Gut and Liver
https://doi.org/10.5009/gnl240081
pISSN 1976-2283 eISSN 2005-1212

Perspective

Accuracy Goals in Predicting Preoperative Lymph Node Metastasis for T1 Colorectal Cancer Resected Endoscopically

Katsuro Ichimasa[1,2], Shin-ei Kudo[1], Masashi Misawa[1], Khay Guan Yeoh[2], Tetsuo Nemoto[3], Yuta Kouyama[1], Yuki Takashina[1], Hideyuki Miyachi[1]

[1]Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama, Japan; [2]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [3]Department of Pathology and Laboratory Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan

Article Info
Received February 25, 2024
Revised April 27, 2024
Accepted May 7, 2024
Published online July 25, 2024

Corresponding Author
Katsuro Ichimasa
ORCID https://orcid.org/0000-0001-6675-1219
E-mail ichimasa@nus.edu.sg

Submucosal invasive (T1) colorectal cancer is a significant clinical management challenge, with an estimated 10% of patients developing extraintestinal lymph node metastasis. This condition necessitates surgical resection along with lymph node dissection to achieve a curative outcome. Thus, the precise preoperative assessment of lymph node metastasis risk is crucial to guide treatment decisions after endoscopic resection. Contemporary clinical guidelines strive to identify a low-risk cohort for whom endoscopic resection will suffice, applying stringent criteria to maximize patient safety. Those failing to meet these criteria are often recommended for surgical resection, with its associated mortality risks although it may still include patients with a low risk of metastasis. In the quest to enhance the precision of preoperative lymph node metastasis risk prediction, innovative models leveraging artificial intelligence or nomograms are being developed. Nevertheless, the debate over the ideal sensitivity and specificity for such models persists, with no consensus on target metrics. This review puts forth postoperative mortality rates as a practical benchmark for the sensitivity of predictive models. We underscore the importance of this method and advocate for research to amass data on surgical mortality in T1 colorectal cancer. Establishing specific benchmarks for predictive accuracy in lymph node metastasis risk assessment will hopefully optimize the treatment of T1 colorectal cancer. **(Gut Liver 2024;18:803-806)**

Key Words: Colorectal neoplasms; Endoscopic mucosal resection; Lymph nodes; Neoplasm metastasis; Risk factors

IMPORTANCE OF PREOPERATIVE LNM RISK STRATIFICATION

Preoperative determination of lymph node metastasis (LNM) risk is crucial for patients with submucosal invasive (T1) colorectal cancer (CRC) following endoscopic resection. While colorectal intramucosal cancer (Tis)/high-grade dysplasia is suitable for endoscopic resection due to the absence of LNM, surgical intervention remains the standard treatment for cancers invading beyond the muscularis propria layer (T2).[1] Notably, approximately 10% of patients with T1 CRC (positioned between Tis and T2 stages) exhibit extraintestinal LNM, leading to a pivotal decision between opting for endoscopic treatment or surgical resection.[2,3] The curative potential of endoscopic resection in T1 CRC or the necessity for additional surgical intervention is contingent upon accurately predicting the risk of LNM from the pathological diagnosis.

The prevalence of endoscopically resected T1 CRC is anticipated to rise, driven by an overall increase in CRC incidence, a higher detection rate of T1 CRC, and a growing preference for endoscopic over surgical intervention. Advances in endoscopic techniques, such as endoscopic submucosal dissection, endoscopic intermuscular dissection, per anal endoscopic myectomy, and endoscopic full-thickness resection, are expected to bolster this trend further.[4,5] Recent meta-analyses challenge the view that deep submucosal invasion (submucosal invasion ≥1,000 μm) inherently presents a high risk of LNM.[6] Findings suggest that deep submucosal invasion in CRCs lacking additional

