



Risk Stratification of T1 Colorectal Cancer Metastasis to Lymph Nodes: Current Status and Perspective

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With the widely spreading population-based screening programs for colorectal cancer and recent improvements in endoscopic diagnosis, the number of endoscopic resections in subjects with T1 colorectal cancer has been increasing. Some reports suggest that endoscopic resection prior to surgical resection of T1 colorectal cancer has no adverse effect on prognosis and contributes to this tendency. The decision on the need for surgical resection as an additional treatment after endoscopic resection of T1 colorectal cancer should be made according to the metastasis risk to lymph nodes based on histopathological findings. Because lymph node metastasis occurs in approximately 10% of patients with T1 colorectal cancer according to current international guidelines, the remaining 90% of patients may be at an increased risk of surgical resection and associated postoperative mortality, with no clinical benefit derived from unnecessary surgical resection. Although a more accurate prediction system for lymph node metastasis is needed to solve this problem, risk stratification for lymph node metastasis remains controversial. In this review, we focus on the current status of risk stratification of T1 colorectal cancer metastasis to lymph nodes and outline future perspectives. ([Gut Liver 2021;15:818-826](#))

Key Words: Lymph node metastasis; Treatment strategy; T1 colorectal cancer; Endoscopic resection; Surgical resection

INTRODUCTION

Colorectal cancer (CRC) is the fourth commonest cancer worldwide with an estimated age-standardized incidence rate of 19.7/100,000 and is the third leading cause of cancer-related death with an estimated age-standardized mortality of 8.9% in 2018.¹ With the prevalence of population-based screening programs for CRC and recent rapid progress in endoscopic techniques, the number of endoscopic resections in early CRC has been increasing.^{2,3} Intramucosal cancers are reported to have no potential for lymph node metastasis (LNM), which are an acceptable indication for endoscopic resection.^{4,5} On the other hand, approximately 10% of patients with submucosal invasion (T1) CRCs have LNM and therefore subsequently require intestinal resection with lymph node dissection after endoscopic resection for cure.

Decisions on surgical resection as an additional treat-

ment after endoscopic resection of T1 CRCs are made on the basis of results of pathological findings of the endoscopically resected specimens and usually in accordance with established guidelines, such as those of the National Comprehensive Cancer Network (NCCN)/American Society for Gastrointestinal Endoscopy (ASGE), the European Society for Medical Oncology (ESMO)/European Society of Gastrointestinal Endoscopy (ESGE), the Korean clinical practice guidelines, or the Japanese Society for Cancer of the Colon and Rectum (JSCCR).⁶⁻¹³ However, even following these guidelines, LNM occurs in only 6% to 16% of such patients.¹⁴⁻²³ Most patients without LNM are routinely exposed to the risk of surgical resection with an associated postoperative mortality rate of 1.5% to 2% and no clinical benefit.²⁴ To reduce these unnecessary surgical resections and provide patients with proper treatment without excess or deficiency, development of a more accurate prediction model for LNM is necessary.

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This review focuses on up-to-date information about risk stratification of T1 CRC metastasis to lymph nodes and outlines further perspectives on determining whether patients should undergo additional surgical resection after endoscopic resection of T1 CRC.

CURABILITY IN THE CURRENT GUIDELINES

The indication criteria for surgical resection as an additional treatment after endoscopic resection of T1 CRC have been defined in the United States, European, Korean, and Japanese guidelines (Table 1).⁶⁻¹³ When the vertical margin is positive, surgical resection is recommended. When the vertical margin is negative, if any of the following findings is observed during histopathological examination of the resected specimen, surgical resection with lymph node dissection is recommended: (1) depth of submucosal invasion; (2) lymphovascular invasion; (3) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; (4) tumor budding. Table 2 presents risk factors for LNM from multivariate analyses of studies with more than 400 cases of T1 CRC.^{14,17-21,25-28} Studies using the same database in the Surveillance, Epidemiology, and End Results (SEER) included one with a longer study period.^{19,29} As mentioned in each guideline, lymphovascular invasion (odds ratio [OR], 4.4 to 10.199), histological differentiation (OR, 2.09 to 18.444), tumor budding (OR, 1.70 to 2.350), and depth of submucosal invasion (OR, 2.14 to 5.404) were reported in many studies to be the main risk factors for LNM in T1 CRCs.

