three groups: main lymph node (MLN), intermediate lymph node (ILN), and pericolic lymph node (PLN) (Fig. 2). The MLN is located at the root of the main feeding artery. The ILN is located between the first and the terminal branch of the main feeding artery, while the PLN is located between the terminal branch of the main feeding artery and the colon. The JSCCR defines D3 LND as removal of the MLN, ILN, and PLN and D2 LND as the removal of the PLN and ILN [10]. The Japanese D3 LND is similar in concept to the Western CME with CVL in which all lymphatic, vascular, and neural tissue in the drainage area of the tumor is excised as a complete mesocolic package [11].

Indication for D3 LND

The JSCCR Guidelines for the Treatment of Colorectal Cancer [3] recommend D3 LND for T3/4 or N+ disease and D2 LND for T1N0 disease. Meanwhile, either D3 or D2 LND can be performed for T2N0 disease. Thus, D3 LND is basically recommended for stage II or III colon cancer. However, for elderly patients, D2 LND is commonly selected regardless of the cancer stage. In this study, the indication for D3 or D2 LND was not standardized and was instead performed according to the surgeon's discretion based on tumor factors, patient age, and comorbidity. The surgery was performed at any of the three participating hospitals and by any of the 13 surgeons who belong to the same surgery group (Yokohama City University, Department of Surgery Group). Thus, the strategy for LND and operating procedure were similar. There was no specific tendency for selecting D3 or D2 LND among the hospitals or surgeons. The JSCCR classification of colorectal carcinoma [10] is used for staging at the three hospitals.

