Review Article

Tumor Location as a Prognostic Factor in T1 Colorectal Cancer

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Abstract
The incidence of T1 colorectal cancer is expected to increase because of the prevalence of colorectal cancer screening and the progress of endoscopic treatment such as endoscopic submucosal dissection or endoscopic full-thickness resection. Currently, the requirement for additional surgery after endoscopic resection of T1 colorectal cancer is determined according to several treatment guidelines (in USA, Europe, and Japan) referring to the following pathological findings: lymphovascular invasion, tumor differentiation, depth of invasion, and tumor budding, all of which are reported to be risk factors for lymph node metastasis. In addition to these factors, in this review, we investigate whether tumor location, which is an objective factor, has an impact on the presence of lymph node metastasis and recurrence. From recent studies, left-sided location, especially the sigmoid colon in addition to rectum, could be a risk factor for lymph node metastasis and cancer recurrence. The treatment of T1 colorectal cancer should be managed considering these findings.

Keywords
tumor location, T1 colorectal cancer, lymph node metastasis, recurrence, risk factor, treatment strategy

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Introduction

Colorectal cancer (CRC) is one of the most common types of cancer worldwide[1]. The number of treated cases of early CRC is expected to increase with increased CRC screening and the application of endoscopic treatment such as endoscopic submucosal dissection and endoscopic full-thickness resection. T1 CRC is defined as carcinoma that is confined to the submucosal layer and does not invade the muscularis propria. Because simultaneous lymph node metastasis (LNM) occurs in approximately 10% of T1 CRC cases, we should determine whether additional surgical resection is necessary after endoscopic resection of T1 CRC according to the risk of LNM based on the pathological findings[2-9]. Several guidelines state the risk factors for LNM, which include the depth of submucosal invasion, lym-

phovascular invasion, tumor differentiation, and tumor budding[10-18]. However, tumor location is not cited as a prognostic risk factor despite the fact that CRC progression is expected to vary according to tumor location due to anatomical differences. Tumor location differs from other histopathological factors and is an objective factor with an impact on treatment selection and management. Focusing particularly on recent studies, this review aimed to investigate whether tumor location has an impact on the rate of LNM and recurrence in T1 CRC. It further considers whether the treatment and follow-up strategy for T1 CRC should be selected according to tumor location.

Category of Tumor Location

Tumor location in CRC is divided into the following two

Table 1. Comparison of LNM in T1 CRC between the Colon and Rectum.

Author (year)	Location	Type of study	Patients, n	LNM %, n Colon	LNM %, n Rectum	OR (95% CI)	P value
Kang et al. (2020)	Korea	Single center	221	10.9% 14/129	16.3% 15/92	1.6 (0.72–3.53)	0.239*
Ronnow et al. (2020)	Sweden	SCRCR database	1439	10.0% 105/1054	11.7% 45/385	0.934 (0.620–1.408)	0.745**
Oh et al. (2019)	Korea	Single center	833	13.1% 70/536	9.1% 27/297	0.67 (0.42–1.06)	0.089*
Barel et al. (2019)	France	FDCR database	234	6.8% 12/177	12.3% 7/57	N/A	0.2616*
Miyachi et al. (2016)	Japan	Single center	653	8.4% 39/463	11.1% 21/190	1.35 (0.73–2.43)	0.299*
Macias et al. (2015)	Germany	Single center	97	13.4% 9/67	16.7% 5/30	N/A	0.675*
Bosch et al. (2013)	Netherlands	Meta-analysis	2722 (10 studies [39, 53–61])	9.9% 169/1699	13.8% 141/1023	1.4 (1.1–1.7)	<0.001

LNM, lymph node metastasis; CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; SCRCR, Swedish Colorectal Cancer Registry; FDCR, Finistère Digestive Cancers Registry; N/A, not applicable; *univariate analysis; **multivariate analysis

categories: 1) colon and rectum; and 2) right- and left-sided. The colon comprises the cecum to the sigmoid colon, while the rectum consists of the upper rectum (Ra), which is the segment from the height of the inferior border of the second sacral vertebra to the peritoneal reflection, and the lower rectum (Rb), which is the segment from the peritoneal reflection to the superior border of the puborectal sling[19]. In addition, CRC is divided into right-sided disease, incorporating the cecum to the transverse colon, and left-sided disease, incorporating the descending colon to the rectum. In embryogenesis, the right colon, which comprises the cecum to the proximal two-thirds of the transverse colon, arises from the midgut. The left colon, which comprises the distal one-third of the transverse colon to the rectum, arises from the hindgut.

