ORIGINAL ARTICLE

Long-term outcomes after endoscopic submucosal dissection for superficial colorectal tumors

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Background and Aims: Endoscopic submucosal dissection (ESD) is an effective procedure for en bloc resection of superficial colorectal tumors regardless of tumor size or location. However, there are few reports on long-term outcomes for patients with superficial colorectal tumors after ESD. We therefore aimed to evaluate the long-term outcomes after ESD for superficial colorectal tumors.

Methods: ESD was performed on 257 colorectal tumors in 255 consecutive patients at Hiroshima University Hospital between June 2003 and July 2010. We investigated the following variables: patient characteristics, the American Society of Anesthesiologists score, tumor location, tumor size, growth type, histology, en bloc resection rate, achievement of curative resection, procedure time, and adverse events. The 5-year overall survival (OS), 5-year disease-specific survival (DSS), local recurrence, and metachronous tumor occurrence were also analyzed.

Results: We identified 224 tumors in 222 patients who were confirmed dead or had follow-up data for more than 5 years. After a median follow-up of 79 months, 5-year OS and DSS rates were 94.6% and 100%, respectively. The local recurrence rate (1.5%) was significantly higher in patients undergoing piecemeal resection (9.1%) compared with en bloc resection (0.6%), in cases of histologic incomplete resection compared with complete resection, and in cases of non-R0 resection compared with R0 resection. The rates of total number of tumors (≥6 mm) and carcinoma metachronous tumors after ESD without additional surgical resection were 18.9% (38/201) and 4.0% (8/201), respectively.

Conclusions: Long-term outcomes after ESD for superficial colorectal tumors are favorable. Patients should be surveyed for both local recurrence and metachronous tumors after ESD. (Gastrointest Endosc 2016;■:1-8.)

INTRODUCTION

Endoscopic submucosal dissection (ESD) is an effective procedure for en bloc resection of large superficial colorectal tumors, and is currently being used to treat such malignancies.[1-14] The safety and convenience of this procedure has gradually become accepted; ESD has also undergone numerous technical refinements. ESD for superficial colorectal tumors is technically more difficult and requires considerable experience compared with EMR; the risk of adverse events, such as perforation, is also greater.[3,15-17] However, clarification of the factors affecting the technical difficulty of ESD,[18-22] improvement of the associated tools and devices,[5] and the

Abbreviations: ASA, American Society of Anesthesiologists; DSS, disease-specific survival; ESD, endoscopic submucosal dissection; HMO, horizontal margin negative; JSCCR, Japanese Society for Cancer of the Colon and Rectum; LST, laterally spreading tumor; OS, overall survival; SD, standard deviation; SM, submucosal; VMO, vertical margin negative.

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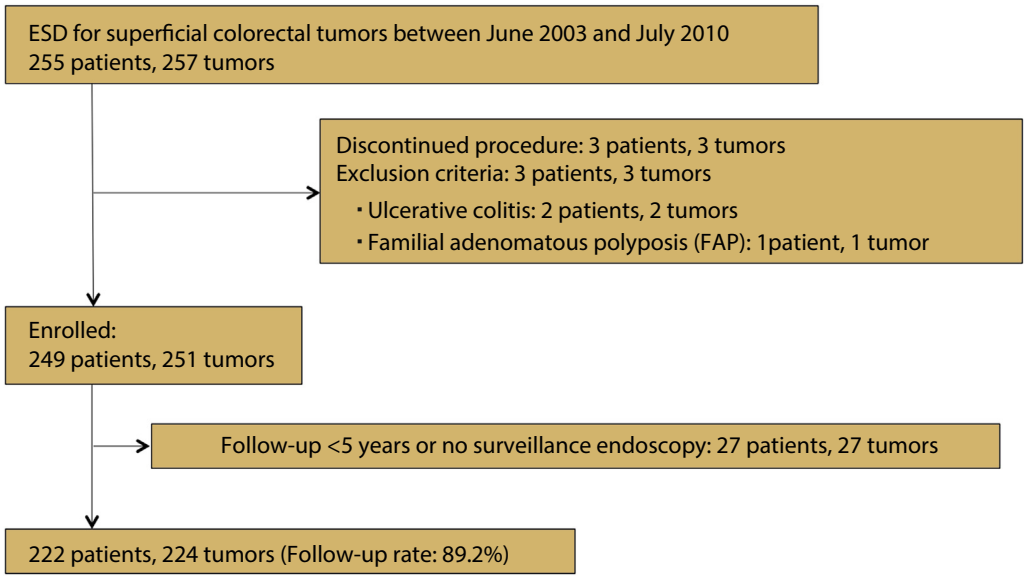

