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Prognostic significance of number versus location of positive mesenteric nodes in stage iii colon cancer

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ABSTRACT

Introduction: Debate persists on the ideal extent of lymphadenectomy for colon cancer (CC). Specifically, it is unknown whether the anatomical location of positive lymph nodes (LN) has any independent prognostic significance. We assessed the prognostic value of positive LN location in stage III CC patients who underwent extensive (D3) lymphadenectomy.

Methods: Patients from Kanagawa Cancer Center, Japan, who underwent D3 dissection for CC from 2000 to 16 were analyzed. Mesenteric LN were classified according to location as paracolic (L1), intermediate (L2), or central (L3). Recurrence-free survival (RFS) and the corresponding hazard function were evaluated with their trends over the L groups. Multivariate Cox models were used to evaluate the association of LN location with RFS.

Results: Four hundred forty-six stage III patients were analyzed. The mean number of examined/positive nodes per patient was 42.5/2.6 in L1 ($n = 310$), 40.9/4.8 in L2 ($n = 111$), and 44.0/9.8 in L3 ($n = 25$). RFS was worse for L3 vs. L2 (HR: 2.00, 95%CI [1.05–3.75], $p = 0.034$) and for L3 vs. L1 (2.62 [1.45–4.71], $p = 0.001$), but not significantly different between L2 and L1 (1.32 [0.89–1.5], $p = 0.17$). In a multivariate model adjusting for age, tumor size, and number of lymph nodes harvested T-stage ($p < 0.001$), adjuvant therapy ($p < 0.0038$), lymphatic invasion ($p = 0.023$), and LNR ($p = 0.038$) were significantly associated with RFS, but not L level or tumor location.

Conclusion: The anatomical location of invaded LN does not significantly correlate with RFS in CC, after adjusting for potential confounders. Central LN are infrequently invaded and confer a worse RFS.

Introduction

Colorectal cancer is the third most common cancer in males and the second in females, with an estimated nearly 1.4 million cases and 700,000 deaths worldwide [1]. Surgery is the only curative treatment option in localized colorectal cancer. In rectal cancer, total mesorectal excision (TME) improves surgical outcome and is considered as the standard surgical procedure [2–4]. In colon cancer (CC), the ideal extent of surgery is a matter of debate. Complete mesocolic excision (CME) with central vascular ligation (CVL) was proposed by some groups in the EU [5–7]. In Japan, extended lymphadenectomy or D3 dissection, in which the main lymph nodes (LN) are dissected with a high vascular tie at the root of the feeding artery, has been performed since decades [8]. Both techniques are considered to be similar in terms of the extent of lymphadenectomy [9].

The cited rationale for 'extended' surgery (CME and D3) is twofold. First, since there is a consistent correlation between the number of examined LN and survival, efforts to surgically remove as many LN as possible may improve outcome [10–17]. Second, assuming a 'stepwise' or Halstedian biology [18,19], which supposes colon cancer cells to spread in a predictable and orderly fashion from the primary CC to nearby LN and henceforth to more

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distant LN, maximally removing potentially involved LN may render the patient cancer free.

There are, however, major objections to the above cited grounds for 'extensive' surgery. First, the correlation between potential prognostic factors such as LN count (LNC) or lymph node ratio (LNR, defined as number of positive nodes over LNC) [20] and survival is almost certainly not causal, but explained by numerous confounding variables, the most important of which probably is the patient's immune response [21,22]. Second, recent genomic and phylogenetic analyses suggest that 1. lymphatic spread and metastasis to distant organs in CC occur in parallel and simultaneously from the onset of primary tumor growth, and 2. that both are essentially random (stochastic) processes [23–27]. In addition, the estimated growth rates of primary CC and liver metastases are comparable [28]. Given the average time frame between resection of the primary and the appearance of metastatic disease in CC, the growth rate of metastases would need to be much higher if the linear progression model was correct. Finally, 'extensive' lymphadenectomy is associated with the potential of increased surgical and functional morbidity, and is difficult to reconcile with current trends towards minimally invasive methods such as sentinel node navigation in CC [29].