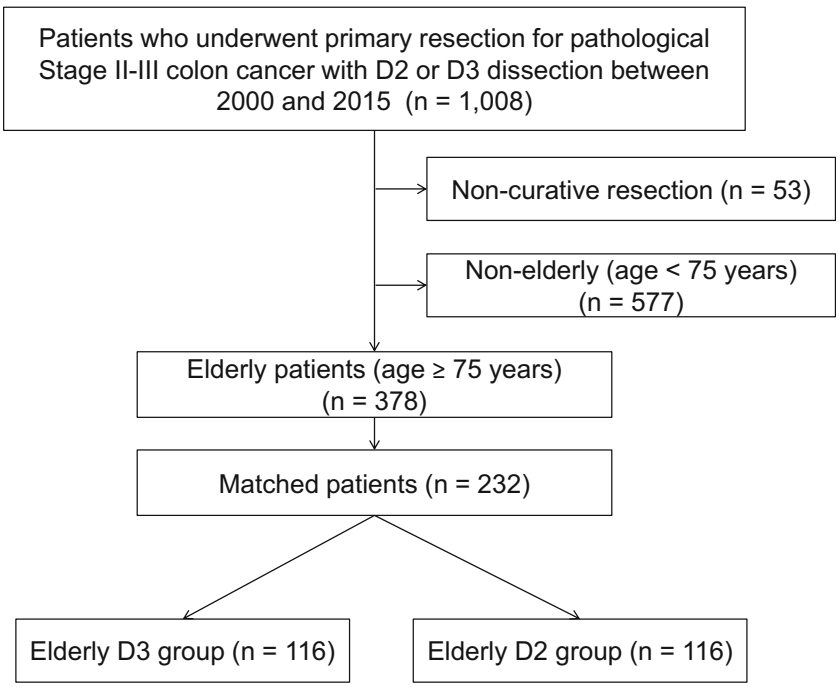

Fig. 1 Consort Diagram

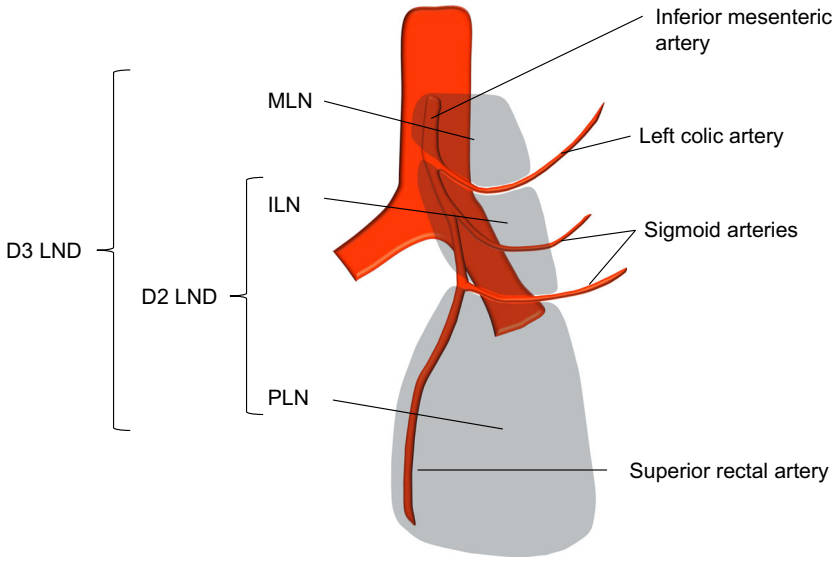

Fig. 2 Schematic image of the mesenteric lymph nodes and the extent of lymph nodedissection. MLN, main lymph node; ILN, intermediate lymph node; PLN, perirectal lymph nodes;LND, lymph node dissection

Table 1 Patient characteristics ($n = 232$)

Parameters	eld-D3 ($n = 116$)	eld-D2 (n = 116)	p value
Age, years	80 (75–79)	80 (75–98)	0.13
Sex			0.89
Male	63	63	
Female	52	52	
Body mass index	22.5 (15.6–31.0)	22.3 (14.8–33.3)	0.76
ASA classification	1		0.84
Class 1	18	16	
Class 2	55	53	
Class 3	43	47	
Tumor location			1.00
Right sided	64	65	
Left sided	52	51	
Tumor diameter (mm)	50 (12–160)	50 (13–114)	0.79
Approach			0.34
Open	97	103	
Laparoscopic	19	13	
Pathological stage			1.00
II	67	68	
III	49	48	
Adjuvant chemotherapy	18	19	1.00
Regimen			0.604
Oral 5-FU based	16	18	
Oxaliplatin based	2	1	

Continuous variables are presented in median value with range

Abbreviations: ASA, American Society of Anesthesiologists; 5-FU, 5-fluorouracil

Table 2 Short-term outcomes ($n = 232$)

Parameters	eld-D3 ($n = 116$)	eld-D2 ($n = 116$)	p value
Operation time (min)	162 (66–356)	140 (57–430)	0.001
Blood loss (ml)	98 (0–2700)	100 (0–1554)	0.30
Harvested lymph nodes	20 (4–58)	14 (3–49)	0.000003
Complications (CD ≥ grade 2)	24 (20.6%)	23 (19.8%)	1.00
Surgical complications	14 (12.0%)	16 (13.7%)	0.84
Wound infection	0	4	
Ileus	12	8	
Anastomotic leakage	1	2	
Abdominal abscess	2	2	
Lymphorrhea	0	2	
Non-surgical complications	12 (10.3%)	11 (9.4%)	1.00
Pneumonia	3	4	
Brain infarction	1	1	
Gastric ulcer	2	1	
Delirium	1	1	
Cholecystitis	2	0	
Catheter infection	0	1	
Urinary retention	1	0	
Renal failure	1	0	
Bed sore	1	0	
Urinary tract infection	1	0	
POS (days)	14 (6–96)	15 (1–146)	0.12
Mortality	2 (1.7%)	0 (0.0%)	0.49
Cause of mortality			
Pneumonia	1	0	
Brain infarction	1	0	

Continuous variables are presented in median value with range

Abbreviations: CD, Clavien-Dindo classification; POS, postoperative hospital stay

Operative procedure

Midline laparotomy was the choice of access for open colorectal resection. Mobilization of the colon was followed by ligation of the main vessels, bowel resection, and bowel anastomosis. For D3 LND, the ligation was performed at the root of main vessels, accompanied with CME. For D2 LND, the ligation level was between the root and first branch of the main vessels.

For laparoscopic operation, first access to the abdomen was usually achieved via the umbilical port. Once pneumoperitoneum was established, four additional ports were placed. Then, vessel ligation with LND was performed, followed by mobilization of the colon. The pathological specimen was extracted via a 4- to 6-cm umbilical incision.

Definition of postoperative complications

Grade 2–5 postoperative complications (Clavien-Dindo classification [12]) 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. In principle, hematological tests including serum CEA and CA19-9 levels, physical examinations, and computed tomography scans were performed every 6 months for 5 years after surgery.

