JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2022-002
http://journal-arc.jp

Original Research Article

Risk Factors for Predicting Lymph Node Metastasis in Submucosal Colorectal Cancer

Kurumi Tsuchihashi[1)], Norikatsu Miyoshi[1)2)], Shiki Fujino[2)3)], Masatoshi Kitakaze[1)], Masayuki Ohue[4)], Katsuki Danno[2)3)], Itsuko Nakamichi[5)], Kenji Ohshima[6)], Eiichi Morii[6)], Mamoru Uemura[1)], Yuichiro Doki[1)] and Hidetoshi Eguchi[1)]

1) Department of Surgery, Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Japan
2) Department of Innovative Oncology Research and Regenerative Medicine, Osaka International Cancer Institute, Osaka, Japan
3) Department of Surgery, Minoh City Hospital, Minoh, Japan
4) Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan
5) Department of Pathology, Minoh City Hospital, Minoh, Japan
6) Department of Pathology, Graduate School of Medicine, Osaka University, Suita, Japan

Abstract

Objectives: The cornerstone of treating colorectal cancer (CRC) is generally a surgical resection with lymph node (LN) dissection. The tools for predicting lymph node metastasis (LNM) in submucosal (SM) CRC are useful to avoid unnecessary surgical resection.

Methods: Retrospectively, we analyzed 526 consecutive patients with SM CRC who underwent surgical resection at the Osaka International Cancer Institute, Osaka University Hospital, and Minoh City Hospital, Japan, between 1984 and 2012. The Osaka International Cancer Institute group and the Osaka University Hospital group were randomly divided into a training set and a test set of 2:1. The prediction model was validated in Minoh City Hospital.

Results: We partitioned patients using three risk factors involved in the presence or absence of LNM in SM CRC: lymphatic invasion (Ly), budding grade (BD) and the depth of submucosal invasion (DSI) (cut-off value 2789 μm) that were significantly different in the multivariate analysis. As a result, a predictive model of "LNM <5%" when "Ly negative and DSI <2789 μm" was evaluated. We similarly partitioned by DSI 3000 μm as easy-to-evaluate values in clinical use. We developed the additional model for predicting LNM is 1.05%, that is, LNM <5%, when there are "Ly negative and DSI <3000 μm."

Conclusions: As a limitation, only patients who underwent surgical resection were included in this study. This predictive model could help clinicians and CRC patients decide on the additional surgery required after endoscopic resection.

Keywords

submucosal colorectal cancer, lymph node metastasis, predictive model, partition

J Anus Rectum Colon 2022; 6(3): 181-189

Introduction

Colorectal cancer (CRC) is the most common type of cancer and is one of the leading causes of cancer-related deaths[1]. In Japan, CRC was the primary and the third leading cause of death among women and men, respectively,

Corresponding author: Norikatsu Miyoshi, nmiyoshi@gesurg.med.osaka-u.ac.jp
Received: January 14, 2022, Accepted: May 1, 2022

in 2020[2]. Currently, CRC is diagnosed at an early stage more frequently due to the recent advances in endoscopic techniques[3,4]. For patients with early-stage CRC, clinicians must consider the more beneficial treatment depending on the tumor stage. The treatment strategies focused on cancer located in the submucosa regardless of lymph node metastasis (LNM). Therefore, the depth of submucosal invasion (DSI) is considered the most important factor in determining a suitable treatment strategy[5]. According to the 2019 Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines, a DSI of ≥1000 μm, lymphovascular invasion positive, budding grade 2/3, or histological type are risk factors for LNM in submucosal (SM) CRC. In the guidelines, intestinal resection with lymph node dissection is recommended as an additional treatment if any observed findings.

Surgical resection with LN dissection is generally recommended; however, the rate of LNM varies from 6% to 13% in T1 tumors[6-9]. Concerning the additional surgery, previous retrospective analyses have reported that the factors described below are significantly correlated with LNM and tumor recurrence. These include histological grade (mucinous carcinoma, poorly differentiated adenocarcinoma, or signet-ring cell carcinoma), lymphovascular invasion, absolute depth of tumor invasion, tumor budding. And recently, the risk factors included poorly differentiated clusters[10,11]. When these risk factors are combined, the probability of LNM ranges from 7.4% to 46.9%[11].