Knowledge of the prognostic significance of the mesenteric LN location (paracolic versus intermediate versus central) would allow to resolve some of the above uncertainties. Indeed, when the Halsted model would hold, patients with positive LN spatially further removed from the primary cancer would have a worse survival compared to those with only paracolic LN involved. In Western practice, pathologists report only the number of retrieved and invaded nodes, not their anatomical location. Therefore, the location of positive LN is unknown. In Japan, on the other hand, surgeons dissect the mesenteric lymph nodes from the resection specimen and classify them into three anatomical levels according the Japanese Classification of Colorectal Carcinoma (JCCRC) [8]. Here, we have analysed the prognostic significance of positive lymph node *location* in a cohort of stage III CC patients who underwent Japanese D3 dissection.

Patients and methods

Patient selection

From the database of the Kanagawa Cancer Center, Yokohama, Japan, CC patients were included based on the following criteria: 1. Patients underwent extensive lymphadenectomy (Japanese D3 dissection); 2. Patients staged as pathological TNM stage III; 3. patients underwent pathological R0 resection. Exclusion criteria were rectal cancer patients and patients with preoperative treatment. The protocol of this retrospective study was approved by the Institutional Review Board of Kanagawa Cancer Center, Japan (N0. Eki-11).

Surgical treatment/chemotherapy

Colonic resection with Japanese D3 lymph node dissection was performed for these patients, which was an anatomical lymph node dissection defined by the dissection of lymph nodes at the root of the tumor feeding artery and the longitudinal length of large intestine to be resected. For right-sided lesions, the vascular pedicles were divided at their origin together with removal of draining lymph nodes (203, 213, 223) along the superior mesenteric vein (Fig. 1b). For left-sided lesions, removal of lymph nodes at the root of the inferior mesenteric artery (253) was performed with high ligation, or with preservation of the left colic artery and ligation of the root of the superior rectal artery. Theoretically, this technique is equivalent with CME [9].

Administration of adjuvant chemotherapy was recommended to pathological stage III patients. Until 2011, adjuvant chemotherapy consisted of oral 5-fluorouracil (5-FU); after 2011, doublet chemotherapy (5-FU+oxaliplatin) was preferably administered because Capecitabine combined with oxaliplatin was approved in Japan at 2011. Detailed data regarding the regimen were not available.

L level classification

The 7th edition of the UICC TNM staging system was used. In the JCCRC, lymph nodes are classified according to anatomical location as paracolic (L1), intermediate (L2), or along the main vascular trunk (L3) (Fig. 1a and b). Depending on the location of positive (cancer invaded) lymph nodes, patients were classified into three groups: L1 (positive paracolic lymph nodes), L2 (positive intermediate lymph nodes) and L3 (positive main (central) lymph nodes).

Statistical analysis

Overall survival (OS) was calculated from the date of surgery until death from any cause, possibly right-censored at 2000 days. Recurrence-free survival (RFS) was calculated from the date of surgery until first evidence of relapse or death from any cause, possibly right-censored at the final follow-up visit at which the absence of relapse was confirmed. Unadjusted OS and RFS in each L-group were estimated using the Kaplan-Meier method. Survival curves were compared with logrank tests. In the subgroup of pathologically node positive (stage III) patients, univariate and multivariate Cox proportional hazards regression were used to evaluate the independent association of OS and RFS with a number of known prognosticators in colon cancer: T-stage, tumor location (right vs. left), age, adjuvant chemotherapy (yes vs. no), LNC, LNR, L

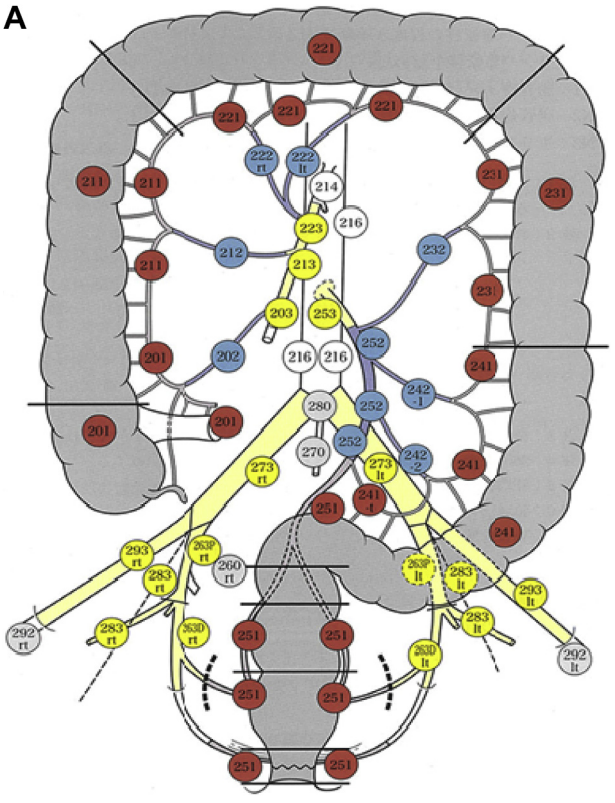

Fig. 1. aLN Classification of JSCCR (quoted from JSCCR guidelines).