ADDITIONAL RISK FACTORS FOR LNM

Several studies have referred to predictive factors other than those of the guidelines to stratify more accurately the metastasis risk to lymph nodes in T1 CRC. Risk factors previously reported have included tumor location, patient's sex and age, the status of muscularis mucosae, and the volume of carcinoma, among others.

Table 1. Curability Criteria for Endoscopic Resection of T1 Colorectal Cancer According to Four Guidelines

| | Lymphovascular invasion | Histological grade | Depth of submucosal invasion | Tumor budding |
|--------------------------|-------------------------|--------------------|------------------------------|---------------|
| USA ^{8,11,13} | ○ | ○ | ○ | ○ |
| Europe ^{7,9,10} | ○ | ○ | ○ | ○ |
| Korea ¹² | ○ | ○ | ○ | ○ |
| Japan ⁶ | ○ | ○ | ○ | ○ |

Many studies investigated tumor location, specifically colon and rectum, as a predictive factor for LNM in T1 CRC. Some authors reported that T1 rectal cancer showed a higher rate of LNM than T1 colon cancer.^{17,25,30-32} By contrast, others reported that there was no significant difference in LNM between rectum and colon.^{18,33-37} Bosch *et al.*¹⁶ conducted a systematic review of 10 studies including a total of 2,722 T1 CRC patients. They concluded that rectum was a risk factor for LNM (rectum 13.8% vs colon 9.9%; relative risk, 1.4; 95% confidence interval [CI], 1.1 to 1.7; $p < 0.001$). Several studies have divided tumor location into left- and right-sided CRCs,^{19,38-40} all of which concluded that left-sided T1 CRCs (10.8% to 12.0%) showed a significantly higher rate of LNM than right-sided tumors (4.8% to 5.4%). Genetic or anatomical features may affect these differences. Taken together, the results show that tumor location could be an effective predictor for LNM in T1 CRC.

Recently, patients' sex was reported to be a predictive factor for LNM in T1 CRC. Miyachi's group firstly referred to female sex as a predictor (OR, 2.22; 95% CI, 1.26 to 3.91) and thereafter conducted a systematic review and meta-analysis to assess whether patients' sex was predictive of LNM.^{14,41} This meta-analysis analyzing four studies from Japan showed an association between female sex and the risk of LNM (OR, 2.45; 95% CI, 1.03 to 3.88). In reports from Korea and China (data from SEER), female sex was also a significant independent risk factor for LNM.^{19,42} Although the mechanism underlying the higher rate of LNM in female patients has remained unclear, epidemiological studies have reported a potential association between sex hormones and CRC.^{43,44} The advantage of tumor location and patients' sex lies in the fact that these are objective indicators, unlike other pathological risk factors.

The muscularis mucosae is a thin, smooth muscle layer that can be observed in the main parts of the alimentary canal. Risk of metastasis is negligible in CRCs when the tumors have not extended beyond the muscular mucosae. The status of muscularis can be classified into two or three categories. In the two-category designation, the status of muscularis mucosae is classified as maintenance or disappearance. Few patients with maintenance muscularis mucosae had LNM (0% to 2%), whereas 10% to 16% of patients with disappearance muscularis mucosae presented with LNM ($p = 0.026$ and $p = 0.02$) followed by good reproducibility, with a kappa value of 0.67 between two pathologists.^{14,45} In the three-category designation, the status of muscularis mucosae was classified as possible to identify (type A), incomplete disruption (type B), or complete disappearance (type C). No patients with type A had LNM (0%, 0/46), and the type C group (17.3%, 31/210) was