Surgical resection of CRC is the cornerstone of the treatment. However, colorectal surgery can be complex. The incidence of anastomotic leakage (AL), one of the major complications of colorectal surgery, varies widely 3%-30%, and the postoperative mortality is high due to AL[12-16].

There is a consensus that comorbidities, such as cardiovascular disease and diabetes play a crucial role in the outcome of the surgery because they increase the postoperative complications. Older patients are more likely to have cardiovascular and pulmonary comorbidities, which are associated with increased perioperative risk. Older patients have less physiological reserves to cope with major surgery. Recent reports suggest that older patients with certain risks might be overtreated[17]. Overtreatment results in the possibility of subsequent excess morbidity and mortality.

In addition, 25%-80% of patients with a low rectal or coloanal anastomosis have postoperative clusters of bowel symptoms. These include stool frequency, fecal incontinence, stool fragmentation, urgency, emptying difficulties, and increased intestinal gas[18,19]. Rectal resection alters the structure and physiology of the anal rectum and causes functional problems.

Therefore, the need and importance of surgical treatment have to be evaluated carefully for each patient. The tools for predicting LNM in SM CRC are useful to avoid unnecessary surgical resection. In addition to clinicians, patients also face a choice of treatment options, and they must consider radical resection, oncological resection, and surveillance. Accurate risk stratification and predictive tools are highly valued for helping them in this decision-making process. We retrospectively examined risk factors in numerous patients using medical records and developed a new predictive model for LNM in SM CRC.

Methods

Patients and datasets

We retrospectively analyzed 526 consecutive patients with SM CRC who were surgically treated at the Osaka International Cancer Institute, Osaka University Hospital, and Minoh City Hospital, Japan, between 1984 and 2012. This study did not include familiar heredity cancer, colitic cancer, neuroendocrine tumor, and gastrointestinal stromal tumors. We assessed the relationship between the clinicopathological characteristics (primary CRC location, macroscopic tumor type, DSI, head invasion, histological grade, lymphatic invasion (Ly), vascular invasion (V), and budding grade (BD)) and LNM. The relationship between DSI and LNM was analyzed by the receiver operating characteristic (ROC), and the area under the curve (AUC) was calculated to determine the cut-off value of DSI[20]. These factors were evaluated in univariate and multivariate analyses. Ly, BD, and DSI (cut-off value 2789 μm) that were significantly different in multivariate analysis and V that was significantly different in the univariate analysis were considered risk factors involved in the presence or absence of LNM.

The Osaka International Cancer Institute group and the Osaka University Hospital group were randomly divided into a training set and a test set of 2:1. The training set included 262 patients, and the test set included 130 patients. The predictive model was validated in Minoh City Hospital (Figure 1).

The data includes the information of the samples in the old period, and some lacked the data of Ly, V, BD, and DSI. We re-evaluated the specimen to obtain information about 16 cases and the histological findings to obtain the information of DSI, lymphovascular invasion, and BD. We examined the immunohistochemical staining by D2-40 and elastica van gieson.

The Ethics Committees of the Osaka International Cancer Institute, Osaka University Hospital, and Minoh City Hospital approved this retrospective study. All patients provided written informed consent. All statistical analyses were performed using the JMP 16.0 statistical software program (SAS Institute, Cary, NC, USA)[21].

