Lymphatic spread patterns in young versus elderly stage III colon cancer patients

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Abstract

Background: The anatomical pattern of lymph node spread differs between young (≤ 45 years) and elderly (≥ 80 years) patients with stage III colon cancer (CC) is poorly investigated.

Materials and Methods: Two groups of patients (young and elderly) with stage III CC who underwent upfront extensive (D3) lymphadenectomy at eight Japanese centers between 1998-2018 were retrospectively analyzed. The primary endpoint was the proportion of positive central lymph nodes. The lymph node spreading pattern and its prognostic impact on recurrence-free survival (RFS) and overall survival (OS) in the two groups were also compared.

Results: Two-hundred and ten young patients and 348 elderly patients were identified and compared. The total number of lymph node harvested and the total number of invaded lymph nodes were significantly higher in younger group comparing elderly (median of 31.5 (3-151) vs. 21 (3-116), P<0.001 and median of 3 (1-21) vs. 2 (1-25), P<0.001, respectively). The proportion of positive central LN was higher in younger than in elderly group (9.52% (95% CI: 6.24-14.2%) vs. 4.59% (95% CI:2.84-7.31%), p=0.012). In multivariate models for RFS, central lymph node invasion was identified as a poor prognostic factor in younger group (HR5.21 (95% CI (1.76-15.39))), but not in elderly group (HR1.73 (95% CI (0.80-3.76))).

Conclusion: Young stage III colon cancer patients have a higher risk of central lymph node invasion, suggesting a more aggressive disease biology. The presence of central LN invasion is associated with a worse outcome in young patients.

Key words: central lymph node, colon cancer, elderly, lymph node spreading pattern, young

Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed worldwide, and has the second highest mortality rate [1]. The incidence of CRC is increasing among young adults, which led to the recommendation of early cancer screening such as fecal occult blood test starting at the age of 45 years in the United States and 40 years in Japan[2, 3]. The definitions of 'young' versus 'elderly' vary geographically due to differences in age distribution of the population. On the other hand, due to longer life expectancy, the incidence of CRC in the elderly is also increasing [4]. Therefore, clinicopathological features of CRC in these two populations need to be clarified.

Lymph nodes (LN) involvement is the most important prognostic factor in CRC [5]. The prognostic impact of the anatomical LN spread pattern of colon cancer (CC) in terms of the location of invaded LN (central LN vs. intermediate/paracolic LN), sidedness (right vs. left) and molecular biomarkers (RAS, BRAF, microsatellite instability (MSI)), was recently reported by our group [6-8]. Additionally, population-based studies suggested age-related variations in the total LN count harvested and invaded in surgically resected CC [9-11]; younger patients were more likely to have a higher total and invaded LN count than elderly patients. However, the relationship between patient age and the anatomical location of lymphatic spread in CC is currently unknown. The presence of metastatic central LNs may be relevant in the decision to perform extensive (D3) lymphadenectomy. It has also been identified as a poor prognostic factor in CC [12-16], however, to the best of our knowledge, it currently remains unclear whether lymph spreading pattern and the risk of positive central LN invasion varies with age.

Therefore, this study aims to investigate the relationship between age and the anatomical pattern of lymphatic spread, and their prognostic impact patients with node positive (stage III) CC.

Materials and Methods

Patients. Pathological stage III CC patients, treated with curative extensive lymphadenectomy (Japanese D3 dissection) at 8 Japanese high-volume centers (Supplementary Materials, Supp. Table) between 1998-2018 were retrospectively analyzed. Rectal cancer patients, and patients treated with neoadjuvant therapy were excluded (Figure 1). This retrospective study was reported in line with the STROCSS criteria [17] and approved by the Institutional Review Board of Hyogo Medical University, Japan (N0. 3789).