LNM

1. Colon vs rectum

Most studies report that rectal cancer patients have a statistically equal or higher rate of LNM compared with T1 CRC patients (Table 1)[6,20-25]. Several studies presented no significant difference in the rate of LNM between colon and rectal T1 cancer patients (colon vs rectum: Oh et al., 13.1% vs 9.1%, p = 0.089; Barel et al., 6.8% vs 12.3%, p = 0.2616; Miyachi et al., 8.4% vs 11.1%, p = 0.299; and Marcias et al., 13.4% vs 16.7%, p = 0.675)[6,23-25]. Using the Swedish Colorectal Cancer Registry with 1439 patients with T1 CRC[22], Ronnow et al. demonstrated that rectal cancer patients (11.7%) showed no significant difference in terms of LNM rate compared with colon cancer patients (10.0%) in univariate (odds ratio [OR] = 1.196, 95% confidence in-

terval [CI] 0.826-1.733, p = 0.343) and multivariate (OR = 0.934, 95% CI 0.620-1.408, p = 0.745) analyses. Although many of these studies showed a higher rate of LNM in rectal cancer patients, there was no significant difference, possibly because of the limited sample size. Bosch et al. performed a systematic review of 10 studies with 2722 patients[5]. In their study, rectal cancer patients demonstrated a significantly higher rate of LNM than those with colon cancer (colon: 9.9%, 169/1699; rectum: 13.8% 141/1023; OR = 1.4, 95% CI 1.1-1.7, p < 0.001).

2. Right-sided vs left-sided CRC

Several studies reported a higher rate of LNM in left-sided cancer patients than in right-sided cancer patients with T1 CRC (Table 2)[9,26-28]. Papers published in 2020-2021 compared the rate of LNM between right- and left-sided colon patients[26-28], and the conclusions were the same for all. Ouchi et al. investigated the rate of LNM in 458 T1 CRC patients and showed that those with right-sided colon cancer had a lower rate of LNM than patients with left-sided CRC (6/126 [4.8%] vs. 36/332 [10.8%], p = 0.04)[28]. The authors referred to genetic and anatomical characteristics as potential reasons for such differences. Mochizuki et al. also reported that left-sided T1 cancer patients showed significantly higher rates of LNM than those with right-sided cancer (left-sided 63/527 [12.0%] vs. right-sided 12/218 [5.5%], p < 0.05) in a retrospective single-center study investigating 745 T1 CRC patients[26]. They speculated that this difference was owing to the frequency of occurrence of lymphatic invasion, which was the most reliable predictor for LNM, was significantly higher in left-sided cancer patients than in those with right-sided cancer (left-sided 32.7% vs. right-sided 23.2%, p < 0.05), although the mechanism was un-

Table 2. Comparison of LNM between Right- and Left-sided T1 CRC.

Author (year)	Location	Type of study	Patients, n	LNM %, n Right	LNM %, n Left	OR (95% CI)	P value
Kudo et al. (2021)	Japan	Multicenter	3134	7.9% 79/995	11.2% 240/2139	1.44 (1.08–1.92)	0.01**
Guo et al. (2020)	China	SEER data	16106	10.0% 668/6655	16.1% 1520/9451	1.59 (1.43–1.76)	<0.001**
Mochizuki et al. (2020)	Japan	Single center	745	5.5% 12/218	12.0% 63/527	2.42 (1.23–4.78)	<0.05**
Ouchi et al. (2020)	Japan	Single center	458	4.8% 6/126	10.8% 36/332	N/A	0.04*

LNM, lymph node metastasis; CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results; N/A, not applicable; *univariate analysis; **multivariate analysis

Table 3. Association between Tumor Location and LNM in T1 CRC.

