



Optimal extent of central lymphadenectomy for right-sided colon cancers: is lymphadenectomy beyond the superior mesenteric vein meaningful?

Kota Sahara¹ · Jun Watanabe² · Atsushi Ishibe¹ · Koki Goto² · Shogo Takei² · Yusuke Suwa² · Hirokazu Suwa³ · Mitsuyoshi Ota⁴ · Chikara Kunisaki² · Itaru Endo¹

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Abstract

Purpose The objective of the current study was to assess the therapeutic benefit of lymphadenectomy according to the extent of lymphadenectomy.

Methods Patients undergoing colectomy for right-sided colon cancer were identified. Distribution of lymph node metastases (DLNM) of 1, 2 and 3 were defined as lymph node metastasis (LNM) in the pericolic nodes, the intermediate nodes and the front of the SMV near the origin of the major artery, respectively. The therapeutic index (TI) was calculated based on the frequency of LNM and the 5 year overall survival (OS) rate of patients with LNM.

Results Among 344 patients who met the inclusion criteria, roughly half had LNM ($n = 150$, 43.7%). While 107 (31.1%) and 30 (8.7%) patients had DLNM1 and DLNM2, respectively, only 13 patients (3.8%) were defined as DLNM3. However, there was no significant difference in 5 year OS by DLNM (DLNM1 71.1%, DLNM2 78.7%, DLNM3 50.4%, $p = 0.61$). Overall, the TI of lymphadenectomy for D3 area was approximately 1/10 of the TI for D1 (1.9 vs.22.1), given the low frequency of LNM (3.8%) and poor 5 year OS of patients with LNM (50.4%). This trend was consistent irrespective of primary tumor locations.

Conclusion The survival benefit from central lymphadenectomy namely D3 was low among patients with right-sided colon cancers.

Keywords Complete mesocolic excision · Central vascular ligation · Therapeutic index · Colon cancer · Survival

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✉ Jun Watanabe
nabe-jun@comet.ocn.ne.jp

¹ Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan

² Department of Surgery, Gastroenterological Center, University Medical Center, Yokohama, Japan

³ Department of Surgery, Yokosuka Kyosai Hospital, Yokosuka, Japan

⁴ Department of Surgery, Yokohama City Minato Red Cross Hospital, Yokohama, Japan

Introduction

Since total mesorectal excision (TME) in the surgical treatment of rectal cancer has improved oncological outcomes [1–3], several studies have reported complete mesocolic excision (CME) with central vascular ligation (CVL) following the same principles of TME surgery [4,5]. The principles of CME are the removal of all lymphatic, vascular and neural tissue in the drainage area of the tumor in a complete mesocolic envelope with intact mesentery, peritoneum and encasing fascia [6]. As with TME, the successful outcomes have been reported after CME with CVL for right-sided colon cancers [7]. In particular, West et al. reported that CME was associated with more mesocolic plane resection and higher number of lymph nodes (LNs) examined, which might have contributed to a better 5 year survival than with standard excisions [4].

However, the optimal extent of CVL still remains controversial. Specifically, Kanemitsu et al. suggested D3

lymphadenectomy extended to the left edge of the superior mesenteric artery (SMA) for right-sided colon cancers using the no-touch isolation technique [8]. A separate study using the largest Japanese cohort noted that D3 lymphadenectomy was associated with a better overall survival (OS) than D2 lymphadenectomy, even after adjusting for confounders by the propensity score matching method [9]. Bertelsen et al., conversely, concluded that there was no theoretical explanation supporting a better oncological outcome after extended lymph node dissection for colon cancers in a systematic review [10]. To this end, there has been increasing interest in the optimal extent of central lymphadenectomy and its therapeutic value for right-sided colon cancers.

The therapeutic index is a metric for evaluating the survival benefit of lymphadenectomy for patients undergoing surgery for gastroenterological cancers. This value is based on the rationale that lymphadenectomy may be most effective among patients with a high estimated frequency of LNM, as well as individuals who are most likely to gain a survival benefit from the ascertainment of nodal status information. This concept has recently been applied to patients with gastric [11,12] and colorectal cancers [13] as well as hepatopancreatobiliary malignancies [14–16]. Tokunaga et al. evaluated the therapeutic index for each LN station to determine whether or not to retrieve posterior pancreatic head LNs for advanced gastric cancer, with the results incorporated into the Japanese Classification of Gastric Carcinoma guidelines [17,18].