Figure 1. Flowchart of enrolled patients and tumors.

establishment of a training system[23] have increased the safety of the procedure for superficial colorectal tumors. In Japan, ESD for superficial colorectal tumors has been covered under the national health insurance since April 2012.

Several studies have reported the outcomes after ESD for superficial colorectal tumors[3,24-28]; however, their median follow-up periods were relatively short. It is important to reveal the local recurrence rate after ESD for superficial colorectal tumors because radical local excision of all tumors cannot be achieved through ESD. In addition, long-term outcomes after ESD for these tumor types are not clear, and the risk of metachronous tumors has not been determined during surveillance for colorectal tumors after ESD. Hence, the aim of this study was to determine long-term outcomes in patients who underwent ESD for superficial colorectal tumors.

METHODS

Patients

A total of 257 colorectal tumors in 255 consecutive patients were resected by ESD at Hiroshima University Hospital between June 2003 and July 2010. The indications for ESD for superficial colorectal tumors at our center were based on the criteria proposed by the Colorectal ESD Standardization Implementation Working Group.[2,4,5,29,30] ESD is indicated for lesions requiring endoscopic en bloc resection for which it is difficult to use the snare technique, including laterally spreading tumor (LST) non-granular type (especially the pseudodepressed type), tumors with type VI pit pattern, superficial invasive submucosal carcinoma, large depressed tumors, and large elevated lesions that are probably malignant (eg, large nodular lesions such as LST granular type). In addition, ESD is also indicated for colorectal lesions accompanied by submucosal fibrosis (induced by biopsy or peristalsis of the lesion), sporadic localized tumors that occur because of chronic inflammation such as ulcerative colitis, and local residual early carcinoma after endoscopic resection. At the same time as the ESD procedure, we removed all synchronous lesions completely and patients achieved a clean colon. We excluded patients according to the following criteria: abandoned procedure (3 tumors in 3 patients), ulcerative colitis (2 tumors in 2 patients), familial adenomatous polyposis (1 tumor in 1 patient), and patients with either less than 5 years of follow-up or those who did not undergo endoscopic surveillance colonoscopy after ESD (27 tumors in 27 patients). Ultimately, 224 tumors in 222 patients (89.2%) who were confirmed dead or had follow-up data for more than 5 years were identified and analyzed (Fig. 1).

The study was performed in accordance with the Declaration of Helsinki. All patients were informed of the risks and benefits of ESD, and each patient provided written informed consent for the procedure. This study protocol was approved by the Institutional Review Board of Hiroshima University Hospital. None of the patients refused ESD for colorectal tumors during the study period.

ESD procedure

ESD was performed by 2 experienced endoscopists (S.T. or S.O.) in this series. An endoscope attached to a transparent tip hood with carbon dioxide insufflation was used. A GIF-Q260J gastroscope for sigmoid colon or rectal