Open or laparoscopic colonic resection with Japanese D3 lymphadenectomy was performed in all patients. When the tumor was right sided, the ileocecal vein and/or right colic vein and/or middle colic vein were divided at its origin and the corresponding mesenteric nodal stations (203, 213, and 223) were removed. High ligation of the inferior mesenteric artery (IMA) was performed for left-sided tumors (sigmoid or rectosigmoid), with the removal of LN at station 253, or the left colic artery was preserved and the superior rectal artery was divided at its origin. In descending colon cancer, the left colic artery was divided at its origin with removal of LN station 253, regardless of preservation of IMA. This technique is theoretically equivalent to complete mesocolic excision (CME) with central venous ligation [18]. The only difference is that the length of the bowel and area of the mesentery removed are more limited in Japanese D3 lymphadenectomy than in the CME technique [19]. Adjuvant therapy (5-FU or oxaliplatin-based mFOLFOX6 or CapOX) was administered according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines [2].

Definition of the level and the lymphatic spread pattern. According to the Japanese Society for Cancer for the Colon and Rectum (JSCCR) staging system, invaded LN were classified into the following three groups, similar to our previous studies [6-8, 20]: L1 (paracolic), L2 (intermediate), and L3 (main or central) (Figure 2, Supplementary Materials Suppl. Figure 1). The 8th edition of

the UICC TNM staging system was used [20]. The definition of 'sequential' and 'skipped' LN metastasis was as follows: when a more centrally located LN was positive with all previous LN being invaded, this lymphatic spread pattern was defined as 'sequential'. On the other hand, when one or two nodal stations (L1 and/or L2) were negative and the more centrally located nodal station (L2 and/or L3) was invaded, the lymphatic spread pattern was defined as 'skipped'.

Statistical analysis. Previous studies reported an increased risk of LN involvement in younger patients [10, 21]. Among LN, central LN metastasis was considered to be a poor prognostic factor and clinically important in CC. Therefore, in this retrospective study, we expected central LN to be more frequently invaded in the younger patients than in elderly patients, and the proportion of positive central LN was compared between pStage III young CC (group Y) and elderly CC (group E). The chi-squared or Fisher's exact test was used to evaluate the significance of differences between proportions, and the Student's *t*-test or Mann-Whitney U test to assess the significance of differences between means where appropriate.

Recurrence-free survival (RFS) and overall survival (OS) were estimated from the date of surgery until recurrence or death from any cause. Unadjusted RFS in the Y and E groups and each L-level were estimated using the Kaplan-Meier method and Log-rank tests were performed to compare survival curves. A Cox proportional hazards model was used to identify the relationships between RFS and several known prognostic factors in CC. Sex, elevated postoperative serum CEA, adjuvant therapy (observation vs. 5-FU/doublet), pT stage (T4 vs. T3/2/1), tumor size >5cm, primary tumor location (right vs. left), Histology (poor/mucinous/signet vs. tubular/papillary), L level (L3 vs. L1/L2), surgical procedure (laparoscopy vs. open), and lymphatic spread pattern (sequential versus skipped) were included as independent variables. All analyses were performed with JMP Pro 15.2.0.

Results

In this retrospective analysis, 210 stage III CC patients aged 45 years or younger (group Y) and 349 stage III patients aged 80 year or older (group E) were identified. Clinical and pathological variables in both groups are shown in Table 1.

