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Research Article

Is Nonoperative Surveillance After Endoscopic Resection an Option in the Treatment of Low-Risk T1b Colorectal Cancer? A Tertiary-Center Experience

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Abstract

Objective: Deep submucosal invasion (≥1000 mm) (T1b) alone is a low-risk condition for lymph node metastasis (LNM) in colorectal cancer (CRC). Nonoperative surveillance is considered to be a valid treatment modality in these patients. The aim of the present study was to report short-term follow-up results in patients with low-risk T1b CRC who opted out of primary endoscopic resection (ER).

Methods: Patients with CRC who underwent endoscopic submucosal dissection (ESD) between July 2019 and February 2023 and who were histopathologically classified as T1b were reviewed. Patients without lymphovascular involvement, poor differentiation, and grade 2-3 tumor budding are considered to be at low risk. Recurrence-free survival in patients with low-risk T1b CRC was the primary outcome.

Results: The study included 12 patients with low-risk T1b CRC. The majority of (83%) patients required endoscopic traction method. No serious adverse events associated with ESD were observed. The median submucosal invasion depth was 1850 μm (range, 1100-3000 μm). Eleven patients received nonoperative surveillance. No recurrence was observed during a median follow-up of 25.5 months (interquartile range: 12-53 months). One patient underwent subsequent surgical resection, but the surgical specimen showed no residual tumor or LNM.

Conclusion: In patients with low-risk T1b CRCs, nonoperative surveillance after ER was found to be promising in terms of short-term recurrence.

Keywords: Colorectal cancer, endoscopic resection, surveillance

INTRODUCTION

Screening programs have resulted in an increase in the diagnosis of T1 colorectal cancers (CRC). To create an optimal treatment plan for CRC, the depth of invasion must be determined.[1] There is no risk of lymph node metastasis (LNM) in intramucosal carcinoma (Tis), and endoscopic resection (ER) can be safely used.[2] However, the risk of LNM in T1 CRC varies between 1% and 34% depending on the histopathological characteristics of the tumor. Risk factors for LNM include deep submucosal invasion (SMd) (≥ 1000mm), lymphovascular involvement (LVI), poor differentiation (PD), and grade 2-3 tumor budding (TB).[3] Recent studies have shown that SMd alone is not an independent risk factor for LNM.[3-5] A meta-analysis by Zwager et al[3] including more than 1000 T1b CRCs from 8 studies found that the absolute risk of LNM in the presence of SMd was 2.6%. However, the majority of the studies reviewed were from Asian countries. It is therefore necessary to validate the risk factors already identified for Western societies. The present study evaluated short-term follow-up results in patients with low-risk T1b CRC who did not undergo primary ER.

MATERIALS AND METHODS

Patient Selection

Files of patients who underwent endoscopic submucosal dissection (ESD) in the Ege University Gastroenterology Clinic between July 2019 and January 2023 and were histopathologically classified as T1b were screened. Deep submucosal invasion (≥ 1000mm) was defined as T1b CRC.[3] Tumors with SMd but without LVI, PD, grade 2-3 TB were classified into low-risk T1b, and those with SMd and any additional risk factor were classified into high-risk T1b. Patients >18 years of age with T1 histopathological classification and a follow-up period longer than 1 year were included in the study. Exclusion criteria were a history of neoadjuvant treatment, familial history of CRC, presence of a synchronous tumor, growth at the base of pedunculated polyps, follow-up length of less than 1 year, piecemeal ER, T1b on histopathology after endoscopic resection, and obvious indication for surgery (positive vertical surgery, LVI, PD, grade 2-3 TB).

Demographic characteristics (age, sex), comorbidities [according to the Charlson Comorbidity Index (CCI)] were assessed.[6]

The study protocol was approved by the Ethics Committee of Ege University (approval date: December 14, 2023, approval number: 23-12T/42). Informed consent was obtained from all patients regarding the ESD procedure and surveillance program.