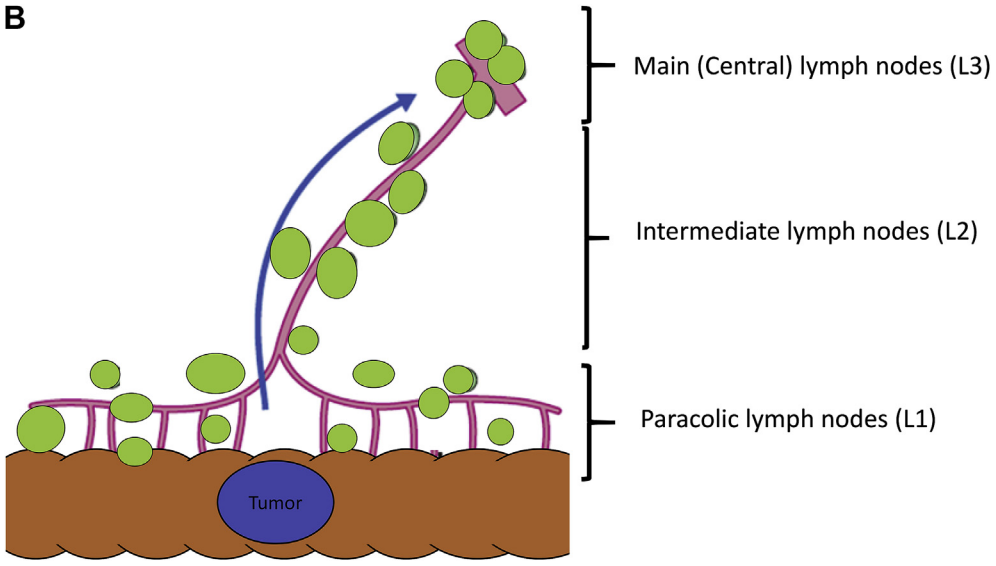

Fig. 1b. Classification of L groups. Patients with no positive lymph nodes were classified into L0.

level, primary tumor size, and lymphatic invasion. Tumor size, age, LNR and LNC were analyzed as continuous covariates. Pathological venous invasion was analyzed as categorial covariate, but 'Lymphatic invasion' was treated as a continuous parameter as the linear trend fitted better than allowing every category to show its own independent effect. The presence of pathological lymphatic invasion and venous invasion were also classified according to the JCCRC: 0; no invasion, 1; mild invasion, 2; moderate invasion, 3; severe invasion [8]. Tumor location was classified as 'right' (caecum, ascending, and transverse colon) or 'left' (descending, sigmoid, rectosigmoid). The multivariate model included covariates that were significant at the 5% level in the univariate Cox model, or a more clinically relevant proxy. In addition, as an exploratory analysis, adjusted hazard functions (instantaneous rate of death or recurrence over time) were estimated in each L group. The hazards are shown for a reference patient with mean age and median tumor size, LNR, T-stage, tumor location (right vs. left), adjuvant therapy, pathological lymphatic invasion and LNC. Analyses were performed using R version 3.3.3 and the flexsurv-package version 1.1.

Results

From the 1401 colorectal cancer patients treated with surgery in the database of Kanagawa Cancer Center, 446 pathological stage III colon cancer patients who underwent D3 surgery with curative intent were included. Table 1 details clinical and pathological variables. Three hundred and ten patients, 111 patients, and 25 patients were allocated to L1, L2 or L3 respectively. Only 25 (6%) patients had positive lymph nodes along the main vascular trunk. Adjuvant chemotherapy was administered to 81.0% of patients. The mean number of examined/positive nodes per patient was 42.5/2.6 (SD: 22.5/2.4) in L1, 40.9/4.8 (19.9/3.5) in L2, and 44.0/9.8 (19.2/12.3) in L3. The median LNR was 0.05 (quartile 1- quartile 3; 0.03–0.09) in L1, 0.11 (0.05–0.19) in L2 and 0.17 in L3 (0.08–0.36). The different patterns of nodal location are shown in Table 2. Thirty percent of patients had invaded L2 or L3 nodes. Within thig group,

Table 1
Clinical and pathological variables.