Pathological examination

Two pathologists, respectively, at the Osaka International

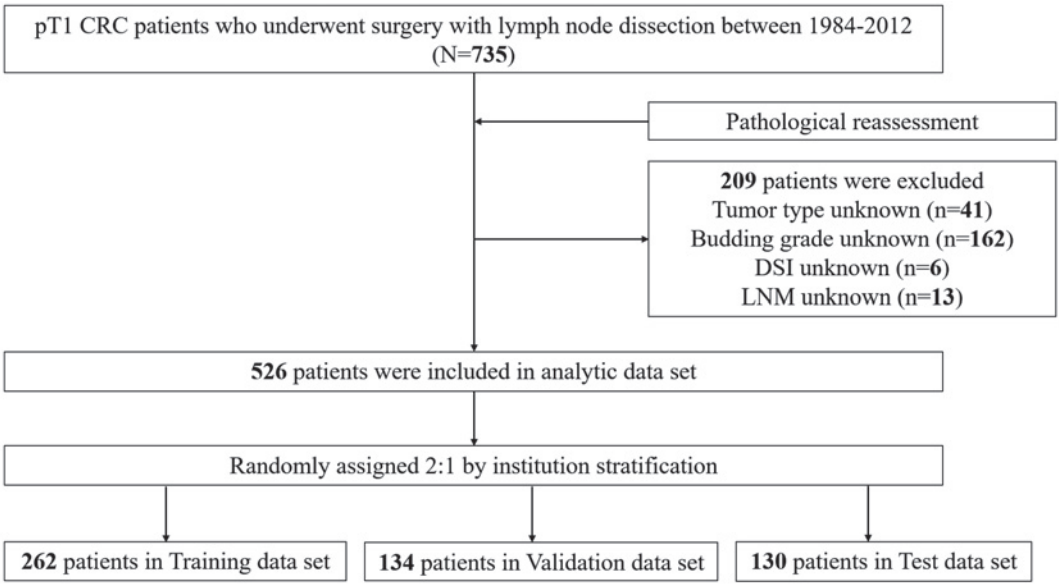

Figure 1. The schema of this study:
We retrospectively analyzed 735 consecutive patients with submucosal (SM) colorectal cancer (CRC) who were surgically treated at the Osaka International Cancer Institute, Osaka University Hospital, and Minoh City Hospital, Japan, between 1984 and 2012. Excluding 209 patients because of lacking data, a total 526 patients were divided into three groups.

Table 1. Patients' Clinical Characteristics.

Factors	Number of patients (N = 526)		
	Training set (N = 262)	Validation set (N = 134)	Test set (N = 130)
Primary CRC location (V, C, A, T/D, S/RS, Ra, Rb, P)	96/62/104	49/49/34	37/38/55
Main tumor type (Polypoid type/Others*)	128/134	76/58	70/60
Main histological grade (tub1/tub2/pap, muc, por, sig)	144/115/3	76/48/10	87/41/2
Head invasion (Absent/Present)	252/10	132/2	125/5
DSI (<3000 μm/≥3000 μm)	130/132	57/77	72/58
Lymphatic invasion (Ly0/Ly1/Ly2)	196/62/4	83/51/0	101/28/1
Venous invasion (V0/V1/V2)	216/42/4	94/35/5	101/28/1
Budding grade (BD1/BD2/BD3)	231/23/8	110/16/8	112/16/2
Lymph node metastasis (N0/N1/N2/N3)	230/30/1/1	120/12/ 20	115/13/2

CRC: colorectal cancer; V: appendix vermiformis; C: caecum; A: ascending colon; T: transverse colon; D: dissent colon; S: sigmoid colon; RS: rectosigmoid; Ra: upper rectum; Rb: lower rectum; P: anal canal; DSI: depth of submucosal invasion.
*Others: type 0-II and 0-III in the Japanese Classification of Colorectal Carcinoma

Cancer Institute and Osaka University Hospital and one pathologist at Minoh City Hospital examined the pathological findings. All specimens were fixed in 10% buffered formalin, followed by graded ethanol solutions in staining. The degree of histological differentiation, DSI, and lymphovascular invasion were evaluated. The DSI was measured according to the Japanese Classification of Colorectal Carcinoma (9th edition)[22]. When the muscularis mucosae (MM) were identified, the vertical distance from the MM to the deepest level of tumor invasion represented the DSI. If the MM could not be identified, the vertical distance from the superficial aspect of the tumor to the deepest level of invasion was measured.

