Lymph node metastasis in T1 colorectal cancer: Risk factors and prediction model

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Received November 16, 2022; Accepted January 24, 2023

DOI: 10.3892/ol.2023.13776

Abstract. Endoscopic resection is typically performed for early T1 stage colorectal cancer (T1 CRC). Additional surgery is subsequently recommended based on pathological findings; however, the current criteria may result in overtreatment. The present study aimed to re-examine the reported risk factors for lymph node (LN) metastasis in T1 CRC and develop a prediction model using a large multi-institutional dataset. In this retrospective study, the medical records of 1,185 patients with T1 CRC who underwent surgery between January 2008 and December 2020 were investigated. Slides pathologically re-assessable for additional risk factors were re-examined. A total of 251 patients with inadequate data were excluded, and 934 patients were randomly assigned at a ratio of 3:1 to the training and validation datasets. In the univariate analysis, left-sided CRC (P=0.003), deep submucosal invasion depth (P=0.005), poor histological grade (P=0.020), lymphatic invasion (P<0.001), venous invasion (P<0.001) and tumor budding grade 2/3 (P<0.001) were significant risk factors for LN metastasis. A nomogram predicting LN metastasis was developed using these variables, with an area under the received operating characteristic curve (AUC) of 0.786. The nomogram was validated using a validation set with an AUC of 0.721, indicating moderate accuracy. No LN metastases were observed in patients with <90 points using the nomogram; therefore, patients with a low nomogram score may avoid undergoing surgical resection. Prediction of LN metastasis using this developed nomogram may help identify patients who are at high-risk who require surgery.

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Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; CRC, colorectal cancer; JSCCR, Japanese Society for Cancer of the Colon and Rectum; LN, lymph node; muc, mucinous carcinoma; OR, odds ratio; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; SM, submucosal

Key words: colorectal cancer, endoscopic resection, lymph node metastasis, multi-institutional dataset, nomogram

Introduction

The cancer incidence rate and cancer-associated death rate are increasing each year worldwide, with colorectal cancer (CRC) being the second leading cause of cancer-related death in 2020 (1). Surgery is one of the most effective treatment options for patients with stage I-III CRC and has been strongly recommended in several treatment guidelines (2-4); however, the development of endoscopic treatments for submucosal (SM) invasive CRC, including endoscopic mucosal resection and endoscopic SM dissection, has led to the cure of early CRC (5). T1 stage CRC [T1 CRC; staged using the Japanese Society for Cancer of the Colon and Rectum (JSCCR) 2020 guidelines (4)] is treated with endoscopic resection only, and T2-T4 CRC cases are treated with surgery; however, the treatment

of T1 CRC is controversial. European and Japanese guidelines recommend additional surgery following endoscopic resection to reduce local recurrence based on pathological findings (4,6). According to the JSCCR guidelines for the treatment of CRC (4), additional surgery with lymph node (LN) dissection is recommended for cases with an SM invasion depth >1,000 μm, vascular invasion, a positive endoscopic vertical margin, poorly differentiated adenocarcinoma (por), signet-ring cell carcinoma (sig) or mucinous carcinoma (muc), and/or grade 2/3 budding at the site of deepest invasion; however, in T1 CRC, the probability of LN metastasis ranges from 7.4 to 46.9%, depending on the combination of these risk factors (7).

In a multi-institutional retrospective study of 758 patients of T1 CRC, there were 106 patients who, despite being at high risk for LN metastasis, did not undergo LN dissection, and the reported 5-year disease-free survival rates for these patients were 96.5% for 69 patients with T1 colon cancer and 77.7% for 37 patients with T1 rectal cancer (8). In total, 5 and 2 patients had local recurrence and distant metastases, respectively; however, the 5-year overall survival rates were 98.3 and 96.2% for patients with T1 colon and rectal cancer, respectively, with additional treatments, including surgery and chemotherapy. Control of distant metastasis and local recurrence may need to be considered separately; in other words, additional surgery to minimize local recurrence for all patients with current risk factors may be considered an overtreatment, especially for patients with low risk of local recurrence and high surgical risk.