Laparoscopic (or laparo-assisted) surgery was performed more frequently in group Y (50.0% vs. and 41.0%, p=0.02). Adjuvant therapy was more frequently received by the younger group than in elderly (P <0.001)**:** In the younger group only 18.1% of patients chose observation without chemotherapy, while 82.5% of the elderly chose observation. In Japan, since mFOLFOX6/CapOX regimen was approved in 2009, only 2.0% (2/99) of younger patients who received surgery in the first 10 year (1998 to 2008) received mFOLFOX6/CapOX, while 47.8% (53/111) of younger patients in the second 10 year (2009 to 2018) received mFOLFOX6/CapOX. Sigmoid and rectosigmoid cancer was more frequently observed in younger group (p <0.001). Younger group had more advanced tumors, a more advanced N stage, and a higher number of total LN harvested (median of 31.5 (3-151) vs. 21 (3-116), P<0.001) and invaded (median of 3 (1-21) vs. 2 (1-25), P<0.001). In contrast, regarding T factors, group Y had less advanced primary tumors compared to elderly, a less advanced T stage, and a smaller primary tumor (median of 40 mm (6-160) vs. 45mm (10-150), p=0.065). The proportion of invaded central LN in younger group was higher than that in elderly (9.52% (95% CI: 6.24-14.2%) vs. 4.59% (95% CI:2.84-7.31%, p=0.012). The observed lymphatic spread patterns are shown in Table 2. The proportion of patients with a 'skipped' lymphatic spread pattern was similar in both groups (11.0% (younger group) vs. 10.9% (elderly group)).

Survivals. Unadjusted 5-year RFS and OS rates were significantly worse in elderly group than in younger group (57.3% vs. 72.8%; p<0.001 and 66.7% vs. 87.4%; p<0.001, respectively) (Figure 3).

RFS according to the L status [6-8] is shown in Figure 4. Five-year RFS rates in L3 (central LN positive) were lower compared to that in L1 and L2 in both groups (younger group: L1/L2/L3: 78.5%/64.9%/55.0% (p=0.031); elderly group: L1/L2/L3 62.1%/49.0%/40.0% (p=0.0065), respectively).

To examine the prognostic significance of the anatomical pattern of lymphatic spread in each group, a Cox multivariate analysis for RFS was performed (Table 3). In the younger group, elevated postoperative CEA, a skipped LN spread pattern, stage pT4, tumor size >5 cm, and the presence of invaded L3 nodes were associated with a poor prognosis. In the elderly, elevated postoperative CEA and stage pT4 were associated with a poor prognosis.

Discussion

Since lymphadenectomy plays a central role in minimizing the risk of recurrence, it is essential to understand the nature of the lymphatic spread pattern. The actual extent of lymphadenectomy may be affected by age; surgeons are more likely to perform radical surgery in young patients, which may affect the total number of lymph node harvested and survival outcome. However, limited information is currently available on the relationship between age and lymphatic spread patterns. In this analysis, age-related differences were observed in the lymphatic spread pattern according to patient age: the total number of harvested LN and the number of invaded LN were higher in young CC patients. The frequency of central LN metastases in young CC patients aged 45 years or younger was significantly higher than that in elderly CC patients aged 80 year or older. Central LN metastasis had a stronger prognostic impact in young CC patients. To the best of our knowledge, this is the first study to report the relationship between age and the anatomical location of invaded LN in stage III CC.

In Japan, LN stations are historically mapped according to anatomical location, allowing unique insights in the prognostic significance of central LN metastasis in CC [12-16]. In the JSCCR guidelines, central LN metastases are categorized as N3 [2] (which is different from the eighth edition of the UICC TNM classification [20]). The present results support this classification: The 5-years RFS rate in the L3 group was poor in both populations (55.0% in the Y group and 40.0% in the E group) and the multivariate analysis identified positive central LN positivity as a poor prognostic factor, particularly in the Y group. When the central LN is anticipated to be negative, D2 lymphadenectomy may be sufficient, which may minimize the risk of postoperative complications. However, extended surgery including D3 lymphadenectomy may benefit young CC patients because the frequency of positive central LN is approximately 10%. However, since central LN invasion reflects aggressive disease with a poor prognosis, it is uncertain whether

more aggressive surgery can impact survival. It may reduce the risk of local (nodal) recurrence and progression. Furthermore, patients with suspected positive L3 nodes may benefit from neoadjuvant treatment (chemotherapy and/or immune therapy). In the E group, the frequency of central LN positivity was similar to our previous report [6], which indicates the prognostic impact of radical surgery may be less than in younger patients.