Author (year)	Location	Type of study	Patients, n	LNM %, n C	LNM %, n A (HF)	LNM %, n T	LNM %, n D (SF)	LNM %, n S	LNM %, n R
Mochizuki et al. (2020)	Japan	Single center	745	5.3% 2/38	3.8% 4/104	7.9% 6/76	4.3% 1/23	12.4% 45/363	12.1% 17/141
Xu et al. (2020)	China	SEER data	8056	11.5% 204/1781	9.1% (10.5%) 181/1989 (42/399)	9.9% 61/615	12.0% (8.3%) 49/410 (13/157)	15.4% 417/2705	N/A
Yim et al. (2017)	China	Single center	252	20.0% 1/5	10.5% 4/38	14.3% 2/14	0% 0/6	8.4% 8/95	17.0% 16/94
Toh et al. (2015)	UK	NYCRIS	206	0% 0/12	0% 0/12	0% 0/5	0% 0/9	12.0% 9/75	10.8% 10/93

LNM, lymph node metastasis; CRC, colorectal cancer; SEER, Surveillance, Epidemiology, and End Results; NYCRIS, Northern and Yorkshire Cancer Registry and Information Service; C, cecum; A, ascending colon; HF, hepatic flexure; T, transverse colon; D, descending colon; SF, splenic flexure; S, sigmoid colon; R, rectum; N/A, not applicable

clear. In addition to these single-center studies, Kudo et al. performed a multicenter study at seven institutions in Japan to develop an artificial intelligence model predicting the presence of LNM in T1 CRC patients[9]. In their study of 3134 patients with T1 CRC, left-sided location was also an independent risk factor for LNM (OR = 1.44, 95% CI 1.08-1.92, p = 0.01). Guo et al. used the Surveillance, Epidemiology, and End Results (SEER) database information for 2004-2016 to investigate a much larger population with T1 CRC[27]. The SEER database is one of the largest publicly accessible databases globally, covering approximately 30% of all cancers and including 18 population-based cancer registries in the USA (http://seer.cancer.gov/about/overview.html). This study of 16,106 T1 CRC patients showed that left-sided cancer was an independent risk factor for LNM in univariate (OR = 1.72, 95% CI 1.56-1.89) and multivariate (OR = 1.59, 95% CI 1.43-1.76) analyses. Thus, Dang et al. investigated the tumor-stroma ratio, which is reported to be a strong independent prognostic factor in advanced stage CRC, with high stromal occupancy being associated with worse prognosis and survival[29]. In their study, the left-sided colon showed a statistically higher stroma ratio than the right-sided colon (34% vs. 20%, respectively), which may be associated with the difference in LNM between the right- and left-sided colon cancer patients. In addition, for advanced CRC, many differences have been reported between right- and left-sided cancer: in right-sided cancer patients, who are more often women, microsatellite instability, CIMP/*BRAF* mutation, MAPK signaling, serrated pathway, mutagenic CYP450 metabolites, and HNPCC were more prevalent; in left-sided cancer patients, who are more likely men, chromosomal instability, *APC*/*KRAS*/*DCC*/*TP53* mutations, EGFR signaling, Wnt signaling, HER1, *HER2* amplification, and FAP were reported[30-34]. From these studies, a consensus that left-sided T1 CRC patients show a higher rate of LNM than those with right-sided cancer was reached.

3. Cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum

The sigmoid colon and rectum present a higher rate of LNM than other locations in T1 CRC patients. Some studies showed a correlation between each location in the colorectum and the presence of LNM (Table 3)[26,35-38]. Miyachi et al. and Mochizuki et al. investigated tumor location and LNM in 745 patients who underwent surgical resection with lymph node dissection[26,35]. Of these, LNM was observed in 10.1% of the patients (75/745). Interestingly, the sigmoid colon and the rectum showed a higher rate of LNM (sig-

Table 4. Comparison of LNM between Lower Rectum and Upper Rectum in T1 Cancer.