Table 2. Risk Factors for LNM on Multivariate Analysis of Patients with T1 Colorectal Cancers (>400 Cases)

| Author [year] | Country | No. of patients | LNM rate, % | Risk factors | OR (95% CI) |
|--|---------------------------|-----------------|-------------|--|--|
| Rönnow <i>et al.</i> (2020) ¹⁸ | Sweden | 1,439 | 10 | Lymphovascular invasion Differentiation Perineural invasion Age (younger) | 7.311 (4.582–11.665) 2.451 (1.302–4.613) 9.717 (2.856–33.064) 2.654 (1.670–3.935) |
| Guo <i>et al.</i> (2020) ¹⁹ | China (data from SEER) | 17,309 | 13.24 | Differentiation (ref; well) Moderately Poorly Undifferentiated Histology (mucinous) Tumor location (left-sided) Tumor size (ref; 1–9 mm) 10–19 mm 30 mm- Age (ref; 18–49 yr) 50–64 yr 65–79 yr ≥80 yr Sex (male) Race (Asian, Pacific Islander) CEA Years of diagnosis (ref; 2004–2007) 2012–2016 Marital status (unmarried) | 1.76 (1.53–2.04) 3.99 (3.31–4.81) 2.33 (1.50–3.53) 2.19 (1.70–2.80) 1.59 (1.43–1.76) 1.24 (1.07–1.44) 1.56 (1.34–1.81) 0.86 (0.75–0.99) 0.61 (0.53–0.71) 0.46 (0.37–0.57) 0.81 (0.74–0.89) 1.19 (1.02–1.39) 0.83 (0.70–0.99) 0.85 (0.76–0.96) 0.90 (0.82–1.00) |
| Yasue <i>et al.</i> (2019) ¹⁷ | Japan | 846 | 8.7 | Lymphovascular invasion Differentiation Tumor budding | 8.09 (3.84–17.1) 2.09 (1.12–3.89) 1.89 (1.09–3.29) |
| Oh <i>et al.</i> (2019) ²⁰ | Korea | 833 | 11.6 | Vascular invasion Differentiation Depth of SM invasion Tumor budding Background adenoma | 8.45 (4.56–15.66) 7.89 (2.89–21.52) 2.14 (1.19–3.86) 1.70 (1.03–2.80) 0.58 (0.36–0.92) |
| Belderbos <i>et al.</i> (2017) ²¹ | Netherlands | 796 | 10.3 | High-risk histology* Tumor location (ref; proximal colon) Distal colon Rectum Lymph nodes evaluated (ref; n=1–3) n=4–7 n=8–11 | 2.213 (1.326–3.695) 2.299 (1.025–5.160) 2.442 (1.148–5.192) 2.496 (1.175–5.304) 2.640 (1.171–5.951) |
| Ha <i>et al.</i> (2017) ²⁸ | Korea | 745 | 12.2 | Vascular invasion Differentiation Tumor budding Depth of SM invasion | 6.631 (3.671–11.979) 7.340 (2.623–20.535) 1.757 (1.044–2.955) 2.193 (1.207–3.984) |
| Miyachi <i>et al.</i> (2016) ¹⁴ | Japan | 653 | 9.2 | Lymphovascular invasion Differentiation Tumor budding Sex (female) | 9.84 (3.42–28.3) 2.31 (1.25–4.27) 1.80 (1.01–3.21) 2.22 (1.26–3.91) |
| Suh <i>et al.</i> (2012) ²⁷ | Korea | 435 | 13.0 | Lymphovascular invasion Differentiation Tumor budding Absence of BGA | 10.199 (3.710–28.041) 18.444 (3.767–90.296) 2.350 (1.054–5.239) 2.612 (1.226–5.568) |
| Okabe <i>et al.</i> (2004) ²⁵ | USA, Japan | 428 | 10 | Lymphovascular invasion Depth of SM invasion | 4.4 (1.7–11) 2.7 (1–7.5) |
| Kitajima <i>et al.</i> (2004) ²⁶ | Japan | 865 | 10.1 | Lymphatic invasion Depth of SM invasion Sprouting | 4.691 (2.768–7.950) 5.404 (1.623–17.933) 2.276 (1.350–3.835) |

LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results; CEA, carcinoembryonic antigen; SM, submucosal; BGA, background adenoma.