Endoscopic Resection-Related Data

Data relating to the location, size, morphologic appearance, chromoendoscopic appearance, ESD technique, and severe perioperative submucosal fibrosis were obtained from endoscopy reports. The cecum, ascending colon, and transverse colon are grouped as the right colon, whereas the descending colon and sigmoid colon are grouped as the left colon. The lesion morphology was defined according to the Paris and Laterally Spreading Tumor Classifications.[7] Chromoendoscopic assessment was performed using the Narrow Band Imaging International Colorectal Endoscopic (NICE).[8] As we reported in our previous study locoregional staging was performed with computed tomography (CT) or magnetic resonance imaging for NICE type 3 lesions before ER.[9]

A submucosal transparent appearance was classified as no fibrosis (F0), submucosal white muscle appearance was classified as severe fibrosis (F2). Other cases were grouped as mild fibrosis (F1).[10]

Histopathological Data

A number of histopathological data, including tumor size, lateral surgical margin, vertical surgical margin, depth of submucosal invasion, presence of LVI (positive and negative), TB (low/moderate/high differentiation), and tumor differentiation (TD) (well/moderately/poorly differentiated) were reviewed. Patients who underwent complementary surgery were assessed for residual tumors and LNM based on the surgical specimen. Histopathological data were evaluated by a pathologist experienced in the gastrointestinal tract. Histopathological examinations were performed according to the Japanese Classification of Colorectal Carcinoma (9th edition).[11]

Patient Management After ESD

Curability after ESD was evaluated using the 2019 guidelines of the Japanese Society for Cancer of the Colon and Rectum.[12] Patients with T1b and no additional risk factors were informed by their primary physician that nonoperative surveillance could be an option, and they were advised of possible risks. Nonoperative surveillance consisted of testing for blood carcinoembryonic antigen (CEA) levels, endoscopic examination, and whole-body CT scans performed every 3 months for the first year, every 6 months for the second year, and once a year thereafter for patients who agreed. Complementary surgery was recommended in T1b patients with any risk factor.

The primary outcome of the study was the risk of recurrence after ESD in low-risk T1b CRC patients who underwent only surveillance. Our secondary outcome was the safety of ESD in low-risk T1b CRC.

MAIN POINTS

- The role of subsequent surgery is controversial for the patients with low-risk T1b colorectal cancer (CRC).
- Further differentiation of noncurative conditions in terms of lymph node metastasis risk may help determine when to use nonoperative surveillance after noncurative endoscopic resection (ER).
- Deep submucosal invasion alone is a low-risk condition for recurrence.
- In the current study, 12 patients with low-risk T1b CRC who received nonoperative surveillance after ER had no recurrence in the course of median 2 years of follow-up.
- Our result shows that ER may be an adequate treatment option in low-risk T1b CRC patients.

RESULTS

Of 1102 cases of colorectal lesions resected using ESD between July 2019 and February 2023, 23 patients were histopathologically classified as T1b CRC. We excluded 1 patient with a synchronous tumor, 3 patients with CRC at the base of a pedunculated polyp, 2 patients with piecemeal endoscopic resection, 2 patients in whom R0 resection could not be achieved, 2 others classified into high-risk T1b after endoscopic resection, and 1 patient with a follow-up length of less than 1 year from this study (Figure 1). Ultimately, 12 patients with low-risk T1b CRC were included in the study (Table 1), of whom 66.7% (8/12) were male. The mean patient age was 60.66 years (range: 42-78 years), and the median CCI was 2 (range, 1-4). Six lesions were located in the left colon, 3 lesions were located in the right colon and the other 3 lesions were located in the rectum. The mean tumor size was 25 mm (range 9-40 mm). Eight lesions had a history of biopsy before ESD. Based on the NICE classification, 3 lesions were classified as NICE type 2 and 8 lesions as NICE type 3. Paris Is+IIa and LST NG-PD subgroups were the most common morphologic classifications. During ESD, severe fibrosis was found in 83% (10/12) of the patients. All patients with severe fibrosis underwent traction. One patient suffered a minor muscle injury, which was repaired using a clip. No complications requiring surgery were observed. The mean procedure duration was 37.38 minutes (range, 15-85 min). The histopathological correlation between biopsy and ESD specimen was 25% (2/8). Moderate TD was observed in a patient. The median submucosal invasion depth was 1850 µm (range, 1100-3000 µm). One patient underwent complementary surgery at 5 months after ESD. No residual tumor or LNM was observed in the surgical specimen (T0N0) of this patient. At a median follow-up of 25.5 months (interquartile range: 12-53 months), none of the low-risk T1b CRC patients who agreed to nonoperative surveillance had recurrence, distant metastasis, or mortality (Table 1). The mean CEA level was below 1.8 g/L at 1 year after the procedure.