tumors (Olympus, Tokyo, Japan) and a PCF-Q260AZI (Olympus) for tumors of the descending colon and cecum were used. A Dual knife (Olympus Medical Systems, Tokyo, Japan), Flex knife (Olympus), SB knife Jr (Sumitomo Bakelite, Tokyo, Japan), or a Hook knife (Olympus) was used as appropriate for each case. We mixed equal volumes of 0.4% sodium hyaluronate (Muco Up; Johnson & Johnson, New Brunswick, NJ) and 10% glycerin solution, and added a small amount of indigo carmine (0.2 mL per 20 mL sodium hyaluronate + glycerin). Endoscopic hemostasis was achieved with hemostatic forceps (Coagrasper; Olympus), and a high-frequency generator was used (ESG-100, Olympus). The pulse cut slow mode setting (25 W) was used for mucosal incisions, and forced coagulation mode (25 W) was used for submucosal (SM) dissection. We used the pulse cut fast mode setting (30 W) and soft coagulation (40 W) with the SB knife Jr. All antiplatelet therapy was interrupted 5 to 7 days before ESD for superficial colorectal tumors, and patients taking warfarin to prevent thromboembolic disease were switched to heparin.

Histologic assessment

Resected specimens were stretched, pinned out, fixed in 10% buffered formalin, sliced into 2-mm sections, and assessed microscopically. Histologic complete resection was defined as horizontal margin negative (HM0) and vertical margin negative (VM0). The definition of R0 resection in this study means histologic complete resection as well as no risk of lymph node metastasis by histologic examination of resected specimen according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guideline criteria: well/moderately differentiated or papillary carcinoma, no vascular invasion, submucosal invasion depth <1000 μm, and budding grade 1.[31] Histopathologic diagnosis was performed according to the World Health Organization classification system.[32] The depth of submucosal invasion was determined according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus as outlined by the JSCCR.[31] Tumors were thus classified as adenoma, intramucosal adenocarcinoma, carcinoma with superficial submucosal invasion (<1000 μm), or carcinoma with deep submucosal invasion (≥1000 μm). According to the JSCCR Guidelines of 2014,[31] colectomy with lymph node dissection must also be performed after ESD when a positive deep tumor margin is present in resected T1 colorectal carcinoma specimens. Moreover, additional treatment should be considered (but is not an absolute requirement) when at least 1 of the following is found: (1) SM invasion depth ≥1000 μm; (2) positive vascular invasion; (3) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; and (4) grade 2/3 budding at the deepest part of SM invasion. The JSCCR Guidelines of 2014 clearly state that additional treatment should be administered only after systematically evaluating the predicted curability on the basis of various lymph node metastasis risk factors and each patient's preference and background (age, physical activity, and adverse events),[31] and only after obtaining informed consent from the patient. We decided to perform additional colectomy with lymph node dissection according to the relevant guidelines of that time.[33-35] In this study, we retrospectively reassessed all of the cases according to the JSCCR Guidelines of 2014.

Surveillance after ESD

All patients underwent intensive follow-up either at our institution or in partnership with their referring centers. Follow-up colonoscopy was performed at 1 year for patients who had histologic complete resection, and at 6 months and again at 1 year for patients with tumors showing a histologic positive horizontal margin.

In order to analyze the long-term outcomes, a questionnaire was sent to patients who had no follow-up medical records at our institution or at our partner centers.

We retrospectively analyzed the 5-year rate of overall survival (OS) and disease-specific survival (DSS), as well as the local recurrence rate and metachronous tumor occurrence. Metachronous tumors included adenomas ≥6 mm in diameter, plus a carcinoma of any size.

Variables investigated

The following variables were investigated: patients' clinical characteristics (including age and sex), the American Society of Anesthesiologists (ASA) score and chronic concomitant disease of patients, tumor location, tumor size, growth type, histology, en bloc resection rate, whether curative resection was achieved according to the JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer,[31] procedure time, and adverse events. Delayed bleeding was defined as an Hb level decreasing by 2 g/dL or more in comparison with the last preoperative level, or apparent bleeding or massive melena.[36] Endoscopically, the degree of submucosal fibrosis was classified as reported previously: no fibrosis (F0), mild fibrosis (F1), and severe fibrosis (F2).[11] The rate of metachronous tumor occurrence was also determined.