In the present study, the aim was to develop a model that accurately predicts the presence or absence of LN metastasis beyond the risk factors recommended by the guidelines. In a previous study, we retrospectively reported the risk factors for LN metastasis and developed a nomogram as a prediction model (9); however, it lacked data on budding, which has been considered a risk factor since 2009 according to guidelines, and it was a single-institution study. The present study aimed to evaluate risk factors, including new data on budding, and to develop a universal predictive model to recommend additional surgical resection in, to the best of our knowledge, the largest dataset of patients with T1 CRC.

Materials and methods

Patients and datasets. In the present multi-institutional study, the clinical records of 1,185 patients with T1 CRC who underwent surgery at The Osaka University Hospital (Suita, Japan), Osaka International Cancer Institute (Osaka, Japan), Japan Community Health Care Organization Osaka Hospital (Osaka, Japan), Osaka Rosai Hospital (Sakai, Japan), Minoh City Hospital (Minoh, Japan) and Toyonaka Municipal Hospital (Toyonaka, Japan) between January 2008 and December 2020 were retrospectively reviewed. Patients with T1 CRC who underwent surgery with lymph node dissection were included in the present study and those without lymph node dissection were excluded. There were 684 males and 501 females, with a median age of 68 (range 30-91) years. Data on primary CRC location, tumor type, head invasion, SM invasion depth, histological grade, lymphatic invasion, venous invasion, budding grade and LN metastasis were collected from the medical records. All patients underwent surgery with LN dissection after endoscopic resection or surgery for primary CRC resection. The presence of LN metastases was evaluated pathologically. SM invasion depth was evaluated as a continuous variable according to the Japanese Classification of Colorectal Carcinoma (9th edition in the Japanese version; 3rd edition in the English version) (10). Vascular invasion was evaluated using hematoxylin and eosin staining alone in 94 cases and immunocytochemistry using D2-40 in the remaining cases. According to the Japanese Classification of Colorectal Carcinoma 9th edition guidelines, venous and lymphatic invasion was divided into four categories: i) 0, no invasion; ii) 1a, slight invasion; iii) 1b, moderate invasion; and iv) 1c, massive invasion. Budding was graded into three categories: i) BD1, 0-4 buds; ii) BD2, 5-9 buds; and iii) BD3, >10 buds. For those cases with missing values in the medical records, but for which tissue sections were stored and could be re-evaluated, the pathologist performed a re-evaluation to supplement the missing values.

The minimum number of samples required for the training set was calculated as 10 times the number of samples for the explanatory variables used in the prediction model, and patients were randomly assigned to training and validation sets per institution. Random allocation was performed using the permuted block method via Microsoft Excel for Mac 2019 (version 16.63.1; Microsoft Corporation). In the training set, risk factors for LN metastasis were analyzed, and a prediction model for LN metastasis was developed using a logistic regression model. The prediction model was validated using the validation set.

This study was performed in accordance with the Declaration of Helsinki and was approved by the Osaka University Ethics Committee (Suita, Japan; approval no. 17448-4) and the ethics committees of all other institutions involved in this study. Comprehensive informed consent for the use of their data for research purposes was obtained from all patients in the form of the opt-out method.

Statistical analysis. Categorical variables were analyzed using the χ^2 test and continuous variables were analyzed using the Mann-Whitney U test. $P<0.05$ was considered to indicate a statistically significant difference. Univariate and multivariate logistic regression models were applied to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) to assess the independent contributions of each risk factor for LN metastasis. Nomograms for the prediction of LN metastasis were constructed using significant variables, one with risk factors that were significant in the univariate analysis and one with risk factors that were significant in the multivariate analysis.

The predictive rates of the nomograms and the risk factors for LN metastasis as defined in the JSCCR guidelines (4) were assessed using the area under the receiver operating characteristic curve (AUC). All statistical analyses were performed using the JMP Pro 16.0.0 statistical software program (SAS Institute, Inc.). A nomogram was constructed using R 3.6.3 (CRAN; The R Foundation for Statistical Computing).

