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Perspective

Challenges in Implementing Endoscopic Resection for T2 Colorectal Cancer

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The current standard treatment for muscularis propria-invasive (T2) colorectal cancer is surgical colectomy with lymph node dissection. With the advent of new endoscopic resection techniques, such as endoscopic full-thickness resection or endoscopic intermuscular dissection, T2 colorectal cancer, with metastasis to 20%-25% of the dissected lymph nodes, may be the next candidate for endoscopic resection following submucosal-invasive (T1) colorectal cancer. We present a novel endoscopic treatment strategy for T2 colorectal cancer and suggest further study to establish evidence on oncologic and endoscopic technical safety for its clinical implementation. **(Gut Liver 2024;18:218-221)**

Key Words: Endoscopic full-thickness resection; Lymph node metastasis; Treatment strategy; T2 colorectal cancer

NEED FOR EVIDENCE ON THE NEW ENDOSCOPIC TREATMENT

We provide a roadmap and evidence we need to establish for introducing endoscopic resection of muscularis propria-invasive (T2) colorectal cancer (CRC). The current standard treatment for all T2 CRC is surgical colectomy with lymph node dissection due to limitations in conventional endoscopic techniques such as endoscopic mucosal resection or endoscopic submucosal dissection.[1] However, advances in endoscopic full-thickness resection (eFTR), endoscopic intermuscular dissection (EID), and peranal endoscopic myectomy (PAEM) now enable endoscopic resection of T2 CRC, as evidenced by published case reports.[2-6] Hence, the concept of a new treatment strategy called "resect and analysis" has emerged for T2 as well as T1 CRC.[7,8] The "resect and analysis" strategy necessitates endoscopic resection followed by a pathological assessment to evaluate lymph node metastasis (LNM) risk and the need for additional bowel resection, with further evidence on oncologic and endoscopic technical safety required for practical implementation.

CURABILITY OF ENDOSCOPIC RESECTION

First, we must establish the curative criteria for endoscopic resection of T2 CRC based on the risk of LNM. According to the current guidelines for the treatment of T1 CRC, the risk factors for LNM are depth of submucosal invasion ≥1,000 μm, lymphovascular invasion positivity, poorly differentiated adenocarcinoma/signet ring cell carcinoma/mucinous carcinoma, and tumor budding grade of 2 or 3 at the site of deepest invasion.[1] For T1 CRC endoscopically resected with a negative vertical margin and no high-risk factors, follow-up without secondary surgery is acceptable, as guidelines effectively stratify the low-risk group, constituting about 30% of T1 CRC, and confirm curability from a prognostic perspective.[9,10] For T2 CRC, however, there are no guidelines or consensuses regarding the risk factors for LNM, although some papers have focused on this topic.[7,11] Previous studies identified lymphovascular invasion, tumor differentiation, and tumor budding as significant risk factors for LNM, with some reports suggesting female sex or myxoid cancer stroma.[11,12] However, these studies faced limitations due

to single-center designs, small sample sizes, and wide 95% confidence intervals (CIs) for LNM rates or odds ratios. In a recent study utilizing random forest known as a machine learning algorithm, the researchers developed an artificial intelligence-based risk-stratification system for LNM in T2 CRC.[7] Their artificial intelligence algorithm incorporates eight clinicopathologic variables, namely: patient age and sex, tumor location and size, lymphatic and vascular invasion, histologic differentiation, and serum carcinoembryonic antigen concentration. With a sensitivity of 96% and a specificity of 88%, this algorithm has the potential to inform decisions regarding endoscopic resection of T2 CRC. Furthermore, while a systematic review investigating the risk factors for LNM in T2 CRC has been published, a meta-analysis has not been conducted because there are too few relevant articles.[13] To determine risk factors for LNM in T2 CRC, large-scale multicenter studies are necessary, enabling the establishment of endoscopic curative criteria based on these identified factors.