Author (year)	Location	Type of study	Patients, n	LNM %, n Lower	LNM %, n Upper/middle	OR (95% CI)	P value
Aytac et al. (2016)	US	Single center	68	11.1% 2/18	18% 9/50	N/A	N/A
Nakadoi et al. (2014)	Japan	Single center	78	18.8% 6/32	10.9% 5/46	N/A	N/A
Nascimbeni et al. (2002)	US	Single center	119	34% 10/34	10% 9/90	N/A	0.007*
Kikuchi et al. (1995)	Japan	Single center	84	17.3% 9/52	3.1% 1/32	N/A	N/A

LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval; N/A, not applicable; *univariate analysis

moid colon: 45/363 [12.4%] and rectum: 17/141 [12.1%]) than the other sites (cecum [C]: 5.3%, ascending colon [A]: 3.8%, transverse colon [T]: 7.9%, and descending colon [D]: 4.3%), which was notably higher in the sigmoid colon in women (26/136 [19.1%]). Furthermore, using the SEER database, Xu et al. reported that the sigmoid colon showed the highest OR (1.26, 95% CI 1.05-1,53], $p = 0.014$) for LNM in adjusted logistic regression analysis compared with other colon sites excluding the rectum (C: ref, A: OR = 0.77, 95% CI 0.62-0.96; HF: OR = 0.91, 95% CI 0.63-1.29; T: OR = 0.81, 95% CI 0.5-1.10; SF: OR = 0.63, 95% CI 0.33-1.11; D: OR = 0.92, 95% CI 0.64-1.28)[36]. A study by Yim et al. showed a different pattern of LNM, in which the cecum presented a high LNM rate (20%, 1/5), but the number of samples might have been insufficient. What these studies have in common is that many T1 CRCs are found in the sigmoid colon and rectum. Furthermore, from these studies, sigmoid colon could present the highest rate of LNM among other colon sites except the rectum in T1 CRC. A high rate of LNM in sigmoid colon is responsible for the high rate LNM in the left-sided colon and may be one of the factors for which there are no statistically significant differences in LNM between the colon and rectum.

4. Lower rectum vs upper rectum

The distance of primary tumor from the anal verge is of critical value, not only to determine the risk of LNM but also to decide whether to perform surgical resection that directly affects patients' quality of life. Therefore, we also reviewed the differences in LNM between the lower rectum and other sites in the rectum (including the upper and middle rectum) (Table 4)[39-42]. Nascimbeni et al. reported that 10 of 29 patients (34%) had LNM in the lower rectum and 9 of 90 (10%) had LNM in other sites in the rectum[39]. In a multivariate analysis that included colon cancer patients (n = 353), the lower rectum showed a significantly higher rate of LNM compared with other sites in the colorectum (OR = 6.0, 95% CI 2.2-14.2; $p < 0.001$). In three of four studies, the lower rectum showed a higher rate of LNM compared with other sites in the rectum, even though they were lim-

ited by their small sample sizes[39-41].