Results

Demographic and pathological characteristics. The characteristics of the 1,185 patients with T1 CRC are shown in Table SI. In total, 251 patients who lacked any of the

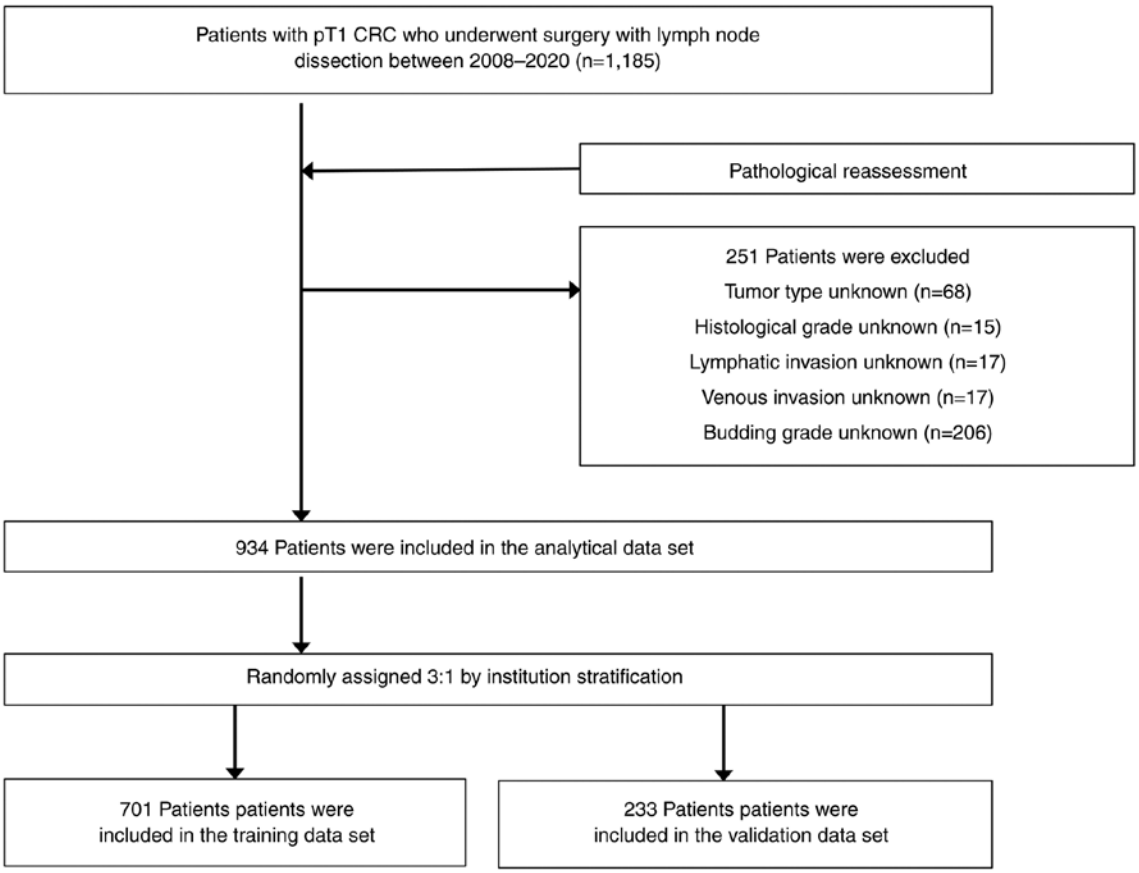

Figure 1. Overview of the analyzed dataset. In total, 1,185 patients with pT1 CRC who underwent surgery with lymph node dissection were included in the present study. Of these patients, 251 were excluded due to the lack of a clinicopathological finding. Some patients were excluded due to a lack of many clinicopathological findings and were therefore included in the patient numbers given for each exclusion criteria. Finally, 934 patients were included in the analysis dataset and randomized to the training and validation datasets. CRC, colorectal cancer; pT1, pathological tumor stage 1.