Based on these risk stratifications of LNM, whether the decision on endoscopic treatment would be acceptable is a comparison with mortality rates for standard surgical procedures. Previous surveys in the United States have found that postoperative mortality rates vary from 1.5% to 8.0% depending on age: 1.5% for patients aged 69 years and younger, and 8.0% for those aged 85 years and older.[14] Similarly, postoperative mortality rates in Japanese and Dutch cohorts, as reported in national surveys, were 1.3% and 2.4%, respectively.[15,16] Therefore, percentages equal to or lower than these may be considered acceptable for the risk of simultaneous LNM. On the other hand, there is currently no evidence available regarding overall survival or disease-free survival. In T1 CRC, the low-risk group for LNM is strictly defined with oncologic safety as the highest priority, and its long-term prognosis have been reported to be acceptable.[9] As these new treatment strategies for T2 CRC are introduced, it is crucial to establish stricter criteria. It would be acceptable if the recurrence rate in the endoscopically treated low-risk group for LNM was equal to or less than that of the surgical group (colon: 6.5%, rectum: 8.3%).[1]

TECHNICAL SAFETY OF ENDOSCOPIC RESECTION

Second, we need to investigate the technical safety of eFTR or EID/PAEM for T2 CRC. The three main indications for eFTR are T1 CRC, including deep submucosal invasion; non-lifting lesions; and secondary treatment after incomplete endoscopic resection, regardless of tumor location. A recent systematic review and meta-analysis underscored the effectiveness of eFTR, citing a technical success rate of 86.5% (95% CI, 83.3% to 89.1%) and a procedure-related adverse event rate of 15.4% (95% CI, 10.6% to 21.9%).[17] The adverse events included perforation (4.4%; 95% CI, 1.6% to 11.2%), delayed bleeding (6.4%; 95% CI, 5.4% to 7.7%), and postpolypectomy syndrome (1.7%; 95% CI, 0.7% to 4.0%). This review also revealed that the R0 resection rates for lesions of <20 mm (84.0%; 95% CI, 79.9% to 87.4%) were significantly higher than for those of ≥20 mm (78.4%; 95% CI, 35.8% to 95.9%).

The indication for EID/PAEM is suspected T1 rectal cancer with deep submucosal invasion or rectal lesions with severe fibrosis.[3,4] Endoscopic dissection for these lesions is performed between the inner and outer parts of the muscu-

Table 1. R0 Resection Rate of T2 CRC According to the Type of Endoscopic Resection

Author (year)	Type of endoscopic resection	Total No.	T2 CRC		Indications for each endoscopic resection
			No.	R0 rate, No. (%)	
Zwager *et al.* (2022)[2]	eFTR	330	23	12/23 (52)	1. Primary treatment for lesions with an optical diagnosis of T1 CRC 2. Primary treatment for non-lifting lesions with histology proven adenocarcinoma 3. Secondary treatment after previous incomplete endoscopic resection of histology-proven low-risk adenocarcinoma (R1, Rx, or R0 with <1 mm lateral and/or deep resection margins)
Didden *et al.* (2022)[18]	eFTR	136	38	25/38 (66)	1. Non-pedunculated polyps with suspected deep submucosal invasion 2. Polyps with suspected superficial invasion or (previous) non-lifting but with a size up to 15 mm
Moons *et al.* (2022)[3]	EID	67	14	NA	Suspicion of T1 rectal cancer with deep submucosal invasion
Toyonaga *et al.* (2018)[4]	PAEM	10	2	1/2 (50)	Rectal lesions with severe fibrosis

CRC, colorectal cancer; eFTR, endoscopic full-thickness resection; EID, endoscopic intermuscular dissection; PAEM, peranal endoscopic myectomy; NA not available.

laris propria and has no tumor size restriction. In one study, the R0 resection rate was 81% (95% CI, 70% to 89%), and minor adverse events occurred in 12% of patients.[3] While most eFTR and EID/PAEM studies focused on adenoma and T1 CRC, some included T2 CRC with R0 resection, and case reports described T2 CRC treated with these techniques (Table 1).[2-5,18] Further investigation of technical success, R0 resection rates, adverse events, and recurrence rates for T2 CRC using these techniques is necessary.

POTENTIAL TREATMENT STRATEGY OF ENDOSCOPIC RESECTION FOR T2 CRC

Drawing from previous findings, Fig. 1 presents a potential treatment strategy for T2 CRC using eFTR or EID/PAEM, with two initial options: (1) eFTR for lesions smaller than 20 mm, regardless of location, or (2) EID/PAEM for rectal tumors, irrespective of size. These treatments are considered technically feasible and account for 25% to 30% (<20 mm) and 25% to 30% (rectum) of all T2 CRCs, respectively.[7] Approximately 35% to 40% of T2 CRC, excluding duplicates, fall into this category. After endoscopic resection, the need for additional surgical resection with lymph node dissection can be determined by comparing the risk of LNM through histopathology and surgical mortality assessment. Considering that the current endoscopic cure rate for T1 CRC is about 30%, it is expected to be less than 30% for extremely low-risk T2 CRC.[9] Therefore, after verifying the safety of the strictly established curative criteria, the indications should be expanded.