Results

The characteristics of all 526 CRC patients, including 262 training set patients, 134 validation set patients, and 130 test set patients, are shown in Table 1. We performed a univariate analysis of the risk factors associated with LNM. DSI (cut-off value 2789 μm) ($P = 0.0144$), Ly ($P < 0.0001$), V ($P = 0.0051$), and BD ($P = 0.0012$) were important risk factors. However, the location and tumor type, DSI (cut-off value 1000 μm), histologic grade, and head invasion were not im-

Table 2. Association of Clinicopathological Factors with Lymph Node Metastasis.

	Variables	N = 526 (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Location	Right/Left	182 (34.6)/344 (65.4)	1.56 (0.86–2.85)	0.1463		
	Colon/Rectum	331 (62.9)/195 (37.1)	1.21 (0.70–2.08)	0.5016		
Tumor type*	Polypoid type/Others	274 (52.1)/252 (47.9)	1.02 (0.60–1.74)	0.9512		
DSI	≥1000μm/<1000μm	455 (86.5)/71 (13.5)	0.81 (0.35–1.86)	0.6235		
DSI (ROC)**	≥2789μm/<2789μm	275 (52.3)/251 (47.7)	0.49 (0.28–0.87)	0.0144	0.53 (0.29–0.97)	0.0407
Head invasion	Present/Absent	17 (3.2)/509 (96.8)	1.02 (0.23–4.56)	0.9825		
Histological grade***	Well-mod/Others	511 (97.1)/15 (2.9)	NA	0.9867		
Lymphatic invasion	Present/Absent	146 (27.8)/380 (72.2)	7.03 (3.95–12.5)	<0.0001	6.11 (3.37–11.1)	<0.0001
Vascular invasion	Present/Absent	115 (21.9)/411 (78.1)	2.26 (1.28–3.99)	0.0051	1.43 (0.76–2.67)	0.2631
Budding grade	Present/Absent	73 (13.9)/453 (86.1)	2.82 (1.51–5.27)	0.0012	2.04 (1.04–4.03)	0.039

CI: confidence interval

OR: odds ratio

DSI: depth of submucosal invasion

NA: Not available

*Polypoid type: type 0-I defined in the Japanese Classification of Colorectal Carcinoma

*Others: type 0-II and 0-III in the Japanese Classification of Colorectal Carcinoma

**DSI (ROC): DSI 2789 μm is a cut-off value derived from the receiver operating characteristic (ROC)

***Well-mod: well and moderately differentiated adenocarcinoma

***Others: poorly differentiated, mucinous, and signet ring cell adenocarcinoma

portant risk factors (Table 2). Similarly, we performed a multivariate analysis of the risk factors associated with LNM. DSI (cut-off value 2789 μm) (P = 0.0407), Ly (P < 0.0001), and BD (P = 0.039) were important risk factors. However, V was not an important risk factor (P = 0.2631) (Table 2). We partitioned using the three risk factors involved in the presence or absence of LNM in SM CRC: Ly, BD, and DSI (cut-off value 2789 μm) which were significantly different in the multivariate analysis. As a result, a predictive model shown in Figure 2A was completed. "Ly negative and DSI <2789 μm" in Figure 2A shows a predictive model in which LNM is 1.10% (1/91), that is, LNM <5% when the DSI cut-off value is 2789 μm and the predictive model with the highest negative predictive value (Table 3).

Figure 3 shows the AUC of the predictive model of Figure 2A. The AUC of the training set is 0.8043, the AUC of the validation set is 0.7774, and the AUC of the test set is 0.7154, so the predictive model of Figure 2A is considered useful. However, DSI 2789 μm is a cut-off value derived from the ROC of DSI, so it is difficult to use clinically. Therefore, in clinical use, we similarly partitioned by DSI 3000 μm as easy-to-evaluate values (Figure 2B). The same predictive model as DSI 2789 μm was obtained, and in the case of that predictive model, "Ly negative and DSI <3000 μm," LNM was concluded to be 1.05% (1/95) (Figure 4A).