required clinicopathological findings were excluded. Finally, 934 patients were included in the analytic dataset (Table SII). LN metastasis was observed in 11.5% of patients, and the 934 patients were randomly assigned to the training and validation sets, in a 3:1 ratio per institution, and then analyzed together (701 and 233 patients were included in the training and validation sets, respectively). A flow chart presenting the recruiting and categorizing of patients in the study is shown in Fig. 1. There were no significant differences in clinicopathological factors between the training and validation sets (Table SII). In the training set, LN metastasis was evident in 87 out of 701 patients (12.4%; Table I). The mean ± SD SM invasion depth was 2,940±102 μm in patients without metastasis and 3,396±268 μm in those with metastasis. In the training set, among the patients in whom LN metastasis was absent or present, lymphatic invasion was observed in 222 (36.2%) and 65 (74.7%) patients, respectively, and venous invasion was observed in 121 (19.7%) and 38 (43.7%) patients, respectively. Budding grades BD2/3 were observed in 103 (16.8%) and 58 (66.7%) patients, respectively. Histological grade was categorized into the main histological and poor histological grades based on the degree of differentiation, in the following order: Papillary adenocarcinoma > well-differentiated tubular adenocarcinoma > moderately differentiated tubular adenocarcinoma > por, sig or muc. Left location (descending colon, sigmoid colon, rectosigmoid, rectum and/or anal canal; P=0.004), deep SM invasion depth (P=0.014), poor histological grade (por/sig/muc; P=0.016), lymphatic invasion (P<0.001), venous invasion (P<0.001) and BD2/3 (P<0.001) were all significant risk factors for LN metastasis.

Risk factors of lymph node metastasis. The results of the univariate and multivariable analyses of clinicopathological risk factors for LN metastasis in the training set are shown in Table II. The cut-off value for the SM invasion depth of 2,600 μm was selected from Youden's index for the receiver operating characteristic curve (11). Left-sided CRC, deep LN invasion, poor histological grade, lymphatic invasion, venous invasion and BD2/3 were all significant risk factors for LN metastasis, and left-sided CRC (OR, 2.035; 95% CI, 1.137-3.614; P=0.017), lymphatic invasion (OR, 3.812; 95% CI, 2.224-6.531; P<0.001), venous invasion (OR, 2.221; 95% CI, 1.332-3.670; P=0.002) and BD2/3 (OR, 1.969; 95% CI, 1.151-3.371; P=0.013) were all independent risk factors.

Nomograms constructed using risk factors. A predictive nomogram for LN metastasis in T1 CRC was constructed using the six significant variables from the univariate analysis, as shown in Fig. 2. The AUC of the training set was 0.786. The prediction model was validated using the validation set, and the AUC was 0.721. The calibration plots for both are shown in Fig. S1. A nomogram with the four independent risk factors from the

Table I. Analysis of risk factors for lymph node metastasis in the training set.

Factors	Lymph node metastasis		P-value
	Absent (n=614)	Present (n=87)	
Primary CRC location, n			0.004[a]
Right	224	18	
Left	390	69	
Tumor type, n			
Main tumor type[b]			
0-I	340	50	0.731
0-II	274	37	
All elements of tumor type[c]			
Including 0-II	221	29	0.722
Not including 0-II	393	58	
Head invasion, n			0.338
Absent	596	83	
Present	18	4	
Submucosal invasion depth			
Measured value[d], μm	2,940 ±102	3,396±268	0.014[a]
≥1,000 μm, n	81	6	0.096
<1,000 μm, n	533	81	
≥2,600 μm, n	287	55	0.004[a]
<2,600 μm, n	327	32	
Histological grade			
Main histological grade, n			0.787
Tub1, 2	586	84	
Muc, por, sig	28	3	
The least differentiated histological grade, n			0.016[a]
Including muc, por, sig	22	8	
Not including muc, por, sig	592	79	
Lymphatic invasion, n			<0.001[a]
Ly0	392	22	
Ly1a, b, c	222	65	
Venous invasion, n			<0.001[a]
V0	493	49	
V1a, b, c	121	38	
Budding grade, n			<0.001[a]
BD1	511	29	
BD2, 3	103	58	