risk factors such as lymphovascular invasion, poorly differentiated histology, and tumor budding is associated with a relatively low LNM-positive rate of 1.3% (95% confidence interval [CI], 0% to 2.4%).[1] Such a reassessment of risk may further subdivide deep submucosal invasion CRCs into low and high risk and shift the treatment paradigm towards more conservative endoscopic management for low-risk deep submucosal invasion cases.[2] The difficulty in preoperatively assessing critical factors linked to LNM, such as lymphovascular invasion and histological grade, often leads to a conservative approach: opting for endoscopic removal first to avoid over-treatment, with the caveat of ensuring negative vertical margins. This strategy aims to minimize surgery-related morbidity and preserve quality of life without compromising the oncologic outcome. Decision-making in T1 CRC treatment is multifaceted, and it considers patient preferences, the potential for cure, treatment invasiveness, and the cost implications. However, the cornerstone of this decision-making process is the stratification of LNM risk, underscoring the urgent need for precise and reliable predictive models.

CURRENT STATUS OF LNM RISK PREDICTION

Current guidelines specify the criteria for additional bowel resection following endoscopic resection of T1 CRC, having identified a subset of patients for whom endoscopic treatment may be curative.[1,7-10] However, there is a need for enhanced precision in stratifying the risk of LNM. According to these guidelines, LNM is present in only about 10% of cases undergoing surgery, suggesting that the vast majority of surgical interventions might be unnecessary. To tackle the limitations of current guidelines in accurately predicting LNM, we introduce three innovative predictive models.[11]

1. Artificial neural network model

Developed using a dataset of 5,131 T1 CRCs from seven centers in Japan, collected between 1997 and 2017, this artificial intelligence (AI) model employs machine learning to evaluate metastasis risk based on eight parameters: patient sex and age, tumor size, location and morphology, lymphatic and vascular invasion, and histological type.[12] Six of these centers contributed to training the model, with one center performing external validation. The artificial neural network significantly outperformed existing guidelines, achieving an area under the curve (AUC) of 0.83, which is markedly higher than the 0.57 AUC of the current CRC treatment guidelines ($p<0.001$).

2. Nomogram

This model provides a visual representation of calculated predictive probabilities, clearly outlining the impact of each variable.[13] It was developed using data from 6,105 cases across 27 centers in Japan, from 2009 to 2016. Out of these, 3,080 cases were used to develop the nomogram, and 1,593 cases were reserved for testing. The nomogram incorporated six factors: patient sex, tumor location, tumor grade, lymphovascular invasion, tumor budding, and submucosal invasion depth. It achieved a concordance statistic (C-statistic) of 0.790, surpassing the 0.777 C-statistic of current guidelines.

3. Whole slide image-based AI model

Addressing the reproducibility issues associated with pathological assessments, a new pathologist-independent model is being developed.[14] This model evaluates LNM risk directly from hematoxylin-eosin stained images, eliminating the need for human diagnosis. It operates by dividing a hematoxylin-eosin stained image (×40) of a T1 CRC into 224×224 pixel patches, stratifying each patch according to ten levels of metastasis risk, and then aggregating these to calculate the overall risk for the lesion. This methodology has demonstrated high diagnostic accuracy, with an AUC of 0.72 for the whole slide image-based AI, significantly reducing the 21% of over-surgery and achieving a sensitivity of 100% and a specificity of 35%. To date, a total of four similar studies have been published.[14-17]

These developments represent a significant advancement in the precision of diagnosing LNM in T1 CRC, aiming to refine treatment strategies and reduce unnecessary surgical interventions.

REALISTIC SENSITIVITY AND SPECIFICITY OF PREDICTIVE MODELS

Establishing the diagnostic accuracy for LNM prediction in T1 CRC involves a critical balance between achieving a high enough sensitivity to detect all potential cases of LNM while maintaining enough specificity to avoid unnecessary surgeries. This balance is crucial, because missed LNM can lead to disease recurrence and death, whereas overly aggressive treatment can increase the rates of morbidity and mortality associated with surgery.