Outcome of interest

The primary outcome of interest of this study was the 5-year recurrence-free survival (RFS), while the secondary outcome of interest is the postoperative complication rate. The 5-year overall survival (OS) and cancer-specific survival (CSS) rates were also evaluated.

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 eld-D3 group (i.e., elderly patients who underwent D3 LND) was matched to a patient in the eld-D2 group (i.e., elderly patients who underwent D2 LND) according to the following factors: surgical approach (laparoscopic/open), American Society of Anesthesiologists (ASA) classification (1, 2/3–5), tumor location (right side/left side), sex (male/female), pathological stage (II/III), adjuvant chemotherapy (yes/no), and operating hospital (A/B/C). Right-sided colon cancer included tumors located on the cecum, ascending colon, and transverse colon, while left-sided colon cancer included tumors located on the descending colon, sigmoid colon, and rectosigmoid colon. The significance of correlations between the extent of LND and clinicopathological parameters was determined using Fisher's exact test or the χ^2 test. The RFS, OS, and CSS curves were calculated using the Kaplan-Meier method and compared via log-rank test. All statistical analyses were performed with EZR (Jichi Medical University, Saitama, Japan) [13]. All p values were two sided, and a p value of < 0.05 was considered to indicate significance.

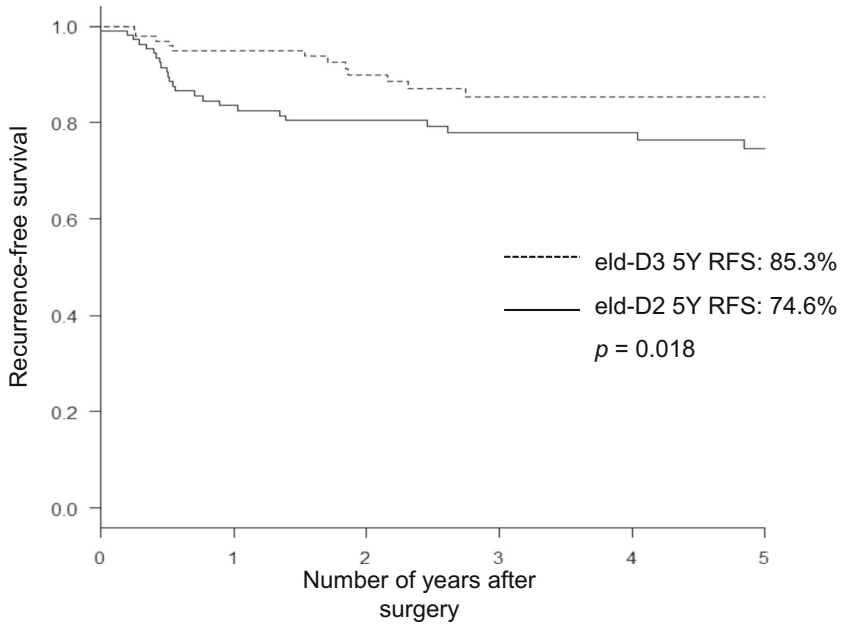

Fig. 3 Recurrence-free survival rates in the eld-D3 and eld-D2 groups. eld-D3, elderly patients who underwent D3 LND; eld-D2, elderly patients who underwent D2 LND; 5Y RFS, 5-year recurrence-free survival