Variable		No. (%)		Variable	No. (%)
Age	Mean (SD[b])	67 (11)	UICC[a] TNM stage (7th edition)	IIIA	55 (12)
				IIIB	262 (59)
Sex	Male	234 (52)	Adjuvant therapy	IIIC	129 (29)
	Female	212 (48)		Yes	361 (81)
Main Location of tumor	Right side	185 (42)		No	85 (19)
	Left side	261 (59)	Pathological venous Invasion	0	112 (25)
				1	189 (42)
T Stage	T1	25 (6)		2	114 (26)
	T2	35 (8)		3	31 (7)
	T3	143 (32)	Pathological Lymphatic invasion	0	238 (53)
	T4a	208 (47)		1	145 (33)
	T4b	35 (8)		2	114 (26)
Size of tumor	Median	41 mm		3	20 (4)
N Stage	N1a	151 (34)	L group	L1	310 (70)
				L2	111 (25)
	N1b	147 (33)		L3	25 (6)
	N2a	88 (20)			
	N2b	60 (13)			

[a] UICC; Unio Internationalis Contra Cancrum
[b] Standard deviation.

Table 2
Pattern of invaded lymph nodes.

L group (N)	LN in D1	LN in D2	LN in D3	N	Percentage among L group
1 (230)	(+)	(-)	(-)	310	100%
2 (111)	(+)	(+)	(-)	85	77%
	(-)	(+)	(-)	26	23%
3 (25)	(+)	(+)	(+)	14	56%
	(-)	(-)	(+)	4	16%
	(-)	(+)	(+)	2	8%
	(+)	(-)	(+)	5	20%

73% showed all lower levels positive, while in the remaining 27%, one or two L levels were 'skipped' (negative). 'Skip' metastases were found in 23% (26/111) of the L2 patients and 44% (11/25) of the L3 patients. RFS and OS curves in each L group are shown in Fig 2a and 2b, respectively. Based on nominal p-values, RFS was significantly worse for L3 compared to L2 (HR: 2.00, 95%CI [1.05–3.75], $p = 0.034$) and L3 compared to L1 (HR: 2.61 [1.45–4.69], $p = 0.001$). However, no statistically significant difference in RFS was found between L2 and L1 (HR: 1.32 [0.89–1.5], $p = 0.17$). Similar trends were observed for OS: L3 was associated with a worse overall survival compared to L2 and L1 (L3 vs. L1; HR: 3.03 [1.53–6.00], $p = 0.002$; L3 vs. L2; HR: 2.45 [1.20–5.40], $p = 0.015$.), but OS was not significantly different between L1 and L2 (HR: 1.25 [0.75–2.09], $p = 0.40$). RFS and OS in the TNM pN stage of each L group are shown in Fig. 3a and 3b. A cox model with pN stage and L group showed no significant interaction between both (RFS; p for interaction = 0.34 and OS; p for interaction = 0.45). The adjusted hazard function estimates are illustrated in Fig. 4. The estimated hazard in L3 reached the highest maximum, while maximum hazards in L1 and L2 appeared close to each other. The vertical dotted line shows the time interval in months after which the adjusted hazard reaches its maximum in each group. This occurred at 6 (95% CI: 4.9–9,3) months in L1, 5.1 (3.4–19.3) months in L2, and 5.1 (1.5–26.2) months in L3.

Univariate analysis showed that age, T stage, administration of adjuvant chemotherapy, lymph node ratio (LNR), number of positive LN, L group, tumor size, and lymphatic invasion were significantly associated with RFS, while age, T stage, adjuvant chemotherapy, LNR, number of positive LN, L group, tumor size and venous invasion as well as lymphatic invasion were correlated with OS (Table 3a). Results of a Cox multivariate regression model are presented in Table 3b. T stage, adjuvant chemotherapy, LNR, and lymphatic invasion were independently associated with RFS. For OS, T stage, age, adjuvant chemotherapy, LNR, venous invasion, and lymphatic invasion were identified as significant predictors. Importantly, neither RFS nor OS was independently associated with the L level. Results of a Cox multivariate regression model including N stage instead of LNR showed very similar results (Supplementary Table).