[a]P<0.05; [b]The tumor type occupying the largest area is described; [c]All tumor types are included, not just the largest area; [d]mean ± SD. CRC, colorectal cancer; Tub1, well-differentiated tubular adenocarcinoma; Tub2, moderately differentiated tubular adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous carcinoma.

multivariable analysis was also constructed (Figs. S2 and S3). The AUCs were 0.775 and 0.692 for the training and validation sets, respectively. The AUC values were higher in the nomogram with six factors than in the nomogram with four factors. Therefore, the nomogram with six factors was determined to be a good prediction model for LN metastasis in patients with T1 CRC.

Next, the developed nomogram was compared with the risk factors recommended for additional surgical resection after endoscopic treatment. The data of the 934 included patients were analyzed, and the AUC was 0.530 for poor histological grade, 0.525 for SM invasion depth (≥1,000 μm), 0.703 for vascular invasion and 0.586 for BD2/3 (Table III). The nomogram utilizing all these factors together had a higher AUC (0.779) than each risk factor alone. Risk is seen not only as additive but also as synergistic. By combining the risk factors in this way as a nomogram, it should be possible to produce a range of low and high risks, which in turn produce an improved prediction. Moreover, the sensitivity and specificity were calculated using several cut-off values

Table II. Univariate and multivariable analyses of lymph node metastasis in the training set.

	Univariate analysis			Multivariate analysis		
Factor	OR	95% CI	P-value	OR	95% CI	P-value
Primary CRC location (left/right)	2.202	1.278-3.7938	0.003[a]	2.035	1.137-3.614	0.017[a]
SM invasion depth, μm (≥2,600/<2,600)	1.959	1.232-3.114	0.005[a]	1.574	0.955-2.596	0.075
The least differentiated histological grade						
Muc, por, sig/others	2.275	1.173-6.328	0.020[a]	1.954	0.774-4.934	0.156
Muc, por, sig/pap	$3.96x10^6$	$1.482-3.96x10^6$	0.022[a]			
Muc, por, sig/tub1	3.273	1.277-7.741	0.015[a]			
Muc, por, sig/tub2	2.295	0.915-5.270	0.074			
Lymphatic invasion (Ly1a, b, c/Ly0)	5.217	3.131-8.694	<0.001[a]	3.812	2.224-6.531	<0.001[a]
Venous invasion (V1a, b, c/V0)	3.160	1.979-5.045	<0.001[a]	2.221	1.332-3.670	0.002[a]
Budding grade (BD2, 3/BD1)	2.481	1.514-4.063	<0.001[a]	1.969	1.151-3.371	0.013[a]

[a]P<0.05. CRC, colorectal cancer; SM, submucosal; OR, odds ratio; CI, confidence interval; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous carcinoma.

