



OPEN Re-examining the optimal extent of lymph node dissection for colon cancer using the lymphadenectomy index

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The optimal extent of lymph node dissection in colon cancer surgery is specified in guidelines based on the results of past analyses. However, with advances in surgical techniques and multidisciplinary treatments, the clinical significance of dissecting each lymph node may change. In this study, we re-examined the optimal dissection range in each colon cancer localization. We retrospectively analyzed 788 cases of T1–T4 colon cancer who underwent radical resection between 2008 and 2018 at our hospital, and evaluated the Lymphadenectomy Index. No metastases to the main lymph node were found in T1 cases. In T2 cases, dissection effect to the main lymph node were observed in cases with tumors localized in the ascending colon and left side of the transverse colon. For tumors localized in the cecum, dissection was effective for lymph nodes in nodal station 213, in the right side of the transverse colon in station 211, in the descending colon in station 221, and in the sigmoid colon in station 231. These lymph nodes could have been considered out of scope for dissection if the Japanese guidelines were followed. In these cases, the extent of lymph node dissection should be carefully considered on a case-by-case basis.

Keywords Colon cancer, Lymph node dissection, The lymphadenectomy index

Abbreviations

A	Ascending colon
C	Cecum
CME	Complete mesocolic excision
CT	Computed tomography
CVL	Central vascular ligation
D	Descending colon
ICG	Indocyanine green
IMV	Inferior mesenteric vein
JSCCR	The Japanese Society for Cancer of the Colon and Rectum
S	Sigmoid colon
SMV	Superior mesenteric vein
Tl	Left side of the transverse colon
Tm	Middle of the transverse colon
Tr	Right side of the transverse colon

Lymph node metastatic status is a crucial factor affecting prognosis in colon cancer¹. Therefore, radical surgery involving appropriate lymph node dissection is essential to improving prognosis². Although many studies have examined the extent of lymph node dissection^{3,4}, most Japanese centers generally determine the extent of dissection according to tumor localization and depth of cancer according to the ninth edition of the

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Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma and the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines, 2022, for treating colorectal cancers^{5,6}. In particular, Japanese D3 which involves dissecting to the main lymph node is often indicated for advanced cancers. However, the significance of the extent of lymph node dissection has changed with improved surgical techniques and advances in multidisciplinary treatments⁷⁻⁹. As such, the optimal extent of dissection remains unclear¹⁰.

The Lymphadenectomy Index, calculated by multiplying the frequency of metastasis in each lymph node by the 5-year survival rate of metastasis-positive cases, is often used to indicate the effectiveness of lymph node dissection in cancer surgery¹¹. In this method, survival benefits are evaluated without any staging of lymph node metastasis. Although it is used in various types of cancer surgery, including gastric, esophageal, and pancreatic cancers¹¹⁻¹³, few reports have evaluated the index in colon cancer surgery.

In this study, we re-examined the optimal dissection extent for each tumor location in colon cancer using the Lymphadenectomy Index. We also evaluated the validity of the range in lymphadenectomy recommended by the JSCCR guidelines for treating colorectal cancer.

Methods

Patients

Patients who underwent radical resection for colon cancer at Kyoto Prefectural University of Medicine Hospital between April 2008 and April 2018 were included in this study. Surgery was performed by laparotomy or laparoscopy. Patients who underwent additional surgery after endoscopic treatment were counted as T1 and included in the study. Patients with distant metastases were excluded because they were considered to have a significant impact on the 5-year survival rate. Finally, 788 cases of T1-4 colon cancer without distant metastasis were retrospectively analyzed in this study.

Informed consent was obtained from all subjects and/or their legal guardians, and research was performed in accordance with relevant guidelines. The study was approved by the institutional review board of the Kyoto Prefectural University of Medicine (Approval Number: ERB-C-1178).