*High-risk histology includes poor/no differentiation, deep SM invasion (sm2/sm3), and/or lymphovascular invasion.

significantly correlated with LNM in multivariate analysis ($p=0.012$, $OR=3.38$).⁴⁶ In addition, the area of submucosal invasion was reported to be a potential predictor of LNM. Toh *et al.*⁴⁷ investigated the correlation between the total areas of carcinoma in submucosal layer and the presence of LNM, and reported the significant correlation ($p<0.001$). In this study, the cutoff value was 35 mm^2 for area of submucosal invasion. Comprehensively considering the above findings, the status of muscularis mucosae was considered to be associated with the horizontal extent or the total area of carcinoma invasion, and thus these indicators (rather than the vertical depth of invasion) could precisely reflect the risk of LNM.

Concerning other factors, younger age, race, tumor size, carcinoembryonic antigen, and absence of background adenoma were also reported to be associated with LNM.^{18-20,27,29} At least now, however, it is difficult to apply these as significant LNM risk factors to actually perform additional surgical resection, and further studies will be needed in the future.

PROBLEMS OF PATHOLOGICAL DIAGNOSIS

Lymphovascular invasion was found to be the most powerful predictor of LNM in many studies. Lymphatic or vascular invasion was defined as invasion of tumor cells into lymphatic vessels or blood vessels.⁴⁸⁻⁵¹ Although lymphovascular invasion can be diagnosed by hematoxylin and eosin (H&E) staining, additional staining techniques such as immunohistochemical stains (e.g., D2-40) or Victoria blue and Elastica van Gieson (EVG) have been used by some pathologists.^{52,53} Despite its high importance as a risk factor, observation of lymphovascular invasion is hampered by its weakness of high interobserver variability between pathologists. Some articles report poor interobserver concordance of lymphovascular invasion assessment. Kojima *et al.*⁴⁹ reported that agreement regarding lymphatic and vascular invasion in Japan produced kappa values of 0.216 (95% CI, 0.133 to 0.299) and 0.524 (95% CI, 0.441 to 0.606), respectively. Among United States and European pathologists, agreements were 0.518 (0.379 to 0.657) and 0.543 (0.405 to 0.682), respectively, for lymphatic invasion and 0.545 (0.407 to 0.684) and 0.560 (0.422 to 0.699) for vascular invasion.⁵⁴ Additional staining techniques increased interobserver agreement in lymphatic invasion from kappa value of 0.30 for H&E staining to 0.56 for D2-40 staining, and in vascular invasion from kappa 0.10 for H&E staining to 0.48 for EVG staining.⁵⁵ In addition, lymphatic invasion diagnosed with D2-40 was reported to be a better indicator of LNM than H&E staining ($OR\ 2.664$

with HE vs 6.048 with D2-40).⁵⁶ Although the concordance in lymphovascular invasion was not good, additional staining was found to improve the interobserver agreement among pathologists.⁵⁷ In the near future, standardization of staining methods and diagnostic criteria should become a global requirement while also bearing in mind cost-effectiveness.

Histological grade is also stated as a risk factor in all guidelines. According to World Health Organization Classification of Tumours, grading is based on the least differentiated component.⁵⁸ On the other hand, as there is no definition on whether to assess histological grade using the most dominant or poorest components in some guidelines, standardization is required. Depth of submucosal invasion as a risk factor was evaluated according to Kudo classification (sm1, sm2, or sm3) or the depth of submucosal invasion (in micrometers).^{48,59} In both cohorts, invasion depth was associated with the presence of LNM ($OR, 2.14$ to 5.404). However, some research groups have reported that depth of submucosal invasion was not a predictive factor for LNM.^{18,60} Japanese guidelines describe that the incidence of LNM is extremely low, 1.3% (95% CI, 0% to 2.4%), in cases with an invasion depth of 1,000 μm or more without risk factors for LNM (other than the invasion depth).⁶ In addition, in assessing the invasion depth, the problem is that the interobserver agreement among pathologists is low and tumor morphology is not taken into consideration.⁶⁰