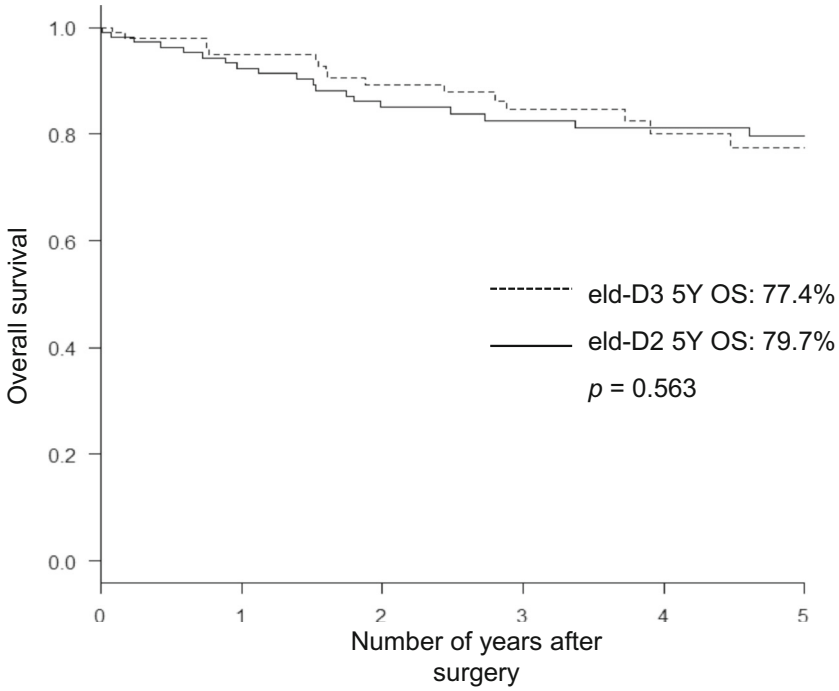

Fig. 4 Overall survival rates in the eld-D3 and eld-D2 groups. eld-D3, elderly patients who underwent D3 LND; eld-D2, elderly patients who underwent D2 LND; 5Y OS, 5-year overall survival

Results

Patient characteristics

Of the 1008 patients identified, 630 were excluded because they did not achieve curative resection ($n = 53$) and were younger than 75 years old ($n = 577$). Propensity matching was then performed for the remaining 378 patients. Finally, 232 matched patients were divided into two groups according to the LND performed: the elderly D3 LND group (eld-D3) and the elderly D2 LND (eld-D2) group (Fig. 1). The characteristics of the patients who underwent curative surgery for pathological stages II and III colon cancer according to the type of LND performed are presented in Table 1. There were no significant differences between the two groups in terms of age, sex, body mass index, ASA classification, tumor location, tumor diameter, surgical approach, pathological stage, and adjuvant chemotherapy. The median follow-up period of the matched patients was 40.7 months.

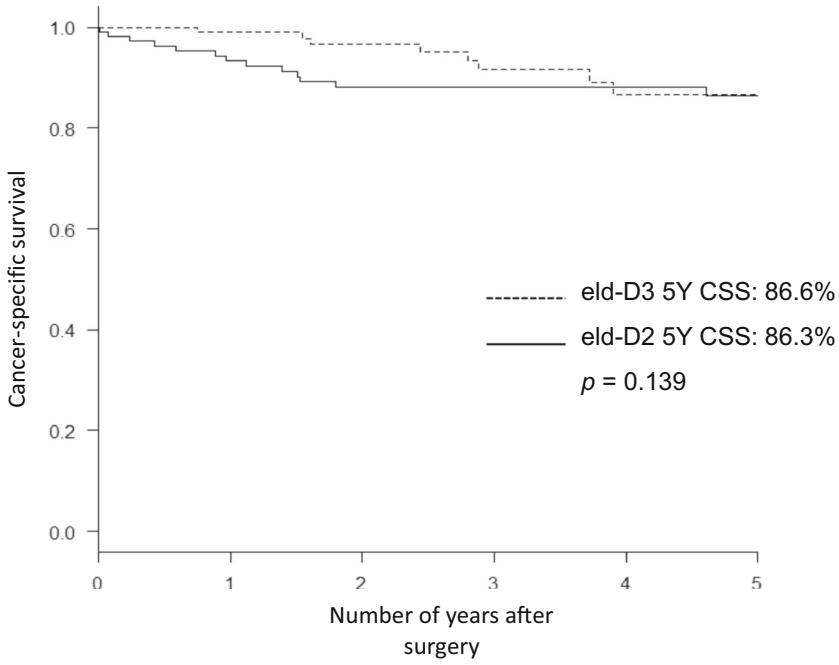

Fig. 5 Cancer-specific survival rates in the eld-D3 and eld-D2 groups. eld-D3, elderly patients who underwent D3 LND; eld-D2, elderly patients who underwent D2 LND; 5Y CSS, 5-year cancer-specific survival