Definitions and preoperative diagnosis

The colon was divided into the cecum (C), ascending colon (A), right side of the transverse colon (Tr), middle of the transverse colon (Tm), left side of the transverse colon (Tl), descending colon (D), and sigmoid colon (S) to describe tumor location. The boundaries of each division were set at the superior border of the Bauhin valve, hepatic curvature, right 1/3 of the transverse colon, left 1/3 of the transverse colon, splenic curvature, and left superior anterior iliac spine; these were evaluated by computed tomography (CT) scan or colonography. Tumor depth was also evaluated by colonoscopy or CT scan and classified into T1 (submucosal), T2 (intrinsic muscle layer), T3 (subchorionic), and T4 (extra-serosal invasion) according to the TNM classification system in the Union for International Cancer Control (8th edition).

Lymph node locations and station numbers were determined based on the lymph node map described in the ninth edition of the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (Fig. 1)⁵. In accordance with the same codes, numbers 203, 213, 223, and 253 were defined as the main lymph nodes, numbers 202, 212, 222, 232, 242, and 252 were intermediate lymph nodes, and numbers 201, 211, 221, 231, 241, and 251 were para-intestinal lymph nodes.

The extent of lymph node dissection was classified as Japanese D1, D2, or D3. Dissection extent was to para-intestinal lymph nodes in D1, to intermediate lymph nodes in D2, and to main lymph nodes in D3. In D3 dissections for right hemicolectomy, lymph nodes up to the left margin of the superior mesenteric vein (SMV) were dissected. In D3 dissections for left hemicolectomy of the colon, lymph nodes around the root of the inferior mesenteric vein (IMV) were dissected.

Operative procedures

The extent of bowel resection and lymph node dissection was reviewed by our surgical team, comprising experts in colorectal cancer treatment based on the JSCCR guidelines for the treatment of colorectal cancer. Namely, dissection was performed to the intermediate lymph node in T1 cases, to the main lymph node in T3 and T4 cases, and to the intermediate or main lymph node in T2 cases. All surgeries were performed by surgeons with extensive experience in colorectal cancer surgery.

All regional lymph nodes were immediately and individually removed from the specimen immediately after excision. The removed lymph nodes were separated by station and immediately fixed in formalin for histological examination. Two independent pathologists performed the histopathologic diagnosis.

Calculation of the lymphadenectomy index

We investigated the rationale for the extent of lymph node dissection by analyzing the relationship between the metastasis at each lymph node station and the prognosis. The frequency of metastasis at each station by dividing the number of patients with metastasis at that station by the number in whom the station was dissected. The Lymphadenectomy Index is usually calculated by multiplying the frequency of metastasis at each station by the 5-year overall survival rate of patients with metastasis, as reported by Sasako et al.¹¹. However, due to recent improvements in post-relapse survival rates resulting from advances in chemotherapy, the 5-year overall survival rate alone does not accurately assess dissection effectiveness¹⁴. Therefore, we calculated the Lymphadenectomy Index by multiplying the frequency of metastasis at each station by the 5-year recurrence-free survival rate of patients with metastasis.