Discussion

Surgical resection is, since almost two centuries, the mainstay of treatment in non-metastatic cancer of the colon. Nevertheless, the ideal extent of surgery remains debated, and this debate is closely linked to the uncertainty regarding the biological behavior of colon cancer. The Halstedian view assumes that lymphatic spread follows a well-defined temporal and anatomical path, from the primary tumor to nearby nodes, henceforth to intermediate nodes, subsequently to central nodes, and eventually to distant organs such as the liver. This model presupposes that 1. progression along the metastatic pathway can only arise when the previous lymphatic nodal barrier is breached; and 2. efforts to remove all cancer invaded nodes may render the patient disease-free. The above arguments are cited by proponents of extensive lymphadenectomy, as exemplified by the complete mesocolic excision (CME) and Japanese D3 approaches. The model originally proposed by Fisher in cancer of the breast, however, assumes that lymphatic as well as hematogenous metastasis occur early and at random. As a consequence, efforts to maximally remove invaded nodes are very unlikely to affect survival (although they do, of course, improve staging accuracy).

A growing body of evidence from molecular, genetic, and mathematical modeling studies indicate that the Halstedian model, which has since long been discredited in breast cancer, does not apply to the progression of colon cancer. In the absence of randomized trials comparing standard with 'extensive' surgery, important information may be generated by investigating how the anatomical location of invaded LN correlates with the risk of recurrence or death. Indeed, when the Halsted model holds, we would expect that the anatomical level (L) of invaded nodes is an independent prognosticator. Available data to assess the prognostic role of anatomical location of invaded nodes are a few in number and come mostly from East Asia [30–32]. The present study is unique, in that it allows this analysis based on careful mapping of the anatomical location of nodes, as is common practice in Japan.

Several findings from the present study merit consideration.

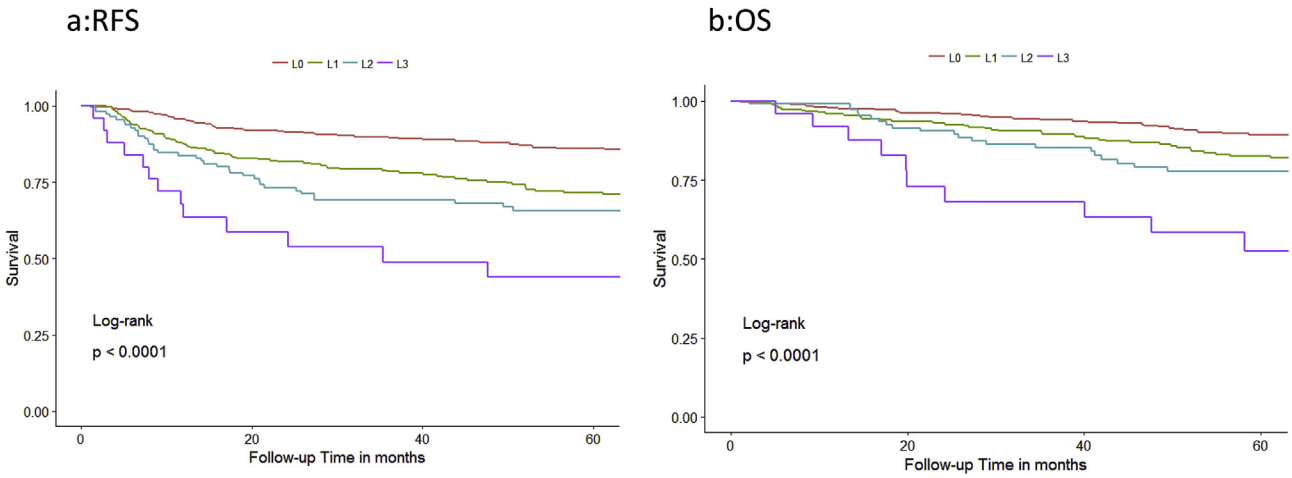

Fig. 2. Kaplan-Meier estimates for recurrence-free (RFS) and overall survival (OS) in each L group. (2a: RFS, 2b: OS).