1. Sensitivity

While the goal of 100% sensitivity is laudable, this includes an inherent risk of false positives and, therefore, requires a more nuanced approach. An acceptable level of sensitivity should minimize the risk of missing LNM with-

Table 1. Postoperative Mortality of Colorectal Cancer

Author (year)	Country	Definition	T-stage	Postoperative mortality, %	No. of patients	Descriptions
Marubashi *et al.* (2021)[18]	Japan	90-day mortalities	All	0.6	21,262	Low anterior resection
				2.0	22,410	Right hemicolectomy
Vermeer *et al.* (2019)[20]	Netherlands	30-day mortalities	T1	1.7	5,170	-
			T2-T3	2.5	34,643	
Jafari *et al.* (2014)[19]	USA	In-hospital mortalities	All	45–64 yr: 1.3	377,129	-
				65–69 yr: 2.0	132,807	
				70–74 yr: 2.9	143,132	
				75–79 yr: 3.7	154,433	
				80–84 yr: 4.9	128,686	
				≥85 yr: 8.0	106,921	

out significantly increasing unnecessary surgical interventions.

2. Specificity and PPV

Elevating specificity and positive predictive value (PPV) aim to reduce over-treatment and limit surgical interventions to patients needing them based on a high probability of LNM. The challenge lies in enhancing these two metrics without substantially impacting the model's sensitivity.

3. Postoperative mortality rates

Using postoperative mortality rates as a benchmark for setting sensitivity and specificity targets offers a pragmatic solution. This approach balances the risk of missed LNM (and the potential for endoscopic treatment alone) against the morbidity and mortality associated with surgical treatments.

4. Reference points for model accuracy

One approach defining this standard involves comparing postoperative mortality rates: the risk of death from missed LNM after endoscopic treatment alone should be similar to or lower than the risk of surgery-related mortality. As noted in Table 1, in Japan, the 90-day postoperative mortality rates are 2.0% for right hemicolectomy (n=22,410) and 0.6% for low anterior resection (n=21,262), encompassing both early and advanced-stage cancers.[18] Similarly, in the United States, age-specific surgery-related mortality rates were reported (total n=1,043,108) across various age groups, showing an increase in mortality with age.[19] For T1 CRC, the surgery-related mortality rate was similar to that of a Dutch study, 1.7% (n=5,170), suggesting that these rates can be used as reference values for acceptable sensitivity thresholds in predictive models.[20] Furthermore, the Japanese Society for Cancer of the Colon and Rectum project on 2,468 cases of T1 CRC in Japan revealed a low LNM-positive rate of 0.3% (1/325; 95% CI, 0.0% to 1.7%) in the guideline-defined endoscopy curative (low-risk) group.[1] The sensitivity, specificity, and PPV achieved were 99.6% (95% CI, 98.0% to 100%), 14.8% (95% CI, 13.3% to 16.3%), and 12.6% (95% CI, 11.3% to 14.1%), respectively, indicating acceptable sensitivity.

SUMMARY

Future predictive models should aim to match the high sensitivity levels outlined in current guidelines while seeking to improve specificity and PPV. This dual objective acknowledges the complexity of balancing diagnostic accuracy with the clinical imperative to do no harm. It is also necessary to provide evidence regarding postoperative mortality for T1 CRC.

CONFLICTS OF INTEREST

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

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI (Grant number 22K16500).

AUTHOR CONTRIBUTIONS

Study conception: K.I., S.K., H.M. Acquisition data: K.I. Interpretation of data: K.I., M.M., Y.K., Y.T. Drafting of the article: K.I. Critical revision of the article for important intellectual content: S.K., M.M., K.G.Y., T.N., Y.K., Y.T., H.M. Final approval of the article: all authors.