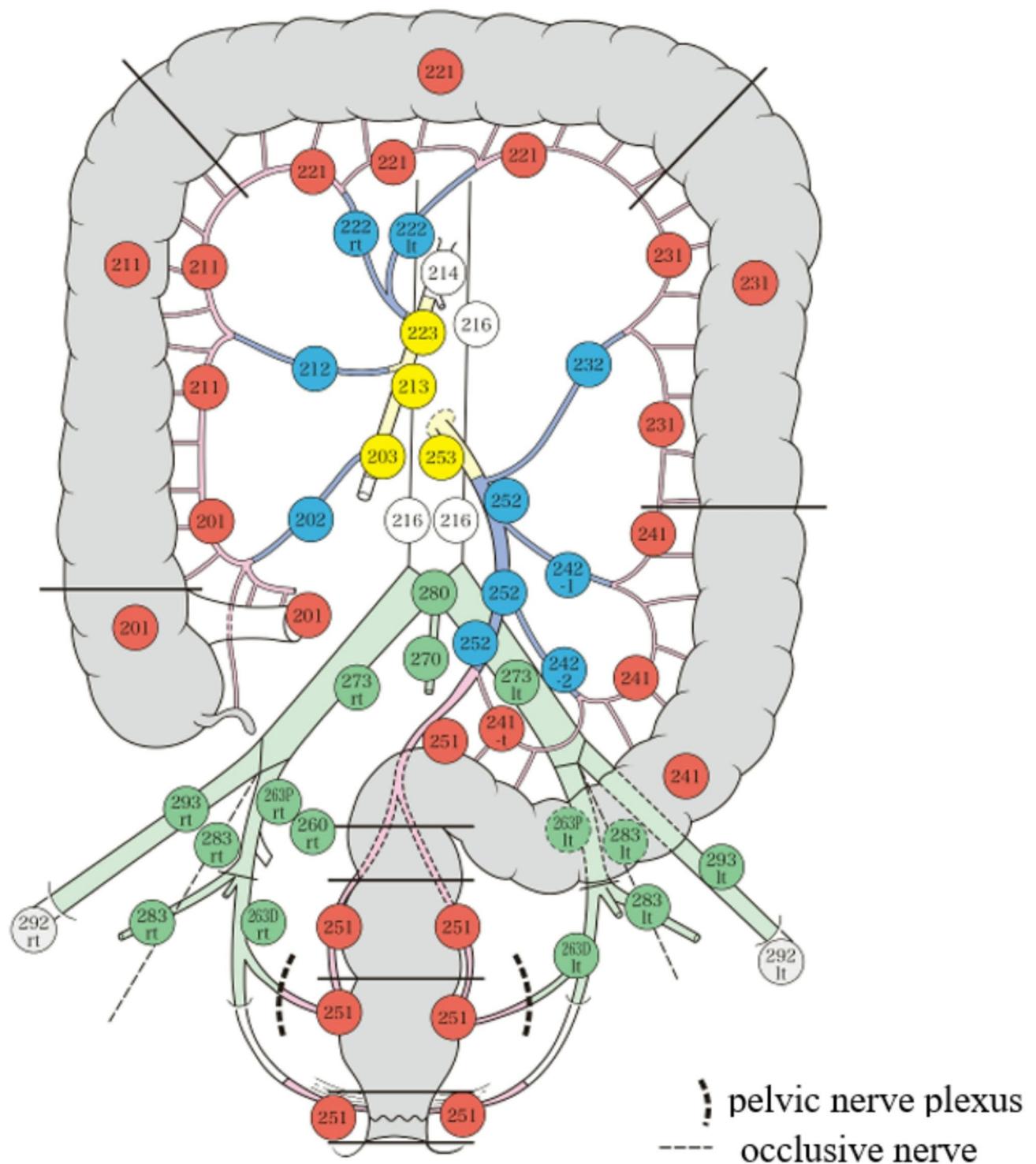


Fig. 1. Lymph node locations and numbers (the nodal station)⁵.

Statistical analysis

Prognostic curves were generated using the Kaplan–Meier method, and the log-rank test was performed to evaluate intergroup differences. The significance of differences was set at $p < 0.05$ derived from two-tailed tests. Statistical analyses were performed using EZR, which is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Patient backgrounds and tumor characteristics

The clinical and surgical characteristics of the 788 cases in this study are shown in Table 1. There were slightly more men than women, and the median age was 69 years (21–94 years). Classified by histological type, 571 cases were well-differentiated tubular adenocarcinomas, 103 were moderately differentiated tubular adenocarcinomas, 21 were poorly differentiated tubular adenocarcinomas, 16 were papillary adenocarcinomas, 34 were mucinous adenocarcinoma, and 2 were signet-ring cell carcinomas. Laparoscopic surgery was performed in 671 cases. Nineteen cases were converted from laparoscopic to open surgery because of bleeding, obesity, adhesions, or invasion of other organs. Adjuvant chemotherapy was administered in 205 cases. In total, 16,276 lymph nodes were dissected, of which 640 (3.93%) had metastasis.