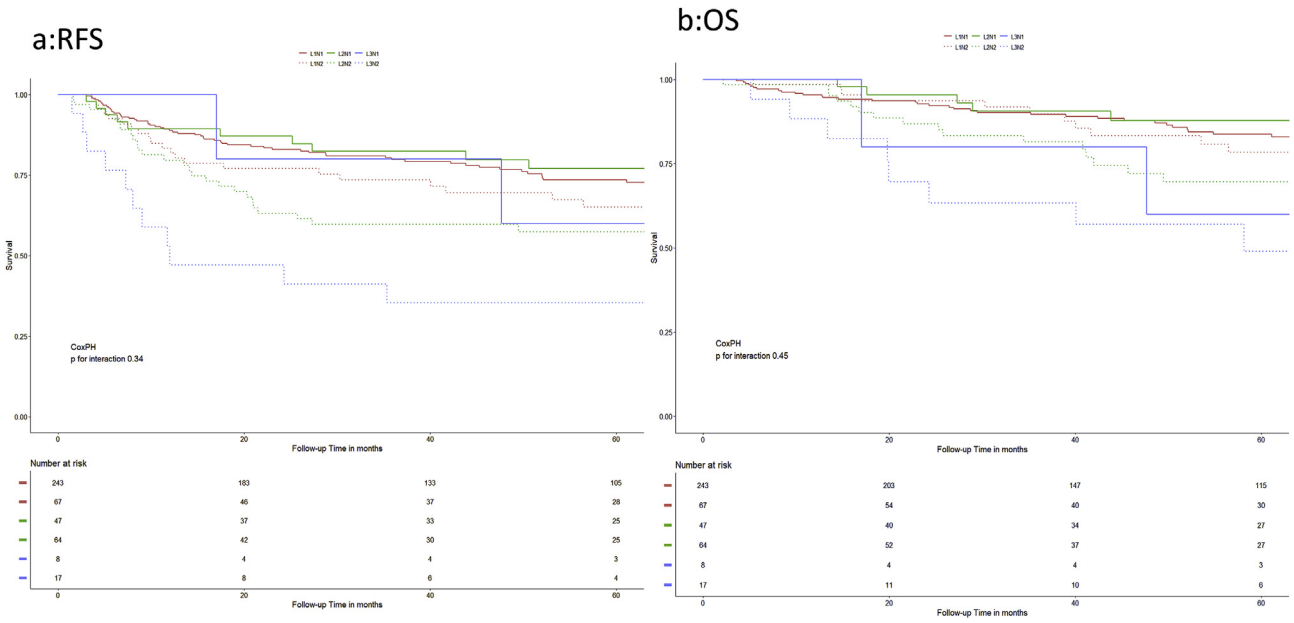

Fig. 3. Kaplan-Meier estimates for RFS and OS for L strata according to TNM pN stage. (3a: RFS, 3b: OS).

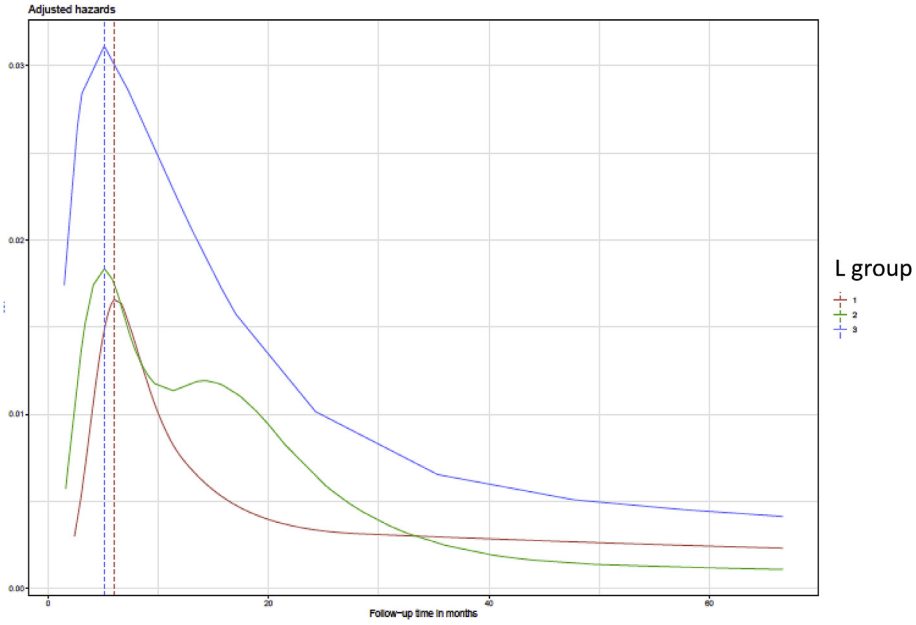

Fig. 4. Adjusted hazard function curve for recurrence-free survival in each L group with vertical line showing thöe month of maximum estimated hazard.