Given the above, the present study assessed the therapeutic benefit of lymphadenectomy by LN area (i.e. D1, D2 and D3) among patients with right-sided colon cancers.

Methods

Study population

Patients undergoing colectomy and extended (D3) lymphadenectomy for Stage 1–3 right-sided colon cancer from 1992 to 2012 were identified at two tertiary institutions in Japan: Yokohama City University Graduate School of Medicine and Yokohama City University Medical Center. All patients included in the study were histologically diagnosed with colon cancer and underwent ileocecal resection (ICR) or right hemi-colectomy (RHC). Patients with multiple primary tumors, as well as individuals with T1 tumor, distant metastatic disease and microscopically positive surgical margins (i.e. R1 resection), were excluded from the analysis. Transvers colon cancers were only included those at the hepatic flexure. The study was approved by the Institutional Review Board of both participating institutions before the study was initiated. Due to the retrospective nature of the study, written

informed consent was not obtained. We used an opt-out approach to disclose the study information.

Patient demographic and clinicopathological data included the age, sex, body mass index (BMI), tumor location and size, surgical procedure and approach, T/N Stage, number of LN evaluated and metastasis, distribution of LN metastasis (LNM), tumor grade, lymph-vascular and perineural invasion as well as adjuvant chemotherapy.

Surgical procedure for right-sided colon cancers

Laparoscopic colectomy was introduced in September 2000 at our institutions. Although laparoscopic right-sided colectomy differs from the open approach in terms of mobilization (e.g. lateral or medial approach), the concepts are the same in the performance of dissection between the mesenteric plane and parietal fascia and the removal of the mesentery within a complete envelope of mesenteric fascia and visceral peritoneum that contains all LNs draining the tumor. As Fig. 1 shows, our central lymphadenectomy extends to the left edge of the superior mesenteric vein (SMV) and not to the SMA. The major veins, including the ileocolic, right colic and middle colic, are ligated and cut at the level of their root, only if those exist in the mesentery within 10 cm from the tumor. In the same manner, major arteries, such

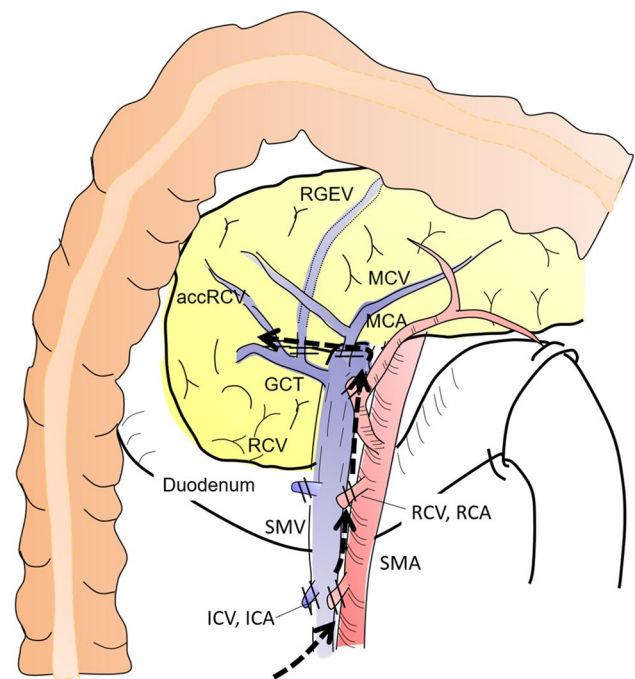


Fig. 1 A surgical schematic drawing displaying the extent of central lymphadenectomy for right-sided colon cancers in this study. RGEV: right gastroepiploic vein; MCA, MCV: middle colic artery, vein; accRCV: accessory right colic vein; GCT: gastrocolic trunk; RCA, RCV: right colic artery, vein; SMA, SMV: superior mesenteric artery, vein; ICA, ICV: ileocolic artery, vein; ICV: ileocolic vein

as the ileocolic, right colic and middle colic arteries, are ligated and cut at the level of the left edge of the SMV. Lymph nodes at the front of SMV were recognized by a titanium clip that ligated the roots of major veins (i.e. ICV, RCV), when lymph nodes were dissected individually from the adipose connective tissue of the specimen after resection.