Frequency of lymph node metastasis by tumor depth

There were 261 cases with a tumor depth in T1, 111 in T2, 242 in T3, and 174 in T4. Table 2 shows the frequency of metastasis to the main, intermediate, and para-intestinal lymph nodes by depth. No metastases were found in T1 cases of the main lymph nodes, but metastasis was observed in other depths (T2: 3.85%, T3: 7.19%, T4: 6.7%). The frequency of metastasis tended to increase with increasing depth but remained almost the same for T3 and T4.

	Cases (%)
Sex	
Male	434 (55.1%)
Female	354 (44.9%)
Age median / range	69/21–94 years
Tumor site	
Cecum (C)	94 (11.9%)
Ascending colon (A)	165 (20.9%)
Right side of the transverse colon (Tr)	53 (6.7%)
Middle of the transverse colon (Tm)	43 (5.5%)
Left side of the transverse colon (Tl)	36 (4.6%)
Descending colon (D)	55 (7.0%)
Sigmoid colon (S)	338 (42.8%)
Tumor depth	
cT1	261 (33.1%)
cT2	111 (14.0%)
cT3	242 (30.7%)
cT4	174 (22.1%)
Lymph node metastasis	
cN0	565 (71.7%)
cN1	164 (20.8%)
cN2	40 (5.1%)
cN3	19 (2.4%)
Histological type	
Well-differentiated tubular adenocarcinoma	571 (72.5%)
Moderately differentiated tubular adenocarcinoma	103 (13.1%)
Poorly differentiated tubular adenocarcinoma	21 (2.7%)
Papillary adenocarcinoma	16 (2.0%)
Mucinous adenocarcinoma	34 (4.3%)
Signet-ring cell carcinoma	2 (0.3%)
Unidentified	41 (5.2%)
Surgical approach	
Laparoscopy	671 (85.2%)
Convert to laparotomy	19 (2.4%)
Laparotomy	98 (12.4%)
Adjuvant chemotherapy	
Present	205 (26.0%)
Absent	583 (74.0%)

Table 1. Patient backgrounds and tumor characteristics (n = 788).

	Cases	Para-intestinal lymph nodes	Intermediate lymph nodes	Main lymph nodes
T1	261	5.53% (14/253)	2.17% (5/230)	0% (0/43)
T2	111	28.0% (30/107)	7.0% (7/100)	3.85% (2/52)
T3	242	36.8% (88/239)	12.6% (28/222)	7.19% (11/153)
T4	174	38.6% (66/171)	12.1% (20/165)	6.7% (8/116)

Table 2. Frequency of lymph node metastasis by depth. *The frequency of lymph node metastasis was calculated by dividing the number of patients with metastasis at that station by the number in whom the station was dissected.