In general, macroscopic appearance is divided into two types polypoid type and flat/depressed type. We evaluated our new predictive model according to polypoid and flat/depressed types. As a result, LNM in the group was 3.70% (3/81) in polypoid types, and LNM was 0.92% (1/109) in flat/depressed types (Figure 4B).

Discussion

The standard treatment for CRC is surgical resection. As endoscopic techniques are developed, low-risk mucosal and SM CRC can be treated by colonoscopic resection. Patients with early-stage CRC remedied by endoscopic resection and/or surgery have good long-term outcomes. Adequate surgical resection with lymphadenectomy is recommended for T1 CRC that do not meet the current indications for endoscopic treatment of T1 CRC[23]. The 5-year disease-free survival and 5-year overall survival in SM CRC after surgical resection are 95%-97% and 97%-99%, respectively[24]. Intraoperative and perioperative complications may occur with surgical treatment[25,26]. Severe complications such as AL may be a major cause of death[27], with a mortality of approximately 5%[24]. Surgical resection, including regional LNs, is the standard treatment for CRC. However, the procedure can cause complications or other functional problems, especially for elderly or vulnerable patients.

Recent reports have suggested that older patients with certain risks (such as cardiovascular disease and diabetes) could be overtreated[17].

A study reported that younger patients with CRC were prone to have a higher risk of LNM compared with older patients[28]. Any surgery always involves risks, such as infection, bleeding, and AL, and especially they are severe problems in older populations. Therefore, the risk of sur-