Distribution of Lymph node metastases

Distribution of LNM 1, 2 and 3 were defined as LNM in the pericolic nodes, the intermediate nodes and the main nodes, respectively [19]. DLNM3 includes metastatic lymph nodes at the root of the ICV or RCV near the ligation clip.

Therapeutic index

The therapeutic index was first proposed by Sasako et al. to assess the survival benefit of lymphadenectomy for each lymph nodal basin and factors [20]. The therapeutic index of lymphadenectomy was calculated by multiplying the incidence of LNM by the 5 year OS rate of individuals with LNM among different patient cohorts, as previously reported. For example, if the frequency of LNM was 30.0% and the 5 year OS rate of patients with LNM was 80.0% in a particular patient group, the therapeutic index was 24.0 (0.300 × 80.0). In addition, the therapeutic index was calculated among different patient groups relative to the DLNM, as well as other clinicopathological factors. According to previous studies, lymphadenectomy was considered to be meaningful when the difference in the therapeutic index was ≥ 10 between groups [11,21].

Statistical analyses

Descriptive statistics were presented as the median [interquartile range (IQR)] and frequency (%) for continuous and categorical variables, respectively. Continuous variables were compared with the Mann–Whitney U or Kruskal–Wallis tests, as appropriate. Categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate. Statistical significance was assessed at $\alpha = 0.05$ (two-tailed). The OS calculated by creating Kaplan–Meier curves and differences was evaluated using the log-rank test. The Cox regression analysis was performed to determine if DLNM3 is an independent prognostic factor of decreased OS adjusting covariates such as age, sex, and T stage. All statistical analyses were performed using the SPSS software program, version 25 (IBM Corp. Armonk, NY, USA) along with the JMP statistical software package, version 15 (SAS Institute Inc., Cary, NC, USA).

Results

Patient's characteristics

A total of 344 patients met the inclusion criteria and were included in the final analytic cohort. The median age was 71 (IQR 62–78) years old, and most patients were female ($n = 176$, 51.1%). The median BMI and CEA were 21.7 (IQR 19.4–24.0) and 3.1 (IQR 1.9–7.6), respectively; the most common primary site was the ascending colon ($n = 221$, 64.2%). A majority of patients underwent RHC ($n = 292$, 84.9%), open colectomy ($n = 222$, 64.5%), had T3 tumor ($n = 230$, 66.9%) and had no LNM ($n = 194$, 56.4%). Of note, while 107 (31.1%) and 30 (8.7%) patients had DLNM1 and DLNM2, respectively, only 13 patients (3.8%) had DLNM3. The median number of LNs evaluated and metastases were 29 (IQR 22–40) and 0 (0–2), respectively. Roughly half of all patients had lymphatic invasion ($n = 167$, 48.8%) and vascular invasion ($n = 186$, 54.4%). One-third of the entire cohort received adjuvant chemotherapy ($n = 71$, 34.6%) (Table 1).

Impact of the DLNM on the survival

In a subgroup of patients with LNM ($n = 150$), patients with DLNM2 and 3 had higher proportions of T4 tumor (DLNM1 21.5% vs. DLNM2 46.7% vs. DLNM3 46.2%, $p = 0.031$) and N2 tumors (DLNM1 13.1% vs. DLNM2 70.0% vs. DLNM3 69.2%, $p < 0.001$) than those with DLNM1. Similarly, a higher proportion of patients with vascular invasion was noted in the DLNM2 and 3 groups than in the DLNM1 group (DLNM1 58.9% vs. DLNM2 73.3% vs. DLNM3 100.0%, $p = 0.008$) (Table 2). During the median follow-up period of 67.5 months (IQR 54.8–93.9), while there was no significant difference in the 5 year OS by DLNM1–3 (DLNM1 71.1%, DLNM2 78.7%, DLNM3 50.4%, $p = 0.61$) (Fig. 2a), N Stage was able to discriminate the 5 year OS well (N0 86.6%, N1 76.2%, N2 55.2%, $p < 0.001$) (Fig. 2b). According to a multivariable analysis after adjusting covariates including age, sex, and T stage, LND3 was not associated with a decreased OS (HR 1.21; 95% CI 0.51–2.88, $p = 0.66$).