Statistical analysis

Values are shown as means ± standard deviation (SD). Differences in continuous variables were analyzed by the Student t test or Mann-Whitney U test, and differences in nominal variables were analyzed by the Pearson χ^2 test and the Fisher exact test. The survival analyses and proportion of patients with metachronous tumors were determined using Kaplan-Meier analyses. $P < .05$ was considered statistically significant. JMP version 10.0 (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

Clinicopathologic characteristics

We identified and analyzed 224 superficial colorectal tumors resected by ESD in 222 patients, including 145 men and 77 women. The mean age of the patients was 66 ± 11 years; 60.4% (134/222) of the patients were 65 years or older. Patient details are shown in Table 1. Chronic concomitant diseases included hypertension in 19.4% of patients, dyslipidemia in 8.6%, heart disease in 6.8%, diabetes in 5.9%, and cerebrovascular disease in 5.0%. Mean (±SD) tumor size was 31 ± 17 mm. Thirty-six SM invasive carcinomas did not meet the JSCCR criteria for curative resection.[31]

Outcomes related to ESD

The outcomes related to ESD are shown in Table 2. The mean (±SD) ESD procedure time was 77 ± 54 minutes; 184 tumors (82.1%) had F0 or F1 fibrosis and 40 tumors (17.9%) were F2. The en bloc resection rate was 89.7% (201/224). The histologic complete resection rate was 85.7% (192/224) and the R0 resection rate was 83.0% (186/224). The rate of delayed bleeding was 6.3% (14/224) and the rate of perforation was 5.4% (12/224). All adverse events were successfully managed endoscopically.

Long-term outcomes after ESD

According to post-ESD pathologic assessments, 186 tumors in 184 patients met the JSCCR criteria for curative resection (R0 resection), whereas 38 tumors in 38 patients did not (non-R0 resection). Of patients with non-R0 resection, 23 underwent additional surgical resection, whereas 15 patients were followed without additional surgery. The median follow-up period was 76.6 ± 21.2 months (range, 7-129 months) for all patients and 79.2 ± 18.6 months (range, 60-129 months) for surviving patients. The median duration between ESD and the final colonoscopy was 63.6 ± 23.2 months (range, 6-117 months). Furthermore, 73.9% (164/222) of patients were followed with surveillance colonoscopy for over 5 years. Details of OS and DSS for all 222 patients are shown in Fig. 2. After a median follow-up period of 6.4 years, the 5-year OS and DSS rates were 94.6% and 100%, respectively. The risk factors of OS, age 65 years or older (versus less than 65 years; odds ratio, 5.56) and ASA score 3-5 (versus ASA score 1-2; odds ratio, 3.83) were significantly related to OS in the multivariate analysis.

Clinicopathologic features of local recurrence after ESD for superficial colorectal tumors without additional surgical resection are shown in Table 3. The local recurrence rate was 1.5% (3/201); none were metastatic; this rate was significantly higher after piecemeal resection than after en bloc resection ($P < .01$). This rate was also significantly higher in cases of histologic incomplete resection than complete resection ($P < .01$) and higher in cases of non-R0 resection than R0 resection ($P < .01$).

The characteristics of the 3 patients who experienced local recurrence after ESD are shown in Table 4. The

TABLE 1. Baseline characteristics of the patients and tumors

Variables	Total (%)
Number of patients	222
Number of tumors	224
Sex	
Male	145 (65.3)
Female	77 (34.7)
Age (years)	
Average ± SD	66 ± 11
<65	88 (39.6)
≥65	134 (60.4)
ASA score	
1	111 (50.0)
2	82 (36.9)
3	29 (13.1)
4	0 (0.0)
5	0 (0.0)
Concomitant disease	
Hypertension	43 (19.4)
Hyperlipidemia	19 (8.6)
Cardiovascular disease	15 (6.8)
Diabetes mellitus	13 (5.9)
Cerebrovascular disease	11 (5.0)
Tumor location	
Right side of colon	71 (31.7)
Left side of colon	43 (19.2)
Rectum	110 (49.1)
Tumor size (mm)	
Average ± SD	31 ± 17
<40	158 (70.5)
≥40	66 (29.5)
Growth type	
LST-G	102 (45.5)
LST-NG	80 (35.7)
Polypoid	42 (18.8)
Histology	
Adenoma	71 (31.7)
Carcinoma	153 (68.3)
Tis	106 (47.3)
T1 (<1000μm)	16 (7.1)
T1 (≥1000μm)	31 (13.8)

SD, standard deviation; *ASA*, American Society of Anesthesiologists; *LST-G*, laterally spreading tumor granular type; *LST-NG*, laterally spreading tumor non-granular type; *Tis*, carcinoma in situ.