Different clinicopathological features were observed between younger and elderly groups in the present study. Right-sided tumors and advanced primary tumors in size and depth were observed more often in the elderly group, whereas the total number of LN harvested and invaded was higher in the younger group. Young CRC patients are more likely to have poorly differentiated and left-sided tumors [22]. Previous studies reported a correlation between age and the number of LN. Sarli et al. revealed an age-related decrease in the number of LN harvested [23]. Quan et al. suggested that surgical specimens from young CRC patients yielded a higher number of LN than those from elderly patients [24]. Furthermore, the host immune response may lead to enlarged LN, and therefore a weaker immune response may lead to smaller LN and fewer LN [25, 26]. The present results were consistent with these findings. The differences in tumor size, N stage, and T stage between both groups are consistent with literature findings that early onset CRC is often diagnosed at a later stage. Also, these differences can be due to random variation since p values were not adjusted for multiple comparisons. A detailed molecular profile was not available in our series. Limited information is currently available on the genetic backgrounds of young and elderly CRC patients[27, 28]. Further investigation is required to investigate age-specific molecular mechanisms in CC.

The incidence of ‘skipped’ metastases in CC varies among studies. A recent systematic review showed an incidence of less than 18% [29]. Our group suggested differences in the proportion of ‘skipped’ LN metastases depending on the molecular biomarker used and tumor sidedness:

this proportion was 9.3% in BRAF mutant vs. 20.0% in BRAF wild type, 4% in MSI-High vs. 10.5% in microsatellite stable, and 13.7% in right-sided CC vs. 9.0% in left-sided CC. The expression of MSI-H was not associated with the incidence of central LN invasion. The present results showed that the anatomical pattern of LN spread was not affected by age. MSI-H is more frequently detected in young CRC patients [30]; however, data on molecular biomarkers were not available for the present study. Therefore, further studies that incorporate molecular data and age are warranted.

There were several limitations that need to be addressed. The molecular profile, such as mutations in RAS or BRAF and the mismatch repair status, was not available in the database. Second, since the opposite patient populations were compared using the data collected from a database spanning 20 years, the survival data should be cautiously interpreted. In this study, OS was much worse in group elderly than in younger group. However, the cause of death was different in the two groups. One hundred and eight out of 186 events of deaths were due to colon cancer in E group, but only 13 out of 35 in Y group. Additionally, the chemotherapy regimen was affected by the year the patients underwent surgery as described in the Results section. Regarding surgery, the concept of D3 extended lymphadenectomy has already been established for more than two decades in Japanese high-volume centers. Since only high-volume centers in which D3 lymphadenectomy is performed as clinical practice since 1998 participated in this present study, the quality of surgery and LN examinations were considered to be high.

In conclusion, differences in the lymphatic spread pattern were observed between young and elderly CC patients. Young CC patients need to undergo extensive D3 lymphadenectomy due to the higher frequency of central LN invasion. When extensive lymphadenectomy is performed on elderly CC patients, a balance between the effects of lymphadenectomy and the fitness of patients' needs to be considered. Surgeons may perform tailored surgery in which the

appropriate extent of lymphadenectomy is defined using these data.

Abbreviations: LN, lymph node; CRC, colorectal cancer; CC, colon cancer; CI, confidence interval; MSI, microsatellite instability; RFS, Relapse-free survival; OS, overall survival; MSS, microsatellite-stable; CME, complete mesocolic excision; HR, Hazard ratio;

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Figure Legends

Figure 1. Patients flow chart

Figure **2**

B, Definition of the L level. When central LN was invaded, patients were categorized as L3. When intermediate LN was positive, they were categorized as L2. When only paracolic LN was positive, they were categorized as L1. Blue arrows indicate the flow of lymphatic tumor spread (L1→L2→L3) following the Halsted model. On the other hand, in the Fisher model, spread of metastatic tumor cells occurs to distant LN and metastatic sites occurred in parallel. T, primary tumor;

Figure 3

Unadjusted RFS and OS according to ages in stage III colon cancer. Young group (aged 45 or younger) = blue, Elderly group (aged 80 or older) = red.