As for adjuvant chemotherapy, among 84 patients with LNM and data on adjuvant chemotherapy, 64.4% of patients in DLNM1 ($n = 38$) received adjuvant chemotherapy, while 76.0% in DLNM2 or 3 ($n = 19$) ($p = 0.44$). According to a bivariate analysis, Adjuvant chemotherapy was not associated with prolonged OS in DLNM1 (HR 0.43; 95% CI 0.15–1.22, $p = 0.11$) or DLNM2/3 (HR 0.80; 95% CI 0.16–3.93, $p = 0.79$).

Table 1 Demographics and patient characteristics in the entire cohort

Variables	Total (N=344)
Age ^a	71 (62–78)
Sex	
Male	168 (48.8%)
Female	176 (51.1%)
BMI ^a	21.7 (19.4–24.0)
CEA (UI/mL) ^a	3.1 (1.9–7.6)
Primary tumor location	
Cecum	92 (26.7%)
Ascending colon	221 (64.2%)
Transverse colon	31 (9.0%)
Type of colectomy	
ICR	52 (15.1%)
RHC	292 (84.9%)
Operative approach	
Open	222 (64.5%)
Laparoscopic	122 (35.5%)
Total operative time (min) ^a	170 (140–212)
Operative blood loss (ml) ^a	100 (27–245)
Tumor size (cm) ^a	5.0 (3.5–7.0)
T stage	
2	14 (4.1%)
3	230 (66.9%)
4	100 (29.1%)
N stage	
0	194 (56.4%)
1	106 (30.8%)
2	44 (12.8%)
Number of LN evaluated ^a	29 (22–40)
Number of LNM ^a	0 (0–2)
LND	
None	194 (56.4%)
1	107 (31.1%)
2	30 (8.7%)
3	13 (3.8%)
Grade	
Well to moderate	300 (87.2%)
Poor to undifferentiated	44 (12.8%)
Lymphatic invasion	167 (48.8%)
Vascular invasion	186 (54.4%)
Adjuvant chemotherapy	
Yes	71 (34.6%)
No	134 (65.4%)
Missing	139

^aMedian (IQR)

BMI body mass index, CEA Carcinoembryonic antigen, ICR ileocecal resection, RHC right hemicolectomy, LN lymph node, LND lymph node distribution, LNM lymph node metastasis

Therapeutic index by the DLNM and perioperative factors

Among all primary locations, the therapeutic index value of D1 lymphadenectomy was 22.1 based on a 33.1% LNM incidence and a 5 year OS of 71.1% among patients with LNM (0.331 multiplied by 71.1), whereas the therapeutic index of D2 lymphadenectomy was at least 10 points lower than that of D1 (D1 22.1 vs. D2 6.8) (Table 3) (Fig. 3). Of note, the therapeutic index was the lowest in D3 lymphadenectomy (1.9), due to the low frequency of LNM (3.8%) and poor 5 year OS of patients with LNM (50.4%). In addition, this trend was consistent among patients with primary sites at the cecum (D1 23.0 vs. D2 8.6 vs. D3 3.2) and ascending colon (D1 22.3 vs. D2 4.8 vs. D3 1.6). Among patients with transverse colon cancer, a therapeutic index difference of more than 10 was noted between D2 and D3 lymphadenectomy (D2 16.1 vs. D3 0) (Fig. 3).

Sites of recurrence after R0 resection and central lymphadenectomy

Of the 344 patients who met the inclusion criteria, after a median follow-up of 67.5 months, 81 (23.8%) developed postoperative recurrence (Table 4). Including the duplicated counts when a patient had ≥ 2 recurrence sites, the most common recurrence site was the liver ($n=36$, 10.5%), followed by the lung ($n=25$, 7.3%) and peritoneum ($n=18$, 5.2%). Of note, among patients with recurrence at LNs, only two patients had para-SMA recurrence, and both LNs were located beyond the SMA (i.e. left side of SMA), indicating that the para-SMA recurrence was not derived from insufficient central lymphadenectomy (Supplemental Fig. 1). Other detailed information on patients with para-SMA recurrence are summarized in Supplemental Table 1.