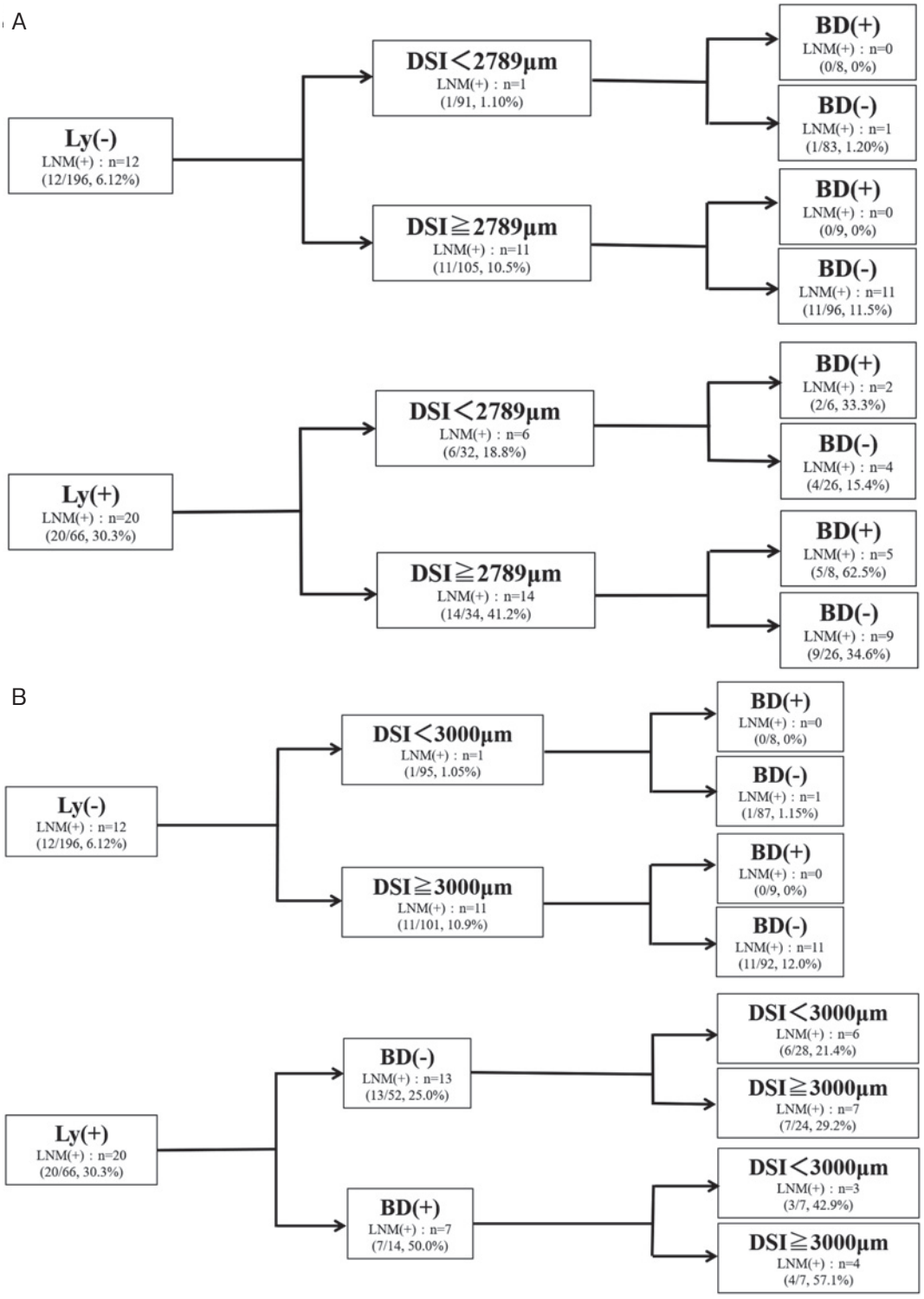

Figure 2. A predictive model with LNM <5%:
DSI 2789 μm is a cut-off value derived from the receiver operating characteristic (ROC) curve of DSI (A). However, it is difficult to use clinically. Therefore, in clinical use, we similarly partitioned by DSI 3000 μm as easy-to-evaluate values (B). The same predictive models as DSI 2789 μm were obtained and LNM was concluded to be 1.05% (1/95).

gery, including perioperative complications, should be taken into consideration, particularly in older and high-risk patients. If such a patient with an underlying disease has a low risk of LNM, it may be possible to follow the patient, con-

sidering the high complication rate related to surgery. The LNM rate of pT1 CRC is 10%-15%[29-33]; therefore, more than 85% of patients with pT1 CRC do not have LNM and undergo unnecessary surgery. The need for surgical treatment has to be evaluated in each case. Consequently, the tool that predicts LNM in SM CRC is useful.

Measuring the DSI is an important component of the JSCCR and ESGE guidelines. In a retrospective multicenter study, Kawachi et al.[30] reported that a DSI of ≥1000 μm is a useful factor for predicting LNM. However, many studies have provided contradictory results about the effectiveness of the treatment strategies based on a DSI cut-off value of 1000 μm. The reports of SM invasive factors that replace DSI of ≥1000 μm are presently controversial[34-37].

Table 3. Prediction Accuracy and Constructed Predictive Model Values According to the Depth of Submucosal Invasion.

	Ly (–)	
	DSI < 2789μm	DSI < 3000μm
Sensitivity	0.031	0.031
Specificity	0.391	0.409
Positive predictive value	0.007	0.007
Negative predictive value	0.744	0.752

DSI: depth of submucosal invasion
Ly (–): lymphatic invasion negative

The 2019 guidelines mention that careful consideration is required for DSI compared with other LNM risk factors (special histological types, lymphovascular invasion, and BD). Not all cases with DSI of ≥1000 μm require additional surgery[38].

Even if the DSI is 1000 μm or more, approximately 90% of the patients do not have LNM. Therefore, additional treatment should also be performed to consider the risk factors for LNM other than DSI. These include the physical and social background of each patient and patient preference. Hence, careful consideration of modifications is important.

We evaluated the risk factors for LNM in SM CRC and developed a new model for predicting LNM. It was constructed using the two significant risk factors, Ly and DSI (cut-off value 3000 μm). In our study, if there were "Ly negative and DSI <3000 μm," a new model for predicting LNM is 1.09%, which is a very low probability.

Recently, several predictive scores and models have been reported for surgical complications, genetic mutational status, and cancer prognosis[39-42].

These scores can predict the prognosis or complications of each patient. In previous reports, the probability of LNM in SM CRC varied depending on a combination of risk factors[43].