Figure **4**

RFS in young and elderly groups according to the L status [6-8]. L1=red, L2=green, L3=blue

Supplementary Figure

Anatomical LN mapping in the Japanese Society for Cancer of the Colon and Rectum (JSCCR).

Figure 1

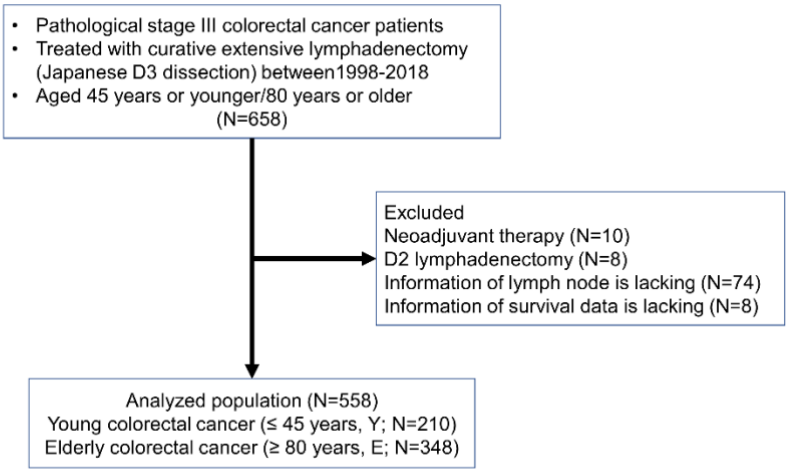


Figure 2

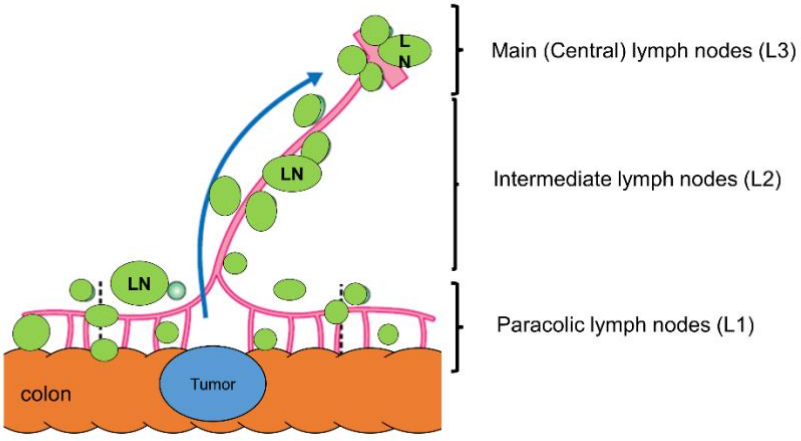
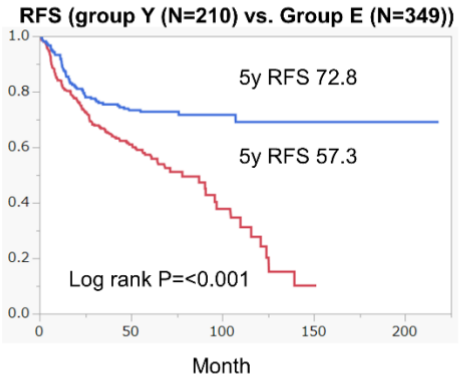
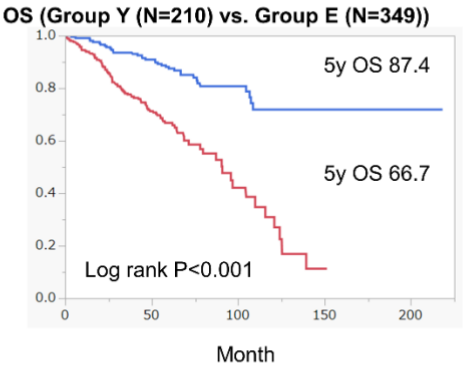