Discussion

Surgery is the mainstay in the treatment of colon cancer, and the number of LNs examined is one of the most important prognostic factors. However, the optimal extent of central lymphadenectomy for right-sided colon cancer remains unclear. In fact, whether the landmark of CVL should be SMV or SMA has not yet been well standardized. To this end, the current study was important because the survival benefit of lymphadenectomy was identified for each LN area (i.e. D1, D2, and D3) based on the therapeutic index reflecting the frequency of LNM and the overall survival among subgroups who underwent lymphadenectomy. Regarding the DLNM, approximately 1 in 30 patients (3.8%) had LNM in front of the SMV. According to the calculated therapeutic index, of interest, the survival benefit of central

Table 2 Clinicopathological factors associated with the extent of lymph node metastasis among patients with lymph node metastasis ($n = 150$)

Variables	Extent of LNM			P value
	DLNM1	DLNM2	DLNM3	
Age ^a	67 (60–76)	71 (62–79)	69 (63–78)	0.43
Sex				
Male	45 (42.1%)	13 (43.3%)	7 (53.9%)	0.72
Female	62 (57.9%)	17 (57.7%)	6 (46.2%)	
CEA (UI/mL) ^a	2.9 (1.9–6.3)	3.9 (2.0–13.3)	4.2 (2.2–11.1)	0.41
Primary tumor location				
Cecum	31 (29.0%)	9 (30.0%)	5 (38.5%)	
Ascending colon	68 (63.5%)	16 (53.3%)	7 (53.9%)	
Transverse colon	8 (7.5%)	5 (16.7%)	1 (7.7%)	
Type of colectomy				
ICR	20 (18.7%)	6 (20.0%)	1 (7.7%)	0.59
RHC	87 (81.3%)	24 (80.0%)	12 (92.3%)	
Operative approach				
Open	69 (64.5%)	21 (70.0%)	9 (69.2%)	0.83
Lap	38 (35.5%)	9 (30.0%)	4 (30.8%)	
Tumor size (cm) ^a	4.8 (3.1–6.3)	6.0 (3.8–7.5)	4.4 (4.0–6.8)	0.28
T Stage				
2	10 (9.3%)	3 (10.0%)	0	0.031
3	74 (69.2%)	13 (43.3%)	7 (53.9%)	
4	23 (21.5%)	14 (46.7%)	6 (46.2%)	
N Stage				
1	93 (86.9%)	9 (30.0%)	4 (30.8%)	<0.001
2	14 (13.1%)	21 (70.0%)	9 (69.2%)	
Number of LN evaluated ^a	30 (22–41)	30 (21–45)	28 (25–40)	0.98
Grade				
Well to moderate	95 (88.8%)	26 (86.7%)	11 (84.6%)	0.88
Poor to undifferentiated	12 (11.2%)	4 (13.3%)	2 (15.4%)	
Lymphatic invasion	71 (66.4%)	25 (83.3%)	10 (76.9%)	0.17
Vascular invasion	63 (58.9%)	22 (73.3%)	13 (100.0%)	0.008

^aMedian (IQR)

DLNM distribution of lymph node metastases, CEA Carcinoembryonic antigen, ICR ileocecal resection, RHC right hemicolectomy, Lap laparoscopic LNM lymph node metastasis, LN lymph node

lymphadenectomy was almost 1/10 of that with pericolic lymphadenectomy (D3 1.9 vs. D1 22.1). Although two patients experienced local LN recurrence beyond the SMA after curative-intent colectomy, no patients developed local recurrence at the right side or in front of the SMA.

The therapeutic index was first proposed by Sasako et al. in 1995 and used to assess the survival benefit of LN dissection in the second-tier stations for advanced gastric cancers by multiplying the incidence of LNM and the 5 year OS among patients who had LNM in a particular LN station [20]. In the same manner, Ueno et al. first adapted this metric to colorectal cancer to identify subgroups likely to receive prognostic benefit from lateral pelvic node dissection for advanced lower rectal cancer [13]. Specifically, the therapeutic index for lateral dissection was calculated as 7.0, which was higher than that of lymphadenectomy in

the superior rectal artery (SRA) area (1.6) and the inferior mesenteric artery area (IMA) (0.4) [13]. This is in line with the findings of the present study showing a low therapeutic index for the D3 area with a range of 0 to 3.2 (Fig. 3). In this context, the therapeutic index is a useful metric that can inform surgeons of the survival benefit of lymphadenectomy, which is intuitively challenging to recognize.