This study evaluated the risk factors for LNM in SM CRC and developed a new model for predicting LNM in individual SM CRC patients. Considering the recent increase

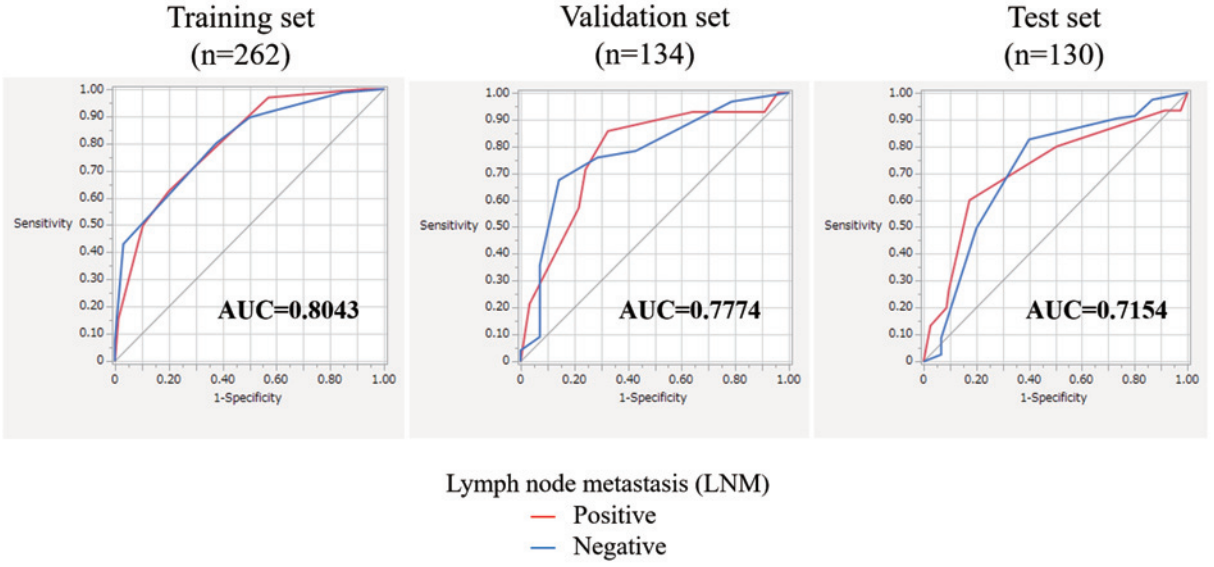

Figure 3. A predictive model with LNM:
The Osaka International Cancer Institute group and the Osaka University Hospital group were randomly divided into a training set and a test set of 2:1. A total of 262 patients were included in the training set and 130 patients included in the test set. The predictive model was validated in Minoh City Hospital. Figure 3 shows AUC of the predictive model of Figure 1. The AUC of the training set is 0.8043, the AUC of the validation set is 0.7774, and the AUC of the test set is 0.7154.