ENDOSCOPIC RESECTION AS A FIRST-LINE TREATMENT

By virtue of recent progress in colonoscopy and diagnostic approaches, many T1 CRCs that were previously treated by radical surgical resections can now be resected endoscopically.⁶¹ Endoscopic submucosal dissection (ESD) is effective for *en bloc* resection of superficial colorectal lesions regardless of tumor size or location and enables accurate histopathological assessment.^{62,63} Endoscopic resection prior to surgical resection has potential adverse effects because endoscopic maneuvers can violate the concept of a “no-touch isolation technique,” and induce the risk of metastasis. However, several studies have reported that endoscopic resection of T1 CRC before surgical resection does not affect adverse events and recurrence.⁶⁴⁻⁶⁹ Overwater *et al.*⁶⁴ described that no significant differences were observed between primary and secondary surgical resection for the presence of LNM ($OR, 0.97$; 95% CI, 0.49 to 1.93; $p=0.940$) and recurrence (hazard ratio, 0.97; 95% CI, 0.41 to 2.34; $p=0.954$). Moreover, Yamashita *et al.*⁶⁵ and Yamaoka *et al.*⁶⁶ reported that there were no significant differences

between primary and secondary surgery groups regarding recurrence after propensity-score matching (1.9% vs 3.1%, $p=0.4740$ and 1.3% vs 1.3%, $p=1.00$, respectively). In addition, unfavorable histological features of T1 CRCs apart from depth of invasion, such as lymphovascular invasion, poor differentiation, or tumor budding, cannot be diagnosed with endoscopic findings before resection. Therefore, the “resect and examine” strategy of primary endoscopic resection and histopathological assessment, that is, an attempted *en bloc* resection of a possible T1 CRC as total excisional biopsy, may be acceptable. Some recent studies reported the effectiveness and safety of endoscopic full-thickness resection for T1 CRC which were difficult to be resected in conventional endoscopic mucosal resection or ESD. Hence, objective histopathological evaluation and an accurate LNM-predicting system are more essential for the “resect and examine” strategy.⁷⁰⁻⁷²

Although surgical resection with lymph node dissection is a more curative option for T1 CRC than endoscopic resection alone, assessment of whether the oncological benefits of resection of potential positive lymph nodes and possible residual cancer tissue outweigh the risks of secondary surgical resection is challenging. A national cohort study from the Netherlands reported 1.7% (87/5,170) post-operative mortality in T1 CRC, which did not significantly differ from 2.5% T2–T3 CRC (880/34,643, $p=0.604$).²⁴ Risk of metastasis, operative risk, quality of life, and cost-effectiveness should be taken into consideration when making a decision concerning additional treatment.⁷³

RISK-SCORING SYSTEM

Some studies have developed scoring systems to stratify the risk of LNM in T1 CRC.^{14,15,19,20,74} Backes *et al.*¹⁵ reported a prediction model that analyzed five histological factors among 708 T1 CRCs from 13 hospitals: lymphovascular invasion, Haggitt level 4 invasion, muscularis mucosae, poorly differentiated clusters, and tumor budding. Discriminating power of their model outperformed the current guidelines (their model, area under the curve [AUC]=0.83; ASGE/ESGE, AUC=0.67; JSCCR, AUC=0.64). Miyachi *et al.*¹⁴ used a decision tree combining five clinicopathological factors: status of muscularis mucosae, lymphovascular invasion, tumor budding, histological grade, and patient's sex. They divided the risk of LNM into four classes and in theory could reduce unnecessary surgical resections by 30% compared with the current Japanese guidelines. A nomogram using clinicopathological factors obtained from multivariate logistic regression was also reported to be effective in prediction of LNM in some studies.^{19,20} Although

OR tables are the most common way to present predictive models in several disciplines, they do not allow the direct calculation of output probabilities. By contrast, nomograms provide excellent graphical depictions of all variables in the model and provide a quick view of the weight of each variable. Both models showed good discriminatory power, although this was limited by retrospective studies or by conducting internal validations of their models.