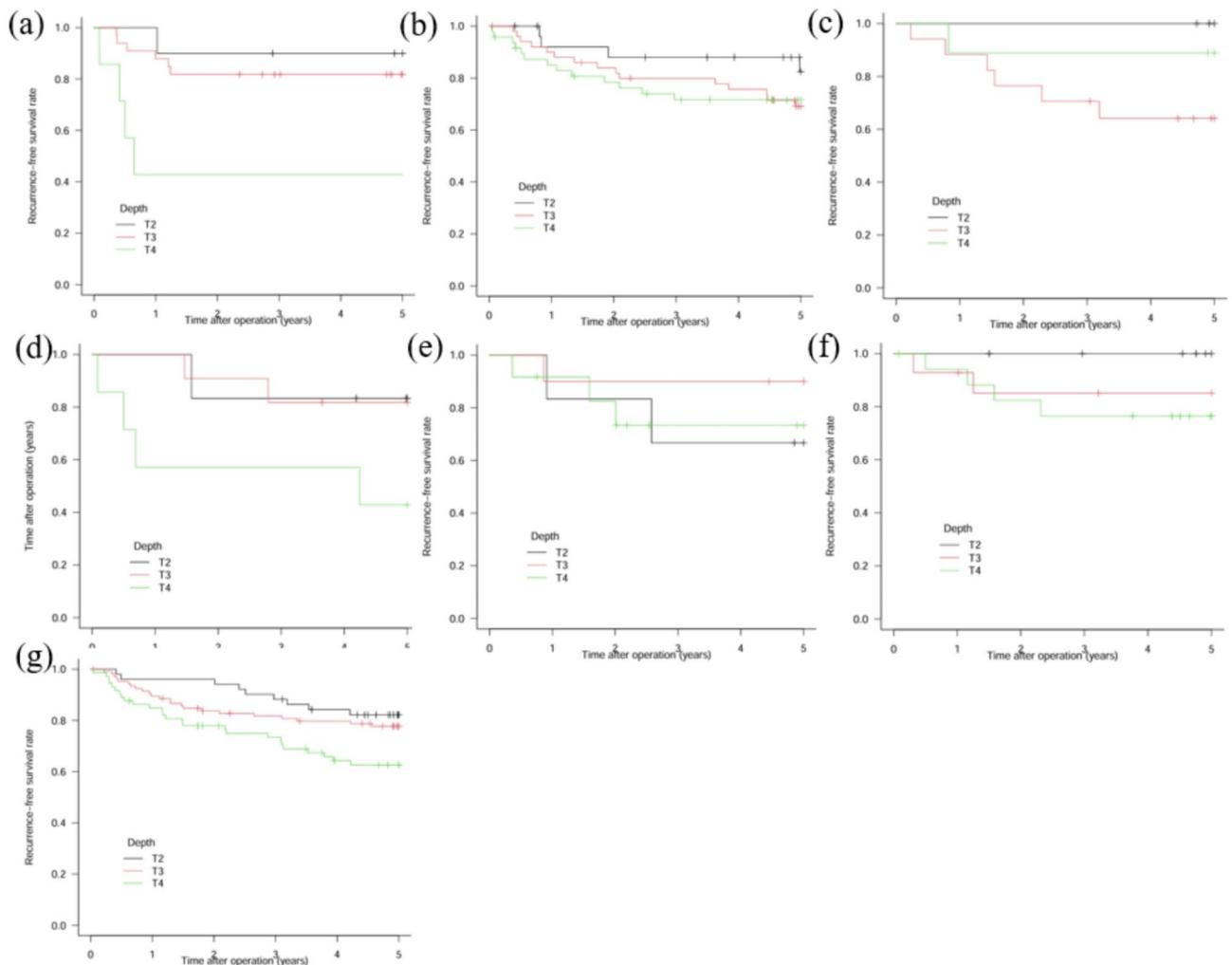


Fig. 2. Recurrence-free survival analysis classified by the localization and depth of colon cancer. (a) Cecum (n = 94), (b) Ascending colon (n = 165), (c) Right side of the transverse colon (n = 53), (d) Middle of the transverse colon (n = 43), (e) Left side of the transverse colon (n = 36), (f) descending colon (n = 55), (g) sigmoid colon (n = 338). In each localization, patients were classified into T2 cases (black line) or T3 cases (red line) or T4 cases (green line).

Recurrence-free survival analysis by tumor localization and depth

Figure 2 shows recurrence-free survival curves by each tumor localization and depth. The median survival times of T2, T3 and T4 cases were compared, and a significant difference was observed in localized C ($p = 0.000921$) and S ($p = 0.0354$).