In addition, the conclusion that central lymphadenectomy to the left edge of the SMV resulted in low survival benefit can also be used to determine whether the landmark of CVL should be the SMV or SMA. Given that the farther the LN area is from the primary tumor, the lower the LNM rate is, the therapeutic benefit of removing LNs in front of the SMA should also be poor. According to the Japanese Classification of Colorectal Carcinoma guidelines [22], although radical surgery of right colon cancer requires D3 cleaning

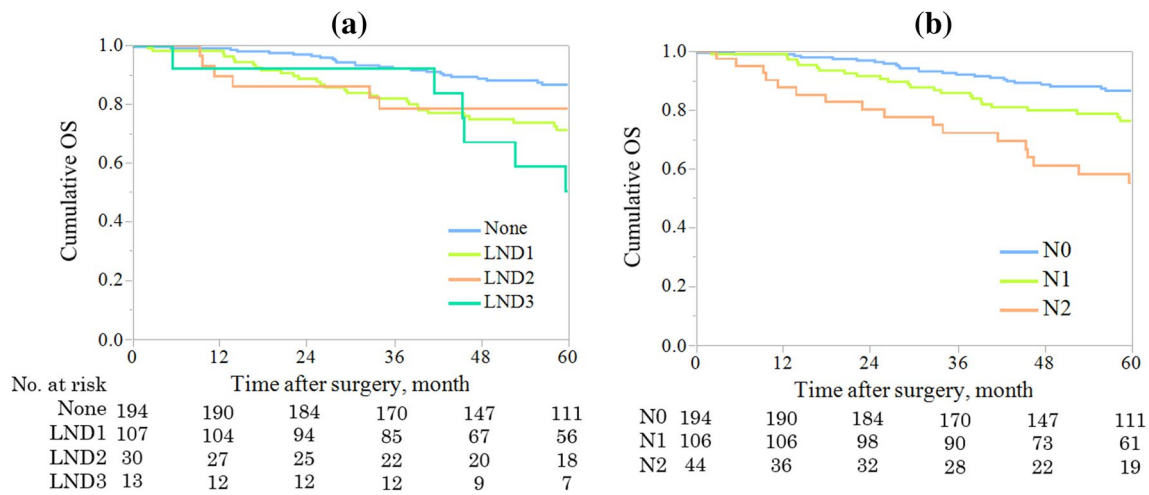


Fig. 2 The overall survivals of patients undergoing colectomy and D3 lymphadenectomy stratified by **a** Lymph node distribution and **b** N staging

Table 3 Frequency of LNM and the 5 year OS used for calculating the therapeutic index in Fig. 3

Primary location	Extent of lymphadenectomy	Frequency of LNM	5-y OS (%)
All	D1	0.311 (107/344)	71.1
	D2	0.087 (30/344)	78.7
	D3	0.038 (13/344)	50.4
Cecum	D1	0.337 (31/92)	68.3
	D2	0.098 (9/92)	87.5
	D3	0.054 (5/92)	60.0
Ascending	D1	0.308 (68/221)	72.4
	D2	0.072 (16/221)	66.7
	D3	0.032 (7/221)	50.0
Transverse	D1	0.258 (8/31)	72.9
	D2	0.161 (5/31)	100.0
	D3	0.032 (1/31)	0

LNM lymph nodes metastasis, OS overall survival

of the LN at the root of the colonic vessels, thus involving exposure of the SMA, the existing literature regarding the outcomes after lymphadenectomy beyond the SMV remains scarce [23]. Future studies are needed to clarify the impact of central lymphadenectomy extending to the SMA on the short- and long-term outcomes in the treatment of right-sided colon cancers.

Extended lymphadenectomy may play a major role in staging patients adequately as well as in removing potentially metastatic LN from an oncological perspective. Previous studies reported that the DLNM classified by the area of LNM has an important role in predicting the patient survival. Specifically, Huh et al. showed that the DLNM was an independent predictor of the survival of patients