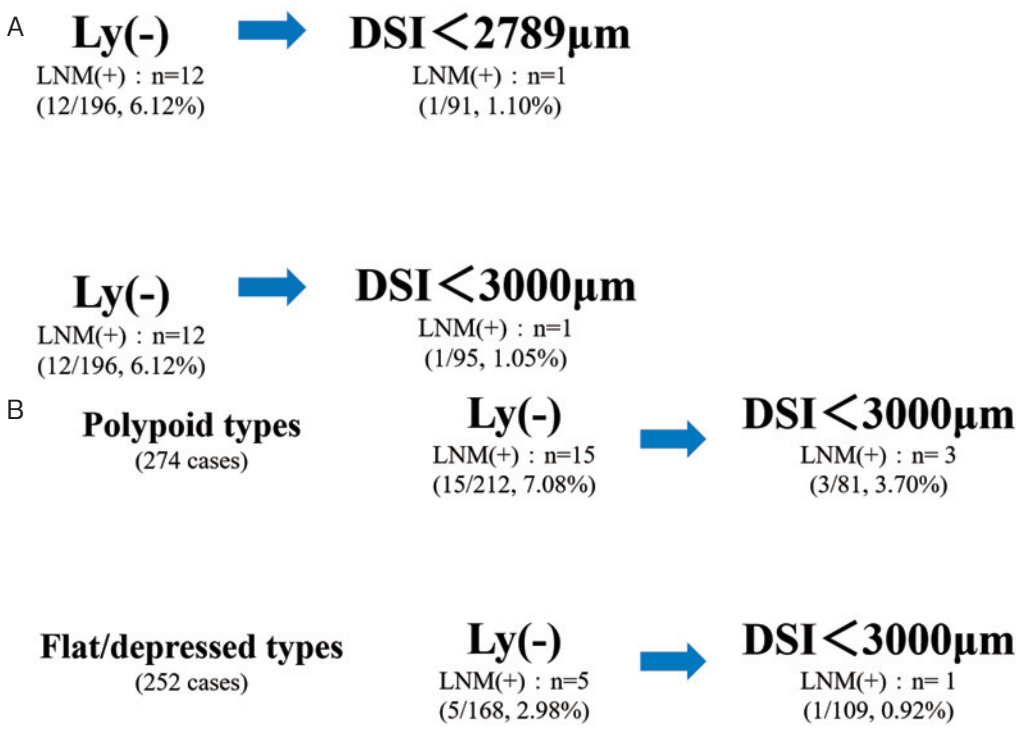

Figure 4. A predictive model for LNM without BD information:
Without BD information, the predictive model as DSI <2789 or 3000 in the case of "Ly negative" showed LNM (A). The macroscopic appearance was divided into two types, polypoid or flat/depressed. In our new predictive model according to polypoid and flat/depressed types, LNM in each group was 3.70% (3/81) in polypoid types and 0.92% (1/109) in flat/depressed types (B).

in the number of surgeries with complications in older patients, our predictive model may help in determining whether additional surgery is necessary after endoscopic resection or not.

This study has several limitations. Only patients who underwent surgery according to the JSCCR guidelines were included in this study. We evaluated five patients who did not undergo additional surgery at the patient's request, as shown in Supplementary Table S1. All patients were not diagnosed with LNM, followed by CT/MRI. However, we think our data are insufficient as a reference, requiring further consideration. And in this study, it is difficult to examine the detail of the tumor type, such as head invasion of non-Ip lesion. And two pathologists, respectively at the Osaka International Cancer Institute and Osaka University Hospital, examined the pathological findings; however, one pathologist at Minoh City Hospital examined the pathological findings.

Furthermore, in this study, it seems insufficient to consider the possibility of the LNM with two factors (Ly and DSI), without the evaluation that BD and/or V factors are positive or negative because of the bias of the sample size. Compared with those in previous studies, there were few participants in this study. The accidental occurrence event might not have been fully examined. A multi-institution study with a higher number of patients is required. However, our new predictive model of LNM in SM CRC may be useful as a clinical tool because it predicts the probability for the individual patient. This method results in enhanced personalized medical care. With the advent of population-based screening for CRC, the incidence of early CRC is increasing. An increasing number of patients have to choose between radical surgery and surveillance. Accurate risk stratification tools are of high value to help them in this decision-making process. We successfully developed a new predictive model for LNM in SM CRC by integrating two pathological factors: DSI and Ly. This tool could help physicians and patients decide the additional surgical treatments required after endoscopic resection.

Acknowledgements

We are grateful to Ayaka Tojo and Aya Ito for helping out with this study.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

KT and NM wrote this article. SF, MK, MO, KD, IN, KO, EM, MU, YD, and HE contributed to the data acquisition. KT, NM, SF, and MK analyzed the data. NM super-

vised this study.

Approval by Institutional Review Board (IRB)

Ethics Committees of the Osaka International Cancer Institute, Osaka University Hospital, and Minoh City Hospital. Written informed consent was obtained from all patients (approval code: 17448-4).

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Supplementary Files

Supplementary Table S1.

Please find supplementary file(s);
http://dx.doi.org/10.23922/jarc.2022-002