Evaluating the lymphadenectomy index of tumors localized in the cecum and ascending colon

Table 3 shows resection margins and the Lymphadenectomy Index of localization in the C and A. In T2 cases localized in A, metastasis to the main lymph node was observed, with a Lymphadenectomy Index of 9.1. In T4

Localization	Depth	Cases	PM (mm)	DM (mm)	Nodal station															
					201	202	203	211	212	213	221	222	223							
C	T2	10	87.3	106	10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	T3	33	88.8	114.6	18.2	9.68	–	–	–	–	33.3	–	0	0	–	–	–	–	–	–
	T4	7	66.6	111	14.3	0	0	–	–	–	–	–	–	–	–	–	–	–	–	–
A	T2	27	115	92.4	16	–	9.1	–	–	–	–	9.1	16.7	–	–	–	–	–	–	–
	T3	51	109	112	20	0	2.6	8.3	–	12.5	8.7	–	–	–	–	–	–	–	–	–
	T4	48	119	109	24.4	6.82	11.8	8.7	–	9.1	0	–	–	–	–	–	–	–	–	–

Table 3. The Lymphadenectomy Index of localization in the cecum (C) and ascending colon (A). C: cecum, A: ascending colon, PM: proximal margin (average), DM: distal margin (average). *Blank spaces mean that none were dissected. “–” spaces mean that there was no metastasis in the lymph nodes dissected.

Localization	Depth	Cases	PM (mm)	DM (mm)	Nodal station																
					201	202	203	211	212	213	221	222	223	231	232	241	242	251	252	253	
Tr	T2	2	368	62.5	–	–	–	–	–	–	–	100	–	–	–	–	–	–	–	–	–
	T3	15	193	64.3	–	–	–	20	–	0	14.3	8.33	–	–	–	–	–	–	–	–	–
	T4	7	258	78.3	–	–	–	–	–	–	42.9	16.7	–	–	–	–	–	–	–	–	–
Tm	T2	7	72.5	53.3	–	–	–	–	–	–	20	–	–	–	–	–	–	–	–	–	–
	T3	13	74.1	80.0	–	–	–	–	–	–	16.7	9.1	–	–	–	–	–	–	–	–	–
	T4	9	165	104	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Tl	T2	6	79.0	108	–	–	–	–	–	–	50	33	100	–	–	–	–	–	–	–	–
	T3	10	45.6	84.1	–	–	–	–	–	–	25	–	–	16.7	–	–	–	–	–	–	–
	T4	12	80.0	147	–	–	–	–	–	–	9.1	–	–	0	–	0	–	–	–	–	–

Table 4. The Lymphadenectomy Index of localization in the right side of the transverse colon (Tr), the middle of the transverse colon (Tm), and the left side of the transverse colon (Tl). Tr: right side of the transverse colon, Tm: middle of the transverse colon, Tl: left side of the transverse colon, PM: proximal margin (average), DM: distal margin (average). *Blank spaces mean that none were dissected. “–” spaces mean that there was no metastasis in the lymph nodes dissected.

cases localized in C, the Lymphadenectomy Index of nodal stations 202 and 203 were 0. For tumors localized in C, despite the dissection effect on nodal station 213, no metastases were found in 211 or 212. In T3 cases localized in C with the right colonic artery, the Lymphadenectomy Index of nodal station 213 was 33.3.

Evaluating the lymphadenectomy index of tumors localized in the right side, middle, and left side of the transverse colon

Table 4 shows resection margins and the lymphadenectomy index of tumors localized in Tr, Tm, and Tl. In T2 cases in Tl, metastasis to the main lymph node was observed in nodal station 223, and the Lymphadenectomy Index was 100. On the other hand, for tumors localized in Tm and Tl, T3 and T4 cases showed no metastasis to the main lymph node, and no dissection effect was observed in Tr. In Tr, no metastases were found in lymph nodes along the ileocecal artery. In Tm, metastases were found only in lymph nodes along the middle colon artery. In Tl, although metastases were found at nodal station 241, no dissection effect was observed. In T3 cases of Tr localization, the Lymphadenectomy Index at nodal station 211 was 20. In T3 cases of Tl localization, the Lymphadenectomy Index at nodal station 231 was 16.7.