Table 3 Site of recurrence ($n = 44$)

	eld-D3 ($n = 15$)	eld-D2 ($n = 29$)	p value
Liver	4 (26.6%)	14 (48.2%)	0.49
Lung	4 (26.6%)	14 (48.2%)	1.00
Peritoneum	4 (26.6%)	4 (13.7%)	0.21
Para-aortic lymph node	3 (20.0%)	1 (3.4%)	0.72
Local	0 (0.0%)	4 (13.7%)	0.29
Others	1 (6.6%)	3 (10.3%)	1.00

Short-term outcomes

Table 2 summarizes the short-term outcomes of the patients. The operation time was approximately 20 min longer in the eld-D3 group than that in the eld-D2 group (162 vs. 140 min, $p = 0.001$). The amount of blood loss was similar between the two groups (98 ml vs. 100 ml, $p = 0.30$). Moreover, the incidence of postoperative complication was almost identical between the two groups (20.6% vs. 19.8%, $p = 1.00$). As regards postoperative complications, there was no specific trend between the two groups. Although the mortality rate was not significantly different, two patients in the eld-D3 group died due to non-surgical complications (pneumonia and brain infarction). Meanwhile, the number of harvested lymph nodes was significantly higher in the eld-D3 group than that in the eld-D2 group (20 vs. 14, $p = 0.000003$).

Survival and recurrence

Throughout the follow-up period, 15 patients (12.9%) and 29 (25.0%) patients in the eld-D3 group and eld-D2 group developed recurrence, respectively. The result of the RFS analysis were favorable in the eld-D3 group with significant difference (5-year RFS: 85.3% vs. 74.6%, $p = 0.01$) (Fig. 3). However, both the OS (5-year OS: 77.4% vs. 79.7%, $p = 0.56$) (Fig. 4) and CSS (5-year CSS: 86.6% vs. 86.3%, $p = 0.13$) (Fig. 5) were not significantly different between the two groups.

During the study period, 10 of the 15 (66.6%) patients in the eld-D3 group and 16 of the 29 (55.1%) patients in the eld-D2 group who developed recurrence died due to progression of primary disease. Comparison of the distribution of the recurrent sites showed similarity between the two groups (Table 3). The major recurrence sites were the liver, lung, and peritoneum in the eld-D3 group, while they were the liver and lung in the eld-D2 group. Consequently, a comparison of treatment after recurrence in the two groups showed that the rate of patients who received any treatment after recurrence was almost similar (Table 4). Meanwhile, the resection rate for metastasis was relatively higher in the eld-D2 group than that in the eld-D3 group, although the difference was not significant.

Table 4 Treatment after recurrence ($n = 44$)

	eld-D3 ($n = 15$)	eld-D2 ($n = 29$)	p value
Any treatment after recurrence, n (%)	7 (46.6%)	14 (48.2%)	1.00
Resection, n (%)	2 (13.3%)	9 (31.0%)	0.26
Chemotherapy, n (%)	5 (33.3%)	5 (17.2%)	0.27

Discussion and conclusion

The favorable oncological impact of extended D3 LND after colon cancer surgery has been described previously [14–16]. There are two possible explanations for the oncological merit of D3 LND. First is the lower risk of primary lymph node metastasis in left-sided colon cancers. A recent systematic review reported that the incidence of detectable primary lymph node metastases for right-sided colon cancers varies between 1 and 22%, while it is < 12% for left-sided colon cancers [17]. In addition, there is a risk of undetectable micro-metastasis around the MLNs, which is reported to be associated with tumor recurrence [18, 19]. Theoretically, if patients with primary lymph node metastasis undergo D3 LND, they could achieve curative resection. Previous studies have reported that the long-term survival rate of these patients reached nearly 40% [14, 15]. However, some researchers argue that if the primary lymph nodes are metastatic, then systemic metastasis already occurs [20]. However, the results of the present study indicate that there is a chance for cure in the patients with primary lymph node metastasis. Second, the retrieved lymph nodes were reported to be larger in D3 LND than those in D2 LND [14]. Retrieving several lymph nodes is known to improve patient survival in stage II [2] and stage III [1] colon cancer because upstaging occurs when more lymph nodes are examined; thus, adequate adjuvant chemotherapy can be performed [21].