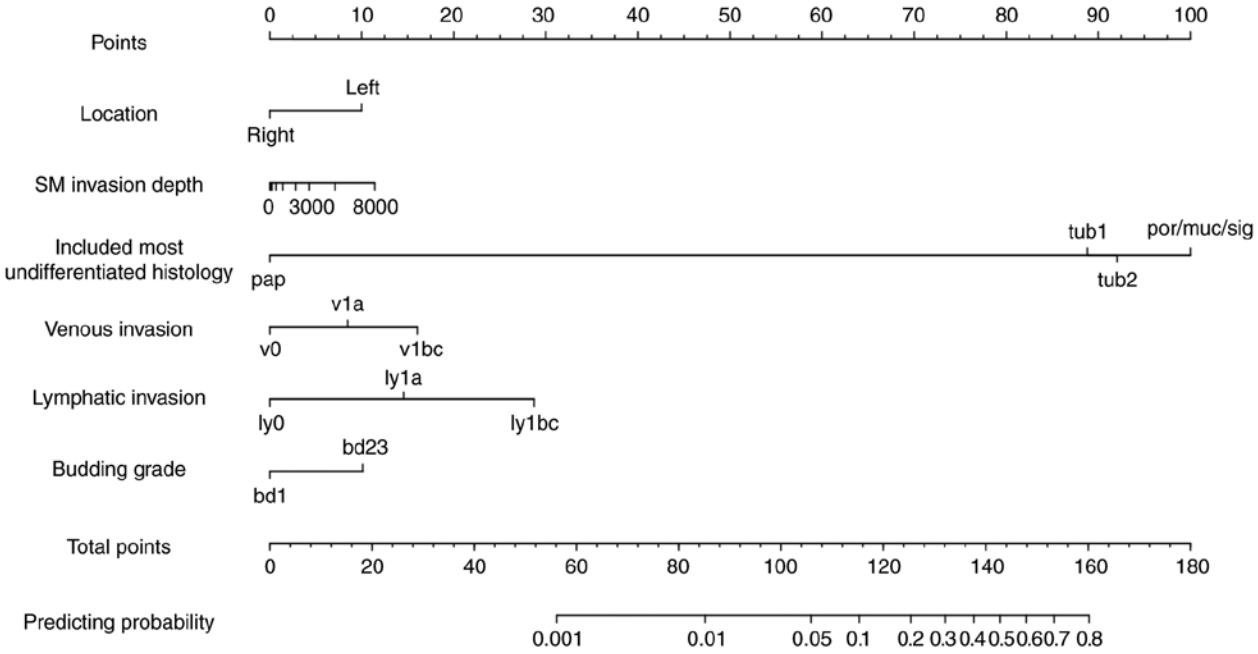

Figure 2. Nomogram predicting lymph node metastasis. The sum of the points for each variable was plotted on the total point axis. By drawing a vertical line from the plotted total point axis straight down to the predicted probability axis, the estimated lymph node metastasis rate can be obtained. muc, mucinous carcinoma; pap, papillary carcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; SM, submucosal; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma.

of the nomogram from the viewpoint of the patient population for whom an operation should be recommended. A total cut-off nomogram score of 114 points was determined as optimal via Youden's index, yielding a sensitivity and specificity of 0.882 and 0.637, respectively (Fig. S4). Among the 560 patients with a score <114 points, 22 had positive LNs (3.9%), and among the 374 patients with a score ≥114 points, 85 had positive LNs (22.7%). The cut-off value corresponding to a sensitivity of 1.000 was 90 points; among the 40 patients with a nomogram score <90, none had positive LNs (0.0%) (Table SIII; Fig S5).

Discussion

With the development of various surgical instruments and methods, surgery has become safer and has resulted in a lower mortality rate in recent years; the mortality rate for CRC surgery is ~3% (12,13), however, in recent years, older patients and those with more severe complications have also undergone surgery for cancer more frequently than before (14), and the survival gain is reportedly smaller in older patients than in younger patients, with the possibility of a subsequent increase in morbidity and mortality rates (15). Authors of

Table III. List of the AUCs from the nomogram and recommended risk factors for additional surgical resection after endoscopic treatment in all datasets.

Characteristics	AUC
Nomogram	0.779
Histological grade (por, sig or muc)	0.530
Depth of invasion (≥1,000 μm)	0.525
Vascular invasion (venous and/or lymphatic invasion)	0.703
Venous invasion	0.608
Lymphatic invasion	0.703
Budding (BD2/3)	0.586

AUC, area under the curve; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous carcinoma.

population-based studies have warned that it is unclear whether surgery is also the best option for elderly patients and those with severe complications; therefore, the non-surgical treatment of older patients with CRC has increased over time (16). Thus, the patient's background must be considered and precision medicine suitable for each individual case should be performed. As drug treatments for CRC have different outcomes depending on tumor characteristics, such as its location and gene mutations, it is important to evaluate the risk of LN metastasis in T1 CRC.