Figure 3

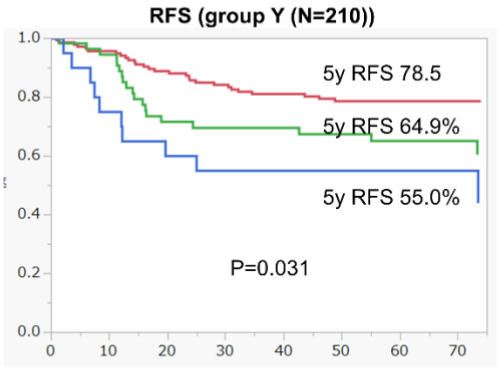


No. at risk	0	50	100	150	200
Young	210	119	35	5	2
Elderly	349	131	15	2	-

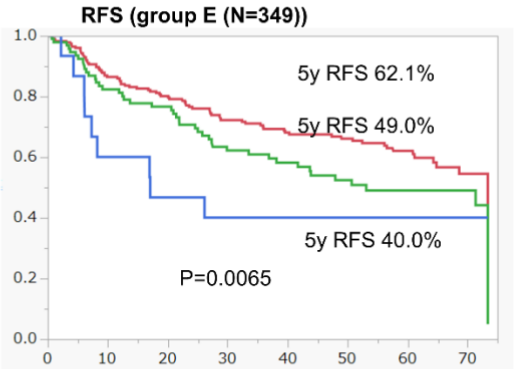


No. at risk	0	50	100	150	200
Young	210	166	43	6	2
Elderly	349	144	15	2	-

Figure 4



	0	10	20	30	40	50	60	70
L1	136	127	117	108	103	96	82	53
L2	54	51	38	35	33	30	28	16
L3	20	16	13	12	12	12	11	7



	0	10	20	30	40	50	60	70
L1	237	187	160	131	111	94	67	26
L2	96	73	67	50	44	33	23	11
L3	16	10	8	7	6	6	4	3

Table1: Patients characteristics

Variables		Group Young (N=210)	Group Elderly (N=349)	P Value
Sex (Male/Female)		94/116	165/184	0.60
Age	Median (range)	43 (20-45)	83 (80-96)	<0.001
Tumor size	Median (range)	40 (6-160)	45 (10-150)	0.065
Anatomical location	vermiform process	2 (0.95%)	0	<0.001
	Cecum	15 (7.1%)	54 (15.3%)	
	Ascending	32 (15.2%)	123 (35.2%)	
	Transverse	26 (12.3%)	44 (12.6%)	
	Descending	22 (10.5%)	22 (6.3%)	
	Sigmoid	88 (41.9%)	93 (26.6%)	
	Rectosigmoid	25 (11.9%)	12 (3.7%)	
T stage	T1	15 (7.1%)	8 (2.3%)	0.02
	T2	21 (10.0%)	27 (7.7%)	
	T3	118 (56.1%)	198(56.7%)	
	T4a	44 (21.0%)	100 (28.6%)	
	T4b	12 (5.7%)	16 (4.6%)	
N stage	N1a	63 (30.0%)	146 (41.8%)	0.007
	N1b	73 (34.8%)	119 (34.1%)	
	N2a	43 (20.5%)	56 (16.0%)	
	N2b	31 (14.8%)	28 (8.0%)	
Histology	Papillary/tubular	183 (87.1%)	301 (86.2%)	0.76
	Poorly/mucinous/signet	27 (12.9%)	48 (13.8%)	
Total number of Lymph nodes	Harvested	31.5 (3-151)	21 (3-116)	<0.001
	positive	3 (1-21)	2 (1-25)	<0.001
Positive anatomical lymph node level (L group)	L1	136 (64.8%)	237 (67.9%)	0.27
	L2	54 (25.7%)	96 (27.5%)	
	L3	20 (9.52%)	16 (4.6%)	
Surgery	Laparoscopic	105 (50%)	143 (41.0%)	0.038
	Open	105 (50%)	206 (59.0%)	
Adjuvant therapy	No	38 (18.1%)	288 (82.5%)	<0.001
	5-FU	111 (52.9%)	51 (14.6%)	
	Doublet (oxaliplatin	61 (29.0%)	10 (2.9%)	