In Western countries, the counterpart of extended LND is CME with CVL, which was initially introduced by Hohenberger et al. [22] in the late 2000s. In general, the primary goal of CME with CVL is mobilization of the bowel via dissection along the anatomical planes to obtain negative circumferential resection margin, accompanied with the root ligation of the feeding vessels for adequate LND. This makes it almost identical to D3 LND. A recent study showed that this technique improved specimen quality [23], and CME with CVL is now associated with better oncological outcome after primary colon cancer surgery [4].

Meanwhile, extended LND has also been associated with more non-surgical complications, such as pneumonia compared with conventional resection for colonic cancer [24]. A questionnaire study of JSCCR revealed that member institutions often used the extended LND regardless of the patient

age [25]. However, elderly patients are generally frail and are at higher risk for postoperative complications, such as pneumonia, compared with young patients [5]. In addition, whether the oncological merit of D3 LND is also applicable to the elderly patients remains unclear. As such, the indication of D3 LND for elderly patients has to be carefully discussed. To the best of our knowledge, this is the first comparative matched study investigating the clinical impact of D3 LND focusing only on elderly patients.

Our result showed that the operation time was longer in the eld-D3 group by approximately 20 min, although the rate of postoperative complications and duration of hospital stay were similar. The postoperative complication rate in the eld-D3 group was 20.6%, which was similar compared with that previously reported for elderly patients after colon cancer surgery [26, 27].

In terms of non-surgical complications, no significant difference was noted between the two groups. A previous study revealed that elderly patients are more susceptible to pneumonia [28], and the most common non-surgical complication in both groups in the present study was pneumonia. Notably, two fatal non-surgical complications that led to death occurred in the eld-D3 group, namely, pneumonia and brain infarction. By contrast, such complications did not occur in the eld-D2 group. Although mortality was not significantly different between the two groups, the longer operation time in the eld-D3 group could have adversely affected these two patients. The median postoperative hospital stay in the eld-D3 and eld-D2 groups was 14 and 15 days, respectively, which was acceptable for major abdominal surgery. When considering our short-term result, it should be noted that Japanese surgeons generally have sufficient experience regarding D3 LND technique, which has been traditionally recommended by the JSCCR Guidelines for the Treatment of Colorectal Cancer [3]. Apparently, the performance of this extended procedure for elderly patients requires surgeons to be sufficiently experienced.

The oncological outcome was the main outcome of interest of this study. Our result clearly showed that D3 LND improved RFS (85.3% vs. 74.6%, $p = 0.018$), indicating that D3 LND had better capability to prevent relapse after primary resection even in elderly patients.

By contrast, the OS and CSS curves were similar in both groups. There are several possible explanations for this discrepancy. First, because our prognostic data after recurrence are immature, analysis on OS and CSS have only limited value. Hospitals B and C often refer patients to other hospitals after recurrence; thus, our data included many censored data after recurrence. This is the main reason for setting the RFS as the main outcome of interest in this study. Second, the treatment after recurrence differed between the two groups; the resection rate for recurrent cancer was relatively higher in the eld-D2 group than that in the eld-D3 group (13.3% vs 31.0%, $p = 0.264$), although the difference was not significant. The cause for this difference is difficult to explain. However, our findings support that D3 LND improves the RFS in the elderly patients, while it is impossible to make any conclusions on OS and CSS from our data because of the abovementioned reasons.

The limitations of the present study should be considered when interpreting the results. The main limitation is the selection bias caused from its retrospective, non-randomized design. The eld-D3 group could have had more favorable clinical characteristics. However, the propensity matching method allowed a balanced cohort and result. The present study is also limited by the small sample size. We only analyzed data from 232 elderly patients recruited from three teaching hospitals at a major city in Japan. Further prospective investigations with larger sample size are needed to confirm our results. However, despite these limitations, our finding was significant for establishing the optimal surgical strategy for elderly patients with colon cancer.

In conclusion, the present study provides evidence that D3 LND resection for elderly patients with pathological stages II–III colon cancer improves RFS and yields similar short-term outcomes compared with D2 LND. Further investigation is needed to clarify the impact of D3 LND on OS and CSS.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Research involving human participants All study protocols were approved by the Yokohama City University Institutional Review Board (Approval No. 170700003).

Informed consent Informed consent was waived owing to the retrospective nature of the study. The details of the study protocol were provided to patients through a notice board in the hospital and were also published on the hospital websites.

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