PERSPECTIVE: NEW CHALLENGES OF RISK-SCORING SYSTEMS

1. Artificial intelligence system

Several studies have devised novel methods to predict the presence of LNM. A first report using artificial intelligence (AI) as a predicting tool was published in 2018.⁷⁵ This AI model using support vector machine provides supervised machine-learning analysis of patients' 45 clinicopathological factors such as patient's age and sex, tumor location and size, and lymphovascular invasion obtained before surgical resection, whereby the positivity or negativity for LNM is determined. The diagnostic ability of the AI model was compared with American, European, and Japanese guidelines. Although the sensitivity was 100% (95% CI, 72% to 100%) in the AI model and the guidelines, specificity of the AI model and the American, European, and Japanese guidelines was 66% (95% CI, 56% to 76%), 44% (95% CI, 34% to 55%), 0% (95% CI, 0% to 3%), and 0% (95% CI, 0% to 3%), respectively, while accuracy was 69% (95% CI, 59% to 78%), 49% (95% CI, 39% to 59%), 9% (95% CI, 4% to 16%), and 9% (95% CI, 4% to 16%), respectively. Although the AI model showed higher discriminating power than the current guidelines, there were two major limitations. First, it did not include the cases undergoing endoscopic resection alone (which form part of the actual prediction targets), evaluating only the surgical resection cases with lymph node dissection. Second, as it used only internal validation, data for machine learning and validation came from the same institution, which might overestimate the performance of AI because clinicopathological characteristics in the training and testing datasets were similar. To overcome these limitations, the research group is now conducting a multicenter trial including more than 4,000 patients with T1 CRCs from seven hospitals.⁷⁶

2. Whole-slide image-based prediction

AI-aided histological evaluation of the colorectal lesion is rapidly emerging.⁷⁷ A random forest algorithm that analyzed whole-slide images of cytokeratin immunohisto-

chemistry was reported in 2019.⁷⁸ The algorithm analyzed 16 morphological parameters, such as total cancerous area (mm²), on a whole-slide digital image. The random forest algorithm showed better LNM predictive ability than the conventional model using pathological risk factors obtained by multivariate analysis (AUC=0.94 vs AUC=0.83). The biggest strength of this model was that the predicted result did not depend on the pathologists. Conventional prediction models using pathological findings diagnosed by pathologists encounter the major problem of interobserver disagreement among the pathologists. Further development of machine learning with larger samples and external validation will be needed to confirm the potential success of this method.

3. Biomarkers

A risk-prediction model using a genome-wide small RNA-sequencing approach was reported by a research group in the United States.^{79,80} These investigators identified five microRNAs (MIR32, MIR181B, MIR193B, MIR195, and MIR411) associated with LNM. These microRNAs identified a high-risk group for LNM with an AUC value of 0.82 in the training cohort and 0.74 in the testing cohort. Also, an mRNA classifier composed of eight mRNA genes (AMT, MMP9, FOXA1, LYZ, MMP1, C2CD4A, PIGR, and RCC1) outperformed the current clinical risk-factor assessment in discriminating the presence of LNM (AUC=0.88 vs AUC=0.59). The strengths of their research included the use of a systematic and comprehensive biomarker discovery approach based on high-throughput microRNA-sequencing data analysis and the use of colonoscopy-derived biopsy samples before endoscopic resection despite the limitation of sampling bias because of heterogeneity in the lesion. In addition, evaluation of adenine-thymine-rich interactive domain 1A (ARID1A) protein expression using immunohistochemical staining was reported to be effective in predicting the presence of LNM.⁸¹

SUMMARY AND CONCLUSIONS

As the number of endoscopic resections of T1 CRCs increases in the future, more accurate prediction models of LNM will be needed. Standardization of pathological diagnosis criteria is also required to make the risk-stratifying systems more objective. Appropriate treatment strategies are required to prevent unnecessary surgery or recurrence as far as is possible. Given that previous studies included mainly retrospective analyses, verification through prospective studies in real time will also be required.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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