	plus 5-FU)			

Group Young: pathological stage III CC patients aged 45 years or younger

Group Elderly: stage III patients aged 80 year or older

L group; L1 (paracolic lymph node positive), L2 (intermediate lymph node positive), and L3 (main or central lymph node positive)

Table 2: Lymph node spreading patterns in young and elderly groups

	Group Young (N=210)	**Group Elderly (N=349)**
Sequential		
+−−	136 (64.7%)	237 (67.9%)
++−	44 (21.0%)	67 (19.2%)
+++	7 (3.3%)	7 (2.0%)
Subtotal	187 (89.0%)	311 (89.1%)
Skipped		
−+−	10 (4.8%)	29 (8.3%)
+−+	9 (4.3%)	3 (0.86%)
−−+	4 (1.7%)	3 (0.86%)
−++	0 (0%)	3 (0.86%)
Subtotal	23 (11.0%)	38 (10.9%)

Sequential; A more centrally located lymph node was positive with all previous lymph node being invaded

Skipped; One or two nodal stations (L1 and/or L2) were negative and the more centrally located nodal station (L2 and/or L3) was invaded

Table 3: Multivariate analysis for Recurrence free survival

	Group Young (N=210)		**Group Elderly (N=349)**	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (male vs. female)	1.59 (0.92-2.73)	0.095	1.20 (0.85-1.69)	0.29
Elevated postoperative CEA	**4.38 (2.06-9.35)**	**0.0001**	**1.96 (1.32-2.92)**	**0.0009**
L3 (vs. L1/L2)	**5.21 (1.76-15.39)**	**0.0028**	1.73 (0.80-3.76)	0.16
Skipped pattern (vs. sequential)	**0.25 (0.070-0.91)**	**0.035**	1.01 (0.57-1.80)	0.96
Adjuvant therapy (obs vs. FU/doublet)	0.85 (0.40-1.81)	0.67	0.70(0.43-1.14)	0.15
T4 (vs. T3/2/1)	**2.99 (1.59-5.59)**	**0.0006**	**1.50 (1.04-2.18)**	**0.031**
Tumor size >5cm	**0.45 (0.22-0.92)**	**0.028**	1.04 (0.72-1.50)	0.84
Primary tumor location Right (vs. left)	0.74 (0.40-1.40)	0.36	0.90 (0.63-1.30)	0.58
Histology poor/mucinous/signet (vs. tubular/papillary)	1.03 (0.46-2.32)	0.94	0.98 (0.59-1.63)	0.94
Laparoscopy (vs. open)	0.68 (0.38-1.22)	0.20	0.78 (0.54-1.12)	0.19

Supplementary Figures and Tables

Supplementary Figure

Anatomical LN mapping in the Japanese Society for Cancer of the Colon and Rectum (JSCCR).

Supplementary Table

List of participating centers

Name of the participating centers	Number of patients included in analyzed populattion (N=558)
Hyogo Medical University, Japan	116
National Cancer Center Hospital, Japan	105
Kanagawa Cancer Center, Japan	68
Shizuoka Cancer Center, Japan	72
Nippon medical school, Japan	53
Yamagata Prefectural Central Hospital, Japan	30
Shimane Prefectural Central Hospital, Japan	72
Gifu University, Japan	42

Supplementary Figure