An endoscopic scoring system for predicting T2 invasion is crucial for the proposed strategy. Recently, two scoring systems for distinguishing T1b from T2 have been reported.[19,20] Sasaki *et al.*[19] assessed six endoscopic findings: tumor size, irregular base of depression, existence of depression, expansion appearance, convergency of folds, and erosion or white coat. Their system achieved an area under the curve of 0.89 with 84.5% sensitivity and 78.9% specificity on internal validation. Koyama *et al.*[20] identified five endoscopic findings associated with T2 CRC: deep depression, demarcated depressed area, four-fold convergency, erosion or white plaque, and morphology of Borrmann types 2 or 3. Their system had an area under the curve of 0.76 on external validation. These scoring systems may enable selection of endoscopic mucosal resection or endoscopic submucosal dissection for T1b CRC and eFTR or EID for T2 CRC.

In conclusion, establishing evidence for both the oncologic and technical safety of eFTR and EID/PAEM is essential to implement these endoscopic techniques for T2 CRC in practice.

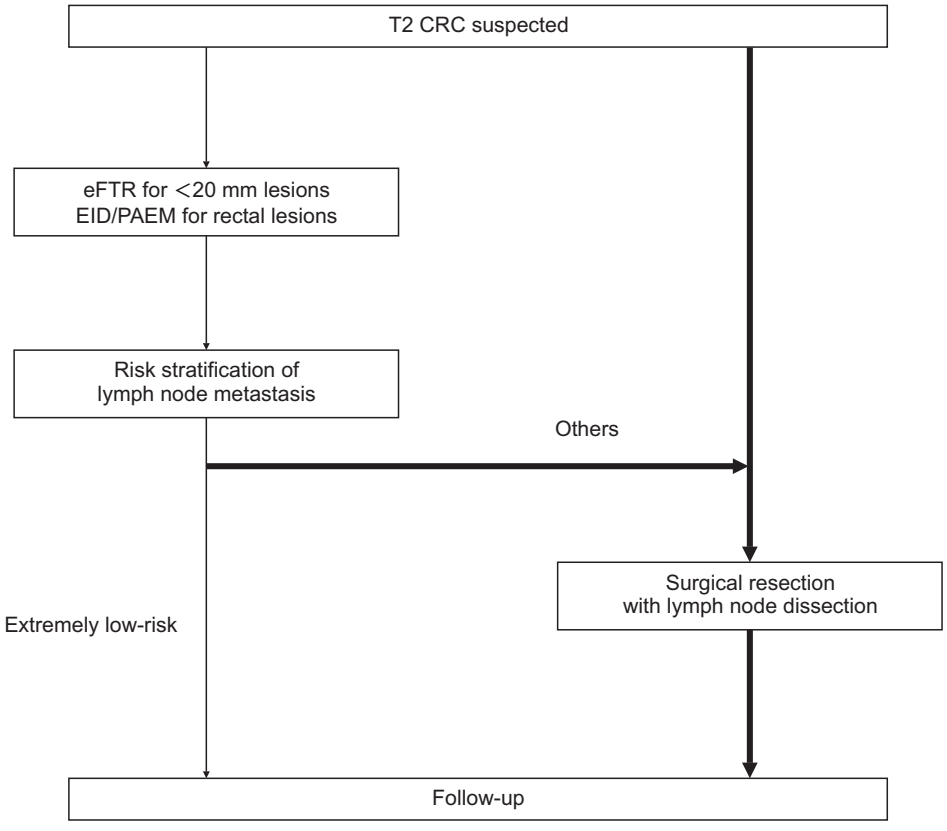

Fig. 1. A new potential treatment strategy for T2 CRC. CRC, colorectal cancer; eFTR, endoscopic full-thickness resection; EID, endoscopic intermuscular dissection; PAEM, peranal endoscopic myectomy.

CONFLICTS OF INTEREST

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

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