TABLE 2. Outcomes related to ESD for superficial colorectal tumors

Variables	Total (%)
Number of tumor	224
Procedure time (min)	
Average ± SD	77 ± 54
Fibrosis	
F0, F1	184 (82.1)
F2	40 (17.9)
Resection status	
En bloc	201 (89.7)
Piecemeal	23 (10.3)
Histological complete resection	
Complete	192 (85.7)
Incomplete	32 (14.3)
Endoscopic curability	
R0 resection	186 (83.0)
Non-R0 resection	38 (17.0)
Adverse event	
Delayed bleeding	14 (6.3)
Perforation	12 (5.4)

SD, standard deviation.

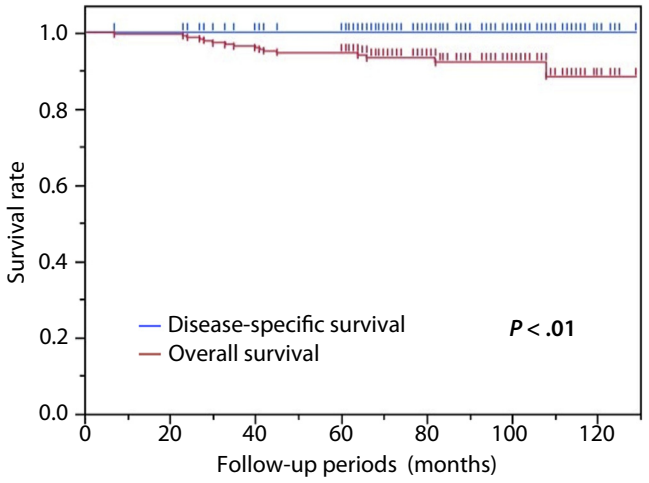

Figure 2. Survival curve after ESD for superficial colorectal tumors.

primary tumors of 2 patients with intramucosal lesions were resected by the piecemeal method; the recurring lesions were cured by additional endoscopic treatment and were diagnosed as adenomas pathologically. The third case of local recurrence was a submucosal superficial invasive carcinoma (SM 100 μm, Budding grade 1, no vessel involvement) with histologically incomplete resection (HM1, VM0). This patient refused additional surgical resection after ESD because of his advanced age. A recurrent submucosal lesion was

TABLE 3. Clinicopathologic features of local recurrent colorectal tumors after ESD

Variables	Local recurrence (%)	*P* value
Number of tumor	3/201 (1.5)	
Sex		
Male	2/131 (1.5)	NS
Female	1/70 (1.4)	
Age (years)		
<65	0/72 (0.0)	NS
≥65	3/129 (2.3)	
Tumor location		
Right side of colon	2/65 (3.1)	NS
Left side of colon	0/40 (0.0)	
Rectum	1/96 (1.0)	
Tumor size (mm)		
<40	1/139 (0.7)	NS
≥40	2/62 (3.2)	
Growth type		
LST-G	2/98 (2.0)	NS
LST-NG	0/72 (0.0)	
Polypoid	1/31 (3.2)	
Fibrosis		
F0, F1	2/165 (1.2)	NS
F2	1/36 (2.8)	
Histology of primary lesion		
Adenoma	1/71 (1.4)	NS
Carcinoma	2/130 (1.5)	
Tis	1/105 (1.0)	
T1 (<1000 μm)	0/12 (0.0)	
T1 (≥1000 μm)	1/13 (7.7)	
Resection status		
En bloc	1/179 (0.6)	.038
Piecemeal	2/22 (9.1)	
Histologic complete resection		
Complete	0/174 (0.0)	.001
Incomplete	3/27 (11.1)	
Endoscopic curability		
R0 resection	0/186 (0.0)	.000
Non-R0 resection	3/15 (20.0)	
Adverse event		
Delayed bleeding		
Positive	1/12 (8.3)	NS
Negative	2/189 (1.1)	
Perforation		
Positive	0/12 (0.0)	NS
Negative	3/189 (1.6)	

LST-G, laterally spreading tumor granular type; *LST-NG*, laterally spreading tumor non-granular type; *NS*, not significant.