DISCUSSION

In patients with T1 CRC, radical surgery is recommended when curative criteria are not met after ER.[2,12] However, >80% of the patients who undergo radical surgery have no LNM.[13] Further differentiation of noncurative conditions in terms of LNM risk may help determine when to use nonoperative surveillance after noncurative ER in high-risk patients for surgery.[14] Of all the criteria for noncurative resection, SMd alone is a low-risk condition for recurrence.[3,5,13,14] The LNM rate in low-risk T1b CRC has been found to be 1.6%-2.2%.[3] Therefore, the role of subsequent surgery in these patients is controversial. In the current study, 12 patients with low-risk T1b CRC who received nonoperative surveillance after ER had no recurrence in the course of median 2 years of follow-up. This result shows that ER may be an adequate treatment option in low-risk T1b CRC patients. In addition, the present study contributes to the limited literature on low-risk T1b CRC.

Of all the criteria for noncurative resection, SMd is the most common and the only predictor.[15] Various chromoendoscopic classifications to predict SMd have been developed.[2] In the present study, the NICE classification was chosen as it does not require magnification. However, the NICE classification has a major shortcoming: insufficient sensitivity

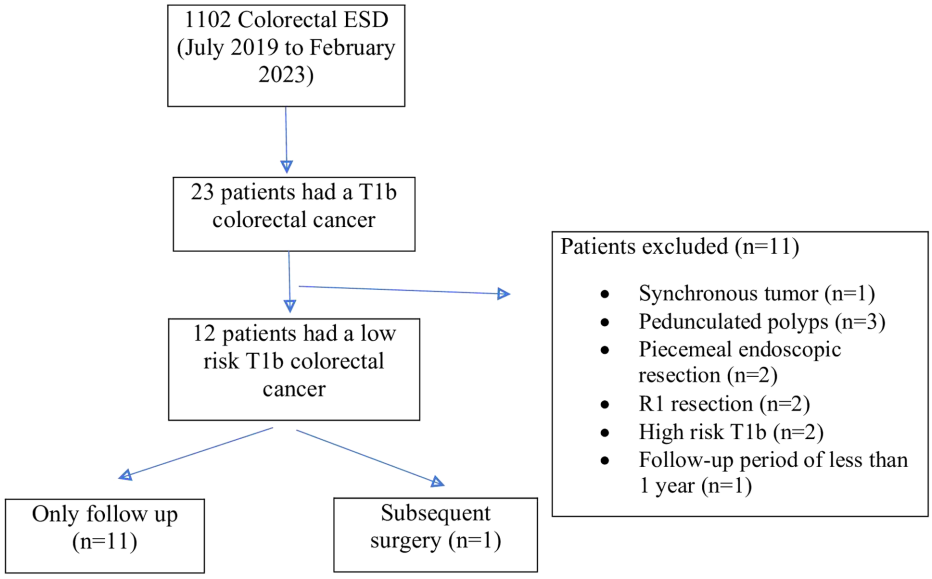


Figure 1. Flowchart of the study population. ESD, endoscopic submucosal dissection.