First, our results suggest that, within the mesocolon that is part of the standard extent of surgery, the anatomical location of invaded nodes *does not* affect the risk of recurrence or death: recurrence free survival and overall survival were not significantly different between L1 and L2. In a multivariate analysis that includes the positive LN count and LNR, considered the most important prognosticators in locally advanced CC, the L level did not correlate significantly with RFS. When inspecting the course of the hazard of recurrence over time, it is apparent that the peak hazard as well as the time frame of recurrent disease are very similar between L1 and L2. These findings argue may against the concept of a stepwise progression from L1 to L2 disease. Similar data were reported by Suzuki and coworkers, who found that in a cohort of 118 stage III colon cancer patients, the number of invaded nodes, but not the L level (L1 versus L2) was associated with OS in a multivariate analysis [33].

Second, we confirm in our patient material that the presence of invaded central or apical nodes confers a significantly worse prognosis. The percentage of positivity of central node is reported to be 1-8% [31,34–39], which is consistent to our series. In the L3 group, adjuvant therapy was not given in 4 out of 25 patients, however no one survived the observation period. Even in the remaining 21 patients who received adjuvant chemotherapy, 7 (33%) patients experienced recurrence. Several authors have previously found that the presence of invaded apical nodes reflects a high risk of systemic spread [40,41]. The analysis using the Japanese

Table 3a
Results of Cox univariate regression analysis for L1, L2 and L3 group.

Variables	Category	RFS		OS	
		Hazard ratio [95% CI]	p- value	Hazard ratio [95% CI]	p- value
T stage	T1	1	<0.001	1	0.001
	T2	1.89 [0.38–9.37]		0.57 [0.08–4.08]	
	T3	2.05 [0.48–8.66]		1.19 [0.27–5.22]	
	T4	5.21 [1.28–21.14]		2.72 [0.66–11.13]	
Tumor location	Left	1	0.31	1	0.25
	Right	1.2 [0.84–1.7]		1.3 [0.83–2.04]	
Gender	Female	1.1 [0.78–1.56]	0.59	0.93 [0.6 ; 1.46]	0.76
Age		1.02 [1–1.04]	0.02	1.04 [1.02–1.07]	0.001
Adjuvant therapy	No	1	<0.001	1	<0.001
	yes	0.47 [0.32–0.68]		0.31 [0.2–0.49]	
L group	1	1	0.011	1	0.017
	2	1.32 [0.89–1.95]		1.25 [0.74–2.09]	
	3	2.62 [1.45–4.71]		3.07 [1.55–6.09]	
LN Ratio		1.16 [1.10–1.23]$^{+}$	<0.001	1.16 [1.08–1.24]$^{+}$	<0.001
Nb of LN harvested		1 [0.99–1]	0.35	1 [0.99–1.01]	0.413
Nb of positive LN		1.05 [1.02–1.07]	<.001	1.05 [1.02–1.07]	<.001
Tumor size		1.01 [1.01–1.02]	0.001	1.01 [1–1.03]	0.005
Pathological venous invasion	0	1	0.09	1	0.03
	1	0.65 [0.42–1]		0.44 [0.25–0.77]	
	2	0.82[0.51–1.31		0.76 [0.44–1.32]	
	3	1.33 [0.7–2.54]		0.58 [0.2–1.65]	
Pathological Lymphatic invasion		1.45 [1.2–1.74]	<.001	1.55 [1.23–1.95]	<.001

LN; Lymph node, Nb; number; $^{+}$ for a difference in LN Ratio of 0.05.

Table 3b
Results of Cox multivariate regression analysis for L1, L2 and L3 group.

Variables	Category	RFS		OS	
		Hazard ratio [95% CI]	p- value	Hazard ratio [95% CI]	p- value
T stage	T1	1	**0.001**	1	**0.028**
	T2	1.67 [0.34–8.30]		0.61 [0.08–4.37]	
	T3	1.65 [0.38–7.06]		1.18 [0.26–5.37]	
	T4	3.66 [0.88–15.3]		2.34 [0.53–10.31]	
Tumor location	Left	1	0.70	1	0.74
	Right	1.08 [0.73–1.58]		1.09 [0.66–1.80]	
Age		1.01 [0.99–1.03]	0.45	1.03 [1.00–1.05]	**0.03**
Adjuvant therapy	No	1	**0.005**	1	**<0.001**
	yes	0.55 [0.36–0.82]		0.41 [0.25–0.68]	
L group	1	1	0.40	1	0.19
	2	1.00 [0.66–1.52]		0.75 [0.43–1.31]	
	3	1.63 [0.80–3.31]		1.65 [0.72–3.79]	
LN Ratio		1.08 [1.00–1.15][a]	**0.045**	1.09 [1.0–1.19][a]	0.07
Nb of LN harvested		1.00 [0.99–1.01]	0.29	1.00 [0.98–1.01]	0.75
Tumor size		1.01 [1.00–1.02]	0.19	1.01 [1.00–1.02]	0.13
Pathological venous invasion	0	NE*	NE*	1	**0.008**
	1			0.39 [0.22–0.71]	
	2			0.63 [0.35–1.12]	
	3			0.29 [0.09–0.92]	
Pathological Lymphatic invasion		1.25 [1.03–1.51]	**0.027**	1.34 [1.02–1.76]	**0.04**