TABLE 4. Clinicopathologic characteristics of local recurrent tumors after ESD

			Primary tumor						
No.	Age (years)	Sex	Location	Size (mm)	Growth type	Histology	Resection status	Horizontal margin	Vertical margin
1	72	M	C	40	LST-G	Tis carcinoma	Piecemeal	(+)	(-)
2	71	F	Rb	35	LST-G	Serrated adenoma	Piecemeal	(+)	(-)
3	86	M	A	45	Polypoid	T1 carcinoma (100 μm)	En bloc	(+)	(-)

M, male; *C*, cecum; *LST-G*, laterally spreading tumor granular type; *APC*, argon plasma coagulation; *F*, female; *Rb*, rectum below the peritoneal reflection; *A*, ascending colon.

detected during surveillance endoscopy 48 months after ESD, after which he agreed to additional surgical resection. All 3 patients remain alive with no further recurrences.

Metachronous tumors after ESD were detected in 38 patients (19.1%). Our analysis did not reveal any risk factors for the occurrence of metachronous tumors. The proportions of patients with metachronous tumors were 0.96%, 4.7%, and 8.3%, at 1, 3, and 5 years after ESD, respectively (Fig. 3). Metachronous carcinoma after ESD was detected in 8 patients (4.0%); as before, our analysis did not reveal risk factors for the occurrence of metachronous carcinoma. The proportions of patients with metachronous carcinomas were 0.0%, 1.6%, and 3.8% at 1, 3, and 5 years after ESD, respectively (Fig. 3).

DISCUSSION

Our results demonstrate that ESD for superficial colorectal tumors results in favorable outcomes. Previous studies have reported favorable long-term outcomes of ESD for superficial colorectal tumors.[3,24-28] In a systematic review of 13 series, Repici et al[24] reported that the local recurrence rate of patients with R0 resection was 0.07% during a median follow-up period of approximately 2 years. Furthermore, another systematic review of mid-term outcomes of 22 studies by Patel et al[25] reported that the en bloc resection rate was 89%, whereas the R0 resection rate was 76%; furthermore, they reported that the overall local recurrence rate was 1% over approximately 2 years of median follow-up. Other studies reporting overall long-term outcome data after colorectal ESD reported local recurrence rates of between 0.4% and 7.9%, with a 5-year OS rate of 95.3%.[26-28] However, the median follow-up periods of only 3 years or less in these studies are too short for the proper assessment of outcomes in colorectal tumors.

Twelve of the 15 patients with non-R0 resection were followed without additional surgical resection; they achieved histologic complete resection with negative risk factors for lymph node metastasis without SM invasion depth. According to the JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer,[31] patients with T1 colorectal carcinoma (≥1000 μm) should be considered for additional colectomy with lymph node dissection; however, the probability of lymph node metastasis is extremely low (1%-2%) if no other risk factors (other than SM invasion depth ≥1000 μm) are present.[37,38] Our results suggest that the long-term outcomes of T1 carcinomas with SM invasion depth ≥1000 μm are favorable after ESD resection following the JSCCR Guideline.[31] As we previously reported,[39] en bloc resection by ESD as total excisional biopsy for clinical T1 colorectal carcinoma is an appropriate and effective treatment.

Regarding endoscopic resection for superficial colorectal tumors larger than 20 mm in diameter, we previously reported that the local recurrence rate after conventional endoscopic resection (including EMR or polypectomy) was significantly