Table 1. Demographic, Procedural, and Histopathological Data of Patients Treated with Endoscopic Submucosal Dissection for T1b Colorectal Cancers

	Age	M/F	Location	Size (mm)	Paris	NICE	LST	TD	LVI	SMI (µm)	Surgery	Follow-Up (Months)
1	51	F	SF	40 × 25	Is+IIa	3	G-NM	Well	–	2400	–	17
2	67	M	DC	9 × 9	IIa+IIc	3	NG-PD	Well	–	1300	–	14
3	72	F	R	50 × 42	Is+IIa	2	G-NM	Well	–	1500	–	15
4	63	M	SC	20 × 10	Is+IIc	3	NG-PD	Well	–	1100	–	27
5	42	M	R	25 × 15	Is+IIc	3	NG-PD	Well	–	2000	–	24
6	52	M	SC	12 × 8	IIa+IIc	3	NG-PD	Well	–	2000	–	12
7	71	F	R	30 × 20	Is+IIa	3	G-NM	Well	–	2000	–	40
8	69	F	AC	25 × 22	Is+IIc	2	NG-PD	Well	–	1700	–	42
9	78	M	SC	32 × 28	Is+IIa	3	G-NM	Well	–	1500	–	37
10	59	M	AC	40 × 35	Is+IIa	3	G-NM	Well	–	2300	RH (T0N0)	53
11	43	M	SF	25 × 15	IIa+IIc	2	NG-PD	Moderately	–	1100	–	30
12	61	M	AC	25 × 20	Is+IIc	2	NG-PD	Well	–	3000	–	20

AC, ascending colon; DC, descending colon; F, female; LST-G-NM, laterally spreading tumor, granular-nodular mixed; LST-NG-PD, laterally spreading tumor nongranular-pseudodepressed; LVI, lymphovascular involvement; M, male; NICE, NBI International Colorectal Endoscopic Classification; SC, sigmoid colon; SF, splenic flexure; SMI, submucosal invasion; R, rectum; RH, right hemicolectomy.

(55%-83%) for SMd.[9] Although SMd was found in all patients in our study, two thirds of them had NICE type-3 appearance. Although NICE recommends surgical treatment for type-3 lesions, this recommendation may change in the future if further studies show the efficacy of ER in low-risk T1b CRC.

Endoscopic submucosal dissection is the ER technique of choice for lesions with suspected submucosal invasion. The major disadvantage of ESD is the required technical skill and difficulty in learning. Of note, in the presence of SMd, the probability of R0 resection with the ESD method is lower (62%-65%).[3] The present study excluded patients who could not achieve R0 resection or patients with high-risk T1b CRC, which precluded the evaluation of the efficacy of ESD in T1b tumors. While the majority of patients required fibrosis-related traction, none developed any ESD-related serious adverse events. The low risk of complications may be attributed to the fact that all procedures were performed by an endoscopist specialized in ESD. Recently, endoscopic full-thickness resection (EFTR) has emerged as an alternative in T1 CRC. The probability of R0 resection with this technique has been found to be 60%, and EFTR-related adverse events have been reported in 3.9% of patients. The main limitation of EFTR is its suitability for lesions less than 20 mm.[16] Prospective studies are required to compare ESD and EFTR. Considering the morbidity and mortality associated with oncologic surgery, ER methods may be a less invasive approach for the treatment of low-risk T1b CRC.[2] Indeed, the latest ESGE guideline states that nonoperative surveillance after ER may be an option for the treatment of low-risk T1b CRCs located in the rectum.[12]

The current study has some limitations, particularly its single-center and retrospective design. A meta-analysis by Hao Dang et al[17] that included 5167 cases from 71 studies that looked into surveillance alone after ER for T1 CRC showed that recurrences can be seen in the first 6 years (76% in the first 48 months). Thus, a longer follow-up period is needed to better interpret the results of the current study in terms of recurrence. Another limitation of our study is that the risk of LNM could not be clearly evaluated because of the small number of patients

and only 1 patient underwent subsequent surgery. We have an ongoing multicenter retrospective study investigating the same subject, which is likely to achieve more conclusive results by analyzing the histopathological data of patients with T1b CRC undergoing surgical resection.

In conclusion, nonoperative ER surveillance in low-risk T1b CRC was found to be promising in terms of recurrence. We anticipate that the criteria for curative resection of CRC, especially for low-risk T1b tumors, may expand in the future.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University (Approval Date: December 14, 2023, Approval Number: 23-12T/42).

Informed Consent: Informed consent was obtained from all patients who participated in this study.

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