Evaluating the lymphadenectomy index of tumors localized in the descending colon and sigmoid colon

Table 5 shows resection margins and the Lymphadenectomy Index of tumors localized in D and S. In D, although metastases were found in lymph nodes along the inferior mesenteric artery, no dissection effect was observed. In D, T3 and T4 cases showed no metastases to the main lymph node. In T4 cases localized in D, the Lymphadenectomy Index at nodal station 221 was 20. In T2 cases localized in S, the Lymphadenectomy Index at nodal station 231 was 20.

Discussion

In this study, we re-examined the optimal dissection range in colon cancer surgery using the Lymphadenectomy Index. In T1 cases, there was no evidence of metastasis to the main lymph node, so dissection to the middle lymph node, generally called Japanese D2, seemed sufficient. This is consistent with the latest Japanese guidelines for colorectal cancer treatment. Additionally, prior study has proposed that Tn protein could serve as a molecular predictor for regional lymph node metastasis in T1 cases, potentially aiding in the development of strategies for organ preservation¹⁵. In surgery for T2-4 cases, it is important to determine whether to dissect the main lymph

Localization	Depth	Cases	PM (mm)	DM (mm)	Nodal station									
					221	222	223	231	232	241	242	251	252	253
D	T2	8	82.5	152				–	–	–	–	–	–	–
	T3	14	67.8	80.3	–	–		11.1	14.3	28.6	–	0	–	–
	T4	18	73.6	103	20	–	–	21.4	90.9	–	12.5	–	0	–
S	T2	51	106	77.0				20	0	11.1	5	25	–	–
	T3	106	73.1	60.5				–	–	9.47	4.49	19.4	5.56	3.8
	T4	73	93	79.6				0	–	17.2	3.57	10.6	0	

Table 5. The Lymphadenectomy Index of localization in the descending colon (D) and sigmoid colon (S). D: descending colon, S: sigmoid colon, PM: proximal margin (average), DM: distal margin (average). *Blank spaces mean that none were dissected. “–” spaces mean that there was no metastasis in the lymph nodes dissected.

node. Kobayashi et al. concluded that dissection to the middle lymph node was sufficient for T2N0 cases¹⁶. However, in this study, effective dissections to the main lymph node were observed in locations A and T1 for T2 cases. On the other hand, for T3 and T4 cases, there was no metastasis to the main lymph node in locations Tm, Tl, and D, and dissection to the main lymph node was ineffective in Tr. In these cases, it may be acceptable to adjust the extent of dissection according to age, comorbidities, and surgical site.

In T4 cases localized in C, no dissection effect was observed for nodal stations 202 and 203. We thought this may be because of a decrease in the five-year recurrence-free survival rate as the frequency of metastasis increased. However, considering that there were only seven cases, it is difficult to assert that less extent of dissection may be acceptable. It seems necessary to collect and analyze a large number of cases. In locations C and A, occasionally, only dissection of the main lymph node was effective despite being along the same artery. Kataoka et al. reported the proportion of patients with a skipped pattern of lymphatic spread, which was significantly higher for right compared with left colon cancer¹⁷; this may affect metastasis frequency at each station. In locations Tr, Tm, and Tl, no dissection effect was observed for the main lymph nodes except for nodal station 223. Considering these results, it may not be necessary to dissect stations 203, 213, and 253 in surgery for transverse colon cancer.

Several stations that are generally considered out of range for dissection, as recommended in the ninth edition of the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, demonstrated dissection effectiveness. Nodal station 213 comprises the main lymph nodes surrounding the right colonic artery, and dissections were effective for this station in location C. Considering this result, even in the absence of a right colonic artery, dissection of the cephalic side of the root of the ileocecal artery may be necessary in location C. In addition, dissection was effective for nodal station 211 in location Tr, station 231 in Tl, station 221 in D, and station 231 in S. In these cases, tumors located at the localization boundaries, such as the hepatic or splenic curvatures, may have caused tumor cells to flow to extra-regional lymph nodes because of lymphatic flow stagnation.

