Endoscopic treatment for high-risk T1 colorectal cancer: is it better to begin with endoscopic or surgical treatment?

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We read with interest the article “*Endoscopic resection of high-risk T1 colorectal carcinoma prior to surgical resection has no adverse effect on long-term outcomes*” by Overwater *et al.*, which was published in Gut (1). Endoscopic resection, including polypectomy and endoscopic mucosal resection (EMR), is a widely recognized treatment for early gastrointestinal malignancies. Endoscopic submucosal dissection (ESD) is accepted as a minimally invasive treatment for early-stage colorectal cancer (CRC), and this approach enables en bloc resection of a specimen (2). In certain cases, endoscopic treatment alone is insufficient for disease control, and additional surgical treatment after EMR is recommended for patients with high-risk T1 CRC (3,4). However, endoscopic resection of T1 CRC prior to surgical resection might worsen oncologic outcomes by accelerating the growth of the remaining tumor and promoting cancer cell dissemination and metastasis. For high-risk T1 CRC, relatively little is known about whether endoscopic resection before surgery influences lymph node metastasis (LNM), recurrence, or long-term survival.

Prior studies showed that the recurrence rate of endoscopically treated T1 CRC is 2.3–7.3% and that the duration of recurrence is 19.7–38.3 months (3,5–7). Asayama *et al.* reported recurrence rates of 4.3% and 6.6% in primary surgery and secondary surgery (endoscopic resection with additional surgical resection) groups, respectively, although this difference was not

significant (7). However, previous investigations have exhibited several limitations, including the examination of a small number of patients, short follow-up periods, and a lack of data regarding pathological findings.

The aforementioned study by Overwater *et al.* was the largest multicenter observational study to evaluate long-term outcomes after surgical resection of high-risk T1 CRC with or without prior endoscopic resection in Western countries. This retrospective study involved 602 patients diagnosed with T1 CRC with one or more histological risk factors for LNM who were treated via primary or secondary surgery between 2000 and 2014 at 13 hospitals in the Netherlands. High-risk T1-CRC was defined as CRC with poorly differentiated histology, positive resection margins, deep submucosal invasion depth (defined as a submucosal invasion depth $\geq 1,000$ μm , Sm2/Sm3 stage for sessile T1 CRC and Haggitt level 3–4 for pedunculated T1 CRC) or the presence of vascular or lymphatic invasion. The present study is particularly important because it was limited to analyzing high-risk T1 CRC for both primary surgical resection and secondary surgical resection (endoscopic resection with additional surgical resection). No differences were observed between primary and secondary surgery with respect to the presence of LNM (OR 0.97; 95% CI: 0.49 to 1.93; $P=0.94$) or recurrence during follow-up (HR 0.97; 95% CI: 0.41 to 2.34; $P=0.954$). In the aforementioned study by Overwater *et al.*, recurrence rates

in the primary surgery group, and in the secondary surgery group were 7.2% (19/263), and 4.8% (15/309), respectively. The overall recurrence rate for T1 CRC treated with primary surgery was 14.7 per 1,000 person-years and did not significantly differ from the overall recurrence rate for T1 CRC treated with secondary surgery, which was 9.7 per 1,000 person-years ($P=0.297$). These outcomes showed that endoscopic resection of high-risk T1 CRC has no adverse effect on the percentages of patients with LNM at resection or patients with local or distant recurrence during follow-up. Rickert *et al.* revealed that endoscopic resection for malignant polyps did not worsen surgical or oncologic outcomes in patients who underwent an additional surgery after endoscopic resection and suggested that oncologic resection should be performed for residual tumors (4). More recently, in a retrospective multicenter cohort study in Japan, the primary surgery and secondary surgery groups exhibited recurrence rates of 5.5% and 3.8%, respectively, and overall survival rates of 92.4% and 91.5%, respectively. These studies supported the hypothesis that endoscopic resection for T1 CRC did not worsen clinical outcomes for patients who required additional surgical resection (8). Importantly, Overwater *et al.* reported a total of 16 treatment-related complications leading to death within 30 days after treatment; 15 of these complications were related to surgery (9 leakages, 5 cardiovascular, and 1 abscess), and only one complication was related to endoscopy. Currently, population aging is occurring throughout Japan, and we should consider a patient's age, wishes, performance status, and quality of life, as well as the operative method (8). Therefore, the indication for endoscopic resection for T1 CRC will be expanded to total excisional biopsy, particularly for limited patients (e.g., patients who are elderly, have concomitant disease, or are restricted with respect to operative method or performance status, among other considerations) in the near future (9).

In the study by Overwater *et al.*, the overall median follow up was 4.3 years, and local or distant recurrence developed in 5.6% (34/602) of all cases of T1 CRC treated with surgical resection. Additionally, incomplete resection was observed for 15.3% of T1 CRCs, 75% of which were already determined to be incompletely resected during endoscopy (1). Importantly, more than half of recurrence cases involved distant metastasis after surgical treatment during long-term follow-up. In both the primary and secondary groups, distant metastasis occurred in the liver ($n=13$), lungs ($n=11$), and peritoneum ($n=7$). Generally, CRC requires a relatively long time to recur,

and approximately 90% of instances of recurrence after curative resection of CRC occur within 5 years of surgery (8,10). However, recurrences have occurred after more than 5 years in a few cases. Therefore, follow-up examinations are typically required for at least 5 years (6,8,11). Additionally, recommendations suggest performing blood tests, including assessments of carcinoembryonic antigen level, chest radiography examinations, and computed tomography of the abdomen and pelvis every 6 months for the first 3 postoperative years and every 12 months thereafter (12).

Regarding the limitations of the study by Overwater *et al.*, the investigation was a retrospective observational cohort study based on clinical records that included a small number of ESD cases. With respect to surgical procedure, a small number of lymph nodes were retrieved. Additionally, there was a lack of data related to tumor budding, which has been identified as a risk factor for LNM (13).

Innovative methods and new devices for endoscopic full-thickness resection (EFTR) as well as suturing devices continue to evolve and may change traditional paradigms to allow minimally invasive surgery for CRC in the near future (14,15). Notably, Overwater *et al.* found that recurrence occurred at a certain frequency despite additional surgical resection after endoscopic treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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