NE: not examined because it was not significant in the Univariate analysis. P<0.05 is highlighted in bold.
[a] Estimates for difference in LN Ratio of 0.05.

nationwide database of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) also showed that L3 group patients had a worse survival (50). Therefore, surgical removal of these nodes is unlikely to affect the probability of cure. Already in 1941, Coller stated that '*If the carcinoma has metastasized to the main group of lymph nodes at the origins of the various vessels, then generalized metastases, undoubtedly, have already occurred, and any operative procedure would only be palliative in character'(42).* Currently, the oncological benefit of extensive lymphadenectomy remains unproven in cancer surgery. In CC, the evidence supporting CME is limited and does not consistently support its superiority [43]. These findings imply that an alternative treatment strategy such as more intensive adjuvant chemotherapy or preoperative chemotherapy can be the option for patients with invaded central nodes. Currently, the Japan Clinical Oncology Group (JCOG) is planning a clinical trial to evaluate the efficacy of preoperative chemotherapy in CC.

When inspecting the anatomical pattern of invaded nodes in stage III patients (Table 2), 73% of patients with stage III occurs in combination with all lower levels positive, while in about 27% of patients one or two L levels are 'skipped'. This observation should not be considered an argument in favor of the Halstedian model. First, the process of identifying LN in a resection specimen is prone to sampling error, and it is known that many nodes harbor micrometastatic disease, which is missed by routine pathology staining [44]. Second, studies that have examined the use of sentinel node mapping in CC have found that aberrant or 'skip' lymphatic metastasis is present in up to 50% of patients [45]. Interestingly, only four patients had positive L3 nodes and, at the

same time, negative L1 and L2 nodes, implying that 'conventional' surgery would result in a very low risk of understaging (or hypothetical undertreatment, if the Halstedian model applies, which we argue to be unlikely).

In our multivariate COX model, several prognostic factors were identified, among them T stage, adjuvant therapy and pathological lymphatic invasion, all of which were previously demonstrated to have prognostic value in CC. In our series, the LNR emerged as one of the most important prognostic factors, a finding which was reported by others [20,41]. This should be confirmed using worldwide data with an appropriate cut-off value because the lymph node count (LNC) may depend on the skills of surgeons and pathologists.

The prognostic value of tumor location is current topic of debate. We did not find any prognostic difference between right and left sided stage III colon cancer. Similarly Patel et al. did not find an association between tumor sidedness and survival in resectable colorectal cancer [42]. Nevertheless, differences in tumor biology and immune environment may exist between left and right colon cancer, which are not detectable in the current study.

Several limitations and uncertainties apply to the present study. First, we examined a homogeneous cohort of Japanese patients, and the biology of CC in this population may differ from that in other parts of the world. Second, survival is comparatively high, with relatively few events, and this limits the power and precision of the statistical analysis. We analyzed a sizeable dataset including 127 first events and 77 deaths. Since the multivariate Cox models involved a total of 12 or 15 coefficients, this yielded a relatively weak information basis for the instantaneous hazards which draw on local data (events and risk set sizes) over time. Future research foresees an extended hazard function analysis after compiling an augmented JSCCR database to further evaluate the trend of the nodal spread pattern in each L group, in order to investigate which models are likely to be applied for colon cancer.

In conclusion, our data suggest that the anatomical location of invaded lymph nodes in stage III colon cancer does not confer added prognostic information. Patients with invaded central (apical, L3) nodes represent a separate category with a high risk of recurrent disease. These patients may need a different, more intensive treatment strategy.

Authors' disclosures of potential conflicts of interest

The authors have no conflicts of interest to disclose with regard to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.05.022.

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