In the West, Hohenberger proposed the complete mesocolic excision (CME) and central vascular ligation (CVL) concepts in 2009, which yielded a lower local recurrence rate and improved five-year survival rate^{18,19}. Subsequently, the advantages of resecting the mesentery without damage have been widely recognized. Japanese D3 and CME + CVL are very similar in terms of complete mesenteric resection and high ligation of the vasculature, and both have demonstrated oncologic efficacy. Regarding the differences between the two techniques, West showed that CME + CVL is associated with a longer length of resected bowel and a greater number of dissected lymph nodes than Japanese D3 dissection²⁰. However, it was also shown that the number of lymph nodes with metastases did not change, and it is unclear whether extensive bowel resection contributes to a reduction in the number of remnant metastatic lymph nodes.

There are several technologies for accurately determining the status of lymph node metastasis. Preoperative positron emission tomography scans can help detect tumor including lymph node metastasis, and may significantly contribute to favorable surgical outcome²¹. During colorectal surgery, indocyanine green (ICG) fluorescence imaging provides easy-to-use and real-time visual feedback for surgeons, assisting in intraoperative decision-making²². Previous reports have demonstrated the safety and feasibility of ICG fluorescent imaging-guided D3 lymphadenectomy in sigmoid and rectal cancer²³, and the efficacy of this method in right-sided colectomy²⁴. Furthermore, ICG fluorescence imaging also contributed to increase the number of harvested lymph nodes in lateral pelvic lymphadenectomy²⁵, and para-aortic lymph node dissection²². An optimal protocol for the clinical utility of ICG fluorescence imaging in colorectal surgery has not been established, but this method may be useful for performing accurate lymph node dissection.

In previous reports, the Lymphadenectomy Index was calculated by multiplying the frequency of metastasis to that lymph node by the five-year survival rate of patients with metastasis to that lymph node¹¹. Considering that the five-year survival rate for patients with recurrent lymph node or distant metastasis has improved with recent medical advances, including chemotherapy, we thought that the five-year survival rate alone could not accurately evaluate dissection effectiveness^{26–28}. Therefore, in this study, we calculated the Lymphadenectomy Index by multiplying the frequency of metastases by the five-year recurrence-free survival rate.

This study includes several limitations. First, it was a single-center, retrospective study. Second, the perioperative and postoperative management and the types of chemotherapy for colon cancer changed during the study period, so historical bias is a possibility. Third, even in surgeries using the same technique and

involving lymph node dissection, dissection quality, especially of the main lymph node, may vary from surgeon to surgeon. Fourth, metastasis to the accessory middle colic artery, which branches off the superior mesenteric artery and supplies the splenic curvature, was not analyzed separately for nodal stations 222 and 223²⁹. Finally, the small number of cases was a problem, particularly in location Tr, Tm and Tl. Consequently, it may not have been feasible to accurately assess the survival curves and the size of the Lymphadenectomy Index. To solve this problem, we need to collect more cases, and we are currently conducting an analysis that includes cases from multiple institutions.

Conclusion

For T1 cases, dissection to intermediate lymph nodes is sufficient, but for T2 cases in A and Tl, dissection to the main lymph node may be necessary. According to our evaluation of the Lymphadenectomy Index by tumor localization, it may be necessary to contemplate the dissection of the cephalic side of the root of the ileocecal artery if tumors locate at C, and para-intestinal lymph nodes near the range of dissection if tumors locate at the localization boundaries.

Data availability

All data generated or analyzed during this study are included in this published article. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Received: 23 October 2024; Accepted: 19 February 2025

Published online: 24 February 2025

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Author contributions

Yuta Marunaka and Jun Kiuchi wrote the main manuscript text and prepared tables. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics declarations

Informed consent was obtained from all subjects and/or their legal guardians. The study was approved by the institutional review board of the Kyoto Prefectural University of Medicine (Approval Number: ERB-C-1178).

Additional information

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