Recurrence

There is a consensus from most studies that rectal T1 cancer presents a higher recurrence rate than colon T1 cancer, regardless of the treatment strategy[43-47]. In a single-center study of 930 T1 CRC patients, Kouyama et al. reported that rectal location was a significant risk factor for recurrence in the total population, including endoscopic resection alone and surgical resection. Rectal cancer accounted for 6 out of 10 cases with recurrence (rectum; 3.6%; colon; 0.5%) and the rectum showed OR = 6.58 (95%CI, 1.83-23.63) for recurrence compared with the colon in Cox regression analysis. Yoda et al. and Yoshii et al. reported a similar tendency (rectum, 9.9% (10/101) and 14.5% (8/55); colon, 1.5% (5/327) and 2.3% (9/323), respectively)[44,45]. In 2020, a meta-analysis of 11 studies by Dang et al. revealed that the rectal cancer also indicated a higher recurrence rate than the colon cancer (colon, 0.8%, 95%CI 0.2-2.8; rectum, 5.7%, 95% CI 2.0-15.2)[47]. Finally, Ikematsu et al. investigated the recurrence rate between the colon and rectum dividing 758 T1 CRC patients into two groups according to the LNM risk in a multicenter study[46]. In the high-risk group for LNM, which had lymphovascular invasion, tumor differentiation, depth of invasion or tumor budding, the recurrence difference (OR, 6.73 [95%CI 1.04-43.43], $p = 0.045$) was stronger compared with the difference in the low-risk group. The possibility that this difference could result from the under-treatment of high-risk rectal T1 cancer cannot be ignored, although there was no significant difference in the rate of endoscopic resection alone for high-risk T1 cancer patients (colon 12.0% vs. rectum 17.3%, $p = 0.06$) in addition to the anatomical or biological differences between the colon and rectum. Similar trends were noted in another study (colon 32% vs rectum 44%)[45]. In particular, patients' refusal of additional surgery after endoscopic resection was observed more frequently in the lower rectum than in other sites in the colorectum, leading to worse prognosis (5-year RFS of 77.7% in the lower rectum, 96.5% in other

sites)[46,48]. Importantly, these studies indicated that surgical resection with lymph node dissection in patients with rectal T1 cancer with high-risk factors for LNM is highly recommended to decrease the recurrence rate. QOL-preserving treatments such as adjuvant chemoradiotherapy after endoscopic resection could be required as an alternative option to replace additional surgical resection for such lesions to reduce the risk of recurrence.

Ouchi et al. investigated the differences in recurrence between right- and left-sided cancer in 458 patients with T1 CRC[28]. Left-sided cancer showed a higher recurrence rate than right-sided cancer (0/126 [0%] vs 7/332 [2.1%], p = 0.10), even though there was no significant difference. Similarly, Guo et al. reported that left-sided cancer presented OR = 1.86 (95% CI 1.36-2.58, p < 0.001) in univariate analysis and OR = 1.43 (95% CI 1.00-2.07, p = 0.054) for distant metastasis compared with right-sided cancer. As well as LNM, the number of recurrences in the sigmoid colon in addition to the rectum was high compared with other colon sites (sigmoid, 3/10 vs other colon sites, 1/10[43]; sigmoid 4/15 vs other colon 1/15[45]). This might be because left-sided CRC, especially in the sigmoid colon and the rectum, was reported to show higher rates of LNM that were correlated with recurrence compared with right-sided T1 cancer. This was despite the fact that although the number of dissected lymph nodes were usually fewer in left-sided CRCs than in right-sided CRCs, with the lowest from rectal cancers, leading to an underestimation of LNM. International guidelines restrict their recommendations to a minimum number of 10 to 12 lymph nodes in CRC to represent both a prognostic marker and an indicator of the quality of surgical resection[14,16,49]. Regarding T1 CRC, Bakes et al. reported that a lymph node yield of <10 was associated with an increased risk of recurrence after surgical resection[50]. In addition, the number of lymph nodes retrieved in left-sided disease including the rectum was less than in right-sided[50,51]. This difference may be because right-sided CRC resection specimens were longer than left-sided CRCs, or there was variable lymphatic anatomy between them[52]. From these studies, the number of retrieved lymph nodes was similar to advanced CRC could be necessary, even for T1 CRC, to reduce the risk of recurrence.

Conclusion

This review investigated the differences in LNM and recurrence in T1 CRC patients according to tumor location. Many T1 CRCs are located in the sigmoid colon and rectum, and the frequency of both LNM and recurrence was higher in left-sided T1 cancer, especially in the sigmoid colon and rectum, than in right-sided T1 cancer in most studies. Although stronger evidence is required regarding any additional treatment or surveillance by tumor location to re-

flect on the treatment guidelines, we must consider these backgrounds when treating and managing T1 CRC.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Conception and design: K.I.; Drafting the article: K.I.; Literature search: K.I., Y.K., K.M., Y.T.; Critical revision: S.K., Y.K., K.M., Y.T., M.M., Y.M., T.H., K.W., H.M.; Study supervision: S.K., H.M.

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