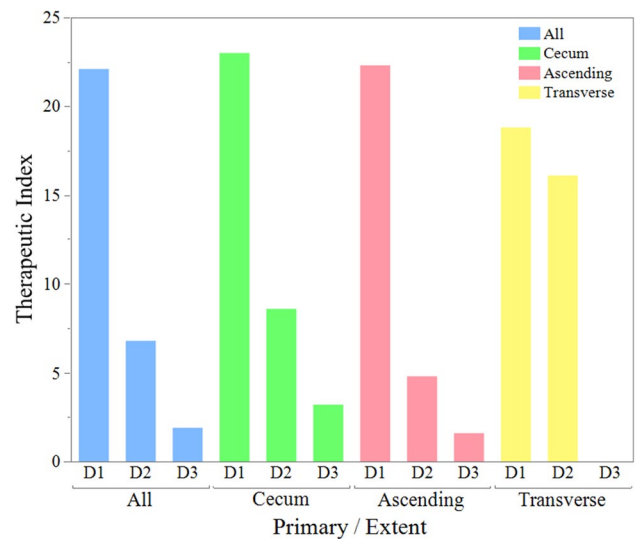


Fig. 3 Comparison of the therapeutic indexes of D1, D2, and D3 lymphadenectomy according to the primary tumor location

with sigmoid colon and rectal cancer and discriminated the 5 year OS rates well [24]. However, Kim et al. from the same group compared the prognostic significance of the number of LNMs versus the DLNM and concluded that the staging system incorporating the number of LNMs predicted the prognosis better than the DLNM [25]. Consistent with the study by Kim et al., the current study found the superiority of N staging (i.e. the number of LNMs) against the DLNM for predicting the 5 year OS of patients undergoing colectomy for right-sided colon cancers. Regarding the number of LNMs, however, a randomized clinical trial revealed that an N-positive status was more common in the D3 group than in the D2 group (46% vs. 26%), indicating the potential

Table 4 Sites of recurrence after colectomy for right-sided colon cancer

Location	N	%
Total	81	23.8
Liver	36	10.5
Lung	25	7.3
Peritonea	18	5.2
Lymph nodes	8	2.3
Para-Aorta	4	
Para-SMA	2	
Distant (mediastinum)	2	
Local	3	0.9
Others	11	3.2

SMA superior mesenteric artery

benefit of D3 lymphadenectomy on accurate staging [26]. Taken together, these findings suggest that central lymphadenectomy for right-sided may be more beneficial for adequately predicting the prognosis than the therapeutic value. However, the median number of LNs evaluated was 29 in the current study, which was more than double the number (at least 10–14 LNs) recommended by the American Joint Committee of Cancer [27]. Therefore, the extent to which D3 lymphadenectomy contributes to adequate staging still remains to be fully elucidated.

The long-term oncological effects of central lymphadenectomy should be clarified. Storli et al. noted that D3 mesenteric excision for T1/2 colon cancers was associated with a better OS and disease-free survival after adjusting for confounders, including the age and T stage [28]. Similarly, a retrospective study using a Japanese cohort of 3425 patients compared the OS of patients with T3/4 colon cancers undergoing D2 lymphadenectomy versus D3. The propensity score-matched analysis revealed that D3 lymphadenectomy was associated with a better OS as well as a higher number of LNs examined [9]. Nevertheless, the conclusions from these studies have been limited due to their retrospective nature and considerable number of confounders that were not adjusted for at the time of the study. For instance, in the study by Kotake et al., the D2 lymphadenectomy group had a higher proportion of patients with LNM even after PSM ($n = 1,389$, 40.6% vs. $n = 1,290$, 37.7%, $p = 0.014$), which presumably affected the difference in the OS. Furthermore, neither study accounted for advances in surgical techniques and multidisciplinary treatments over time, such as minimally invasive surgery and chemotherapy regimens.

Several limitations associated with the present study warrant mention. Due to the retrospective design, the current study was subject to information and selection biases. Furthermore, the utilized data were derived from two contributing hospitals, and the conclusions may not be generalizable

to patients treated at other institutions. In addition, due to the nature of the metric, it was not feasible to determine the cut-off value of the therapeutic index associated with a significant benefit of DLNM for a certain patient group. Finally, given that the therapeutic index was based on the frequency of LNM and the 5 year OS of a certain patient group, the therapeutic value may not be robust among small subgroups, such as patients with transverse colon cancer. In addition, despite the failure to demonstrate the impact of DLNM on OS in the current study, it might be due to a small number of the cohorts including DLNM2 or 3. Future studies are called for to validate the results on the therapeutic index using a larger number of patients.

In conclusion, based on the metric of the therapeutic index, the survival benefit from central lymphadenectomy namely D3 was low compared with D1 and D2 lymphadenectomy among patients with right-sided colon cancers. Although several studies have proposed central lymphadenectomy beyond the SMV, it may nevertheless not be beneficial for the survival.

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Compliance with ethical standards

Conflict of interest none.

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