ORCID

Katsuro Ichimasa https://orcid.org/0000-0001-6675-1219
Shin-ei Kudo https://orcid.org/0000-0002-4268-1217
Masashi Misawa https://orcid.org/0000-0002-8520-2036
Khay Guan Yeoh https://orcid.org/0000-0002-7802-4606
Tetsuo Nemoto https://orcid.org/0000-0001-8959-2601
Yuta Kouyama https://orcid.org/0000-0002-9663-247X
Yuki Takashina https://orcid.org/0000-0002-2473-7520
Hideyuki Miyachi https://orcid.org/0000-0002-8404-0899

REFERENCES

1. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020;25:1-42.
2. Ichimasa K, Kudo SE, Miyachi H, et al. Current problems and perspectives of pathological risk factors for lymph node metastasis in T1 colorectal cancer: systematic review. Dig Endosc 2022;34:901-912.
3. Ichimasa K, Kudo SE, Misawa M, Takashina Y, Yeoh KG, Miyachi H. Role of the artificial intelligence in the management of T1 colorectal cancer. Dig Liver Dis 2024;56:1144-1147.
4. Zwager LW, Bastiaansen BA, van der Spek BW, et al. Endoscopic full-thickness resection of T1 colorectal cancers: a retrospective analysis from a multicenter Dutch eFTR registry. Endoscopy 2022;54:475-485.
5. Moons LM, Bastiaansen BA, Richir MC, et al. Endoscopic intermuscular dissection for deep submucosal invasive cancer in the rectum: a new endoscopic approach. Endoscopy 2022;54:993-998.
6. Zwager LW, Bastiaansen BA, Montazeri NS, et al. Deep submucosal invasion is not an independent risk factor for lymph node metastasis in T1 colorectal cancer: a meta-analysis. Gastroenterology 2022;163:174-189.
7. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16:874-901.
8. Benson AB 3rd, Venook AP, Cederquist L, et al. Colon cancer, version 1.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15:370-398.
9. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv263.
10. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi64-vi72.
11. Ichimasa K, Kudo SE, Lee JW, Nemoto T, Yeoh KG. Artificial intelligence-assisted treatment strategy for T1 colorectal cancer after endoscopic resection. Gastrointest Endosc 2023;97:1148-1152.
12. Kudo SE, Ichimasa K, Villard B, et al. Artificial intelligence system to determine risk of T1 colorectal cancer metastasis to lymph node. Gastroenterology 2021;160:1075-1084.
13. Kajiwara Y, Oka S, Tanaka S, et al. Nomogram as a novel predictive tool for lymph node metastasis in T1 colorectal cancer treated with endoscopic resection: a nationwide, multicenter study. Gastrointest Endosc 2023;97:1119-1128.
14. Takashina Y, Kudo SE, Kouyama Y, et al. Whole slide image-based prediction of lymph node metastasis in T1 colorectal cancer using unsupervised artificial intelligence. Dig Endosc 2023;35:902-908.
15. Takamatsu M, Yamamoto N, Kawachi H, et al. Prediction of lymph node metastasis in early colorectal cancer based on histologic images by artificial intelligence. Sci Rep 2022;12:2963.
16. Song JH, Hong Y, Kim ER, Kim SH, Sohn I. Utility of artificial intelligence with deep learning of hematoxylin and eosin-stained whole slide images to predict lymph node metastasis in T1 colorectal cancer using endoscopically resected specimens; prediction of lymph node metastasis in T1 colorectal cancer. J Gastroenterol 2022;57:654-666.
17. Brockmoeller S, Echle A, Ghaffari Laleh N, et al. Deep learning identifies inflamed fat as a risk factor for lymph node metastasis in early colorectal cancer. J Pathol 2022;256:269-281.
18. Marubashi S, Takahashi A, Kakeji Y, et al. Surgical outcomes in gastroenterological surgery in Japan: report of the National Clinical Database 2011-2019. Ann Gastroenterol Surg 2021;5:639-658.
19. Jafari MD, Jafari F, Halabi WJ, et al. Colorectal cancer resections in the aging US population: a trend toward decreasing rates and improved outcomes. JAMA Surg 2014;149:557-564.
20. Vermeer NC, Backes Y, Snijders HS, et al. National cohort study on postoperative risks after surgery for submucosal invasive colorectal cancer. BJS Open 2018;3:210-217.