Previously, a re-examination of risk factors for LN metastasis in T1 CRC was reported to consider criteria for additional surgical resection (17). A meta-analysis also identified that an SM invasion depth >1,500 μm, vascular invasion, poorly differentiated histology and tumor budding were significantly associated with LN metastasis (18). To the best of our knowledge, the present study includes the largest number of cases to date for this topic in terms of being a complete dataset. Additionally, to the best of our knowledge, the present study is the first to show left-sided CRC as an independent significant risk factor for LN metastasis in T1 CRC. A nomogram was developed that accurately predicts the presence or absence of LN metastasis using significant risk factors, and if a cut-off value of 90 points was selected, 40 out of 934 (4.3%) patients in the dataset could have avoided undergoing surgery, with none of them having LN metastases. Undoubtedly, even if the score was 90-100 points, the predicted rate of LN metastasis was <5%, which is not considered high-risk; however, the nomogram may help reduce overtreatment and assess the benefits of surgery according to the individual's surgical risk and risk of LN metastasis.

However, the present study did have certain limitations in determining the best treatment for T1 CRC. The present study focused on surgical treatment aimed to reduce local recurrence and developed a nomogram by using existing clinicopathological factors. *BRAF* mutation is reportedly related to LN metastases (19); however, the study data lack information on the genetic status. Furthermore, although a high LN metastasis rate predicted by a combination of transcriptomic biomarkers has been reported (20,21), this issue was not examined in the present study. Further combinations of these useful molecular biological parameters may lead to an improvement in predictions. By contrast, local recurrence at the resection site or regional LNs can be prevented through surgical resection with LN dissection, but not distant metastasis. There have been reports of cases where no local recurrence or distant metastasis was observed in endoscopically treated T1 CRC (8,22). Distant metastases may be caused by other tumor characteristics that influence mortality. The *KRAS*, *NRAS*, *BRAF* and microsatellite stability statuses do not seem to be useful for prognosis in T1 CRC cases (19) and may differ from that in cases of advanced cancer. Further genetic analysis in T1 CRC should improve prognosis. In addition, information on the number of LNs dissected in this multi-center study was not collected, since there was no significant association between the number of retrieved LNs and the presence of LN metastases in the data set of the previous study (9).

Despite these limitations, the new nomogram for the prediction of LN metastasis in T1 CRC established in the present study is a useful clinical tool that may help clinicians provide personalized medical care, resulting in a reduction of overtreatment.

In conclusion, left-sided CRC, SM invasion depth, poor histological grade, lymphatic invasion, vascular invasion and BD2/3 were significant factors for the prediction of LN metastasis in T1 CRC cases. A nomogram using these variables may be able to predict LN metastases with high accuracy.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SF, NM and CSGOCG were responsible for the study conceptualization and design. MK, MY, MO, HO, YI, TS, MT, TT, KD, YS, KM, HY and SN made substantial contributions to acquisition and interpretation of data. KO and EM were responsible for pathological examination. SF, NM, MK, MY, HO, TS and YS confirm the authenticity of all the raw data. HT, MU, YD and HE were responsible for the analysis and interpretation of data. SF was responsible for drafting the manuscript. SF and NM were responsible for statistical analysis. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by The Osaka University Ethics Committee (Suita, Japan; approval no. 17448-4), The

Minoh City Hospital Ethics Committee (Minoh, Japan; R0203B92), The Toyonaka Municipal Hospital Ethics Committee (Toyonaka, Japan; 2019-03-04-5), The Osaka International Cancer Institute Ethics Committee (Osaka, Japan; 1607229069-3), The Japan Community Health Care Organization Osaka Hospital Ethics Committee (Osaka, Japan; 2019-50) and The Osaka Rosai Hospital Ethics Committee (Sakai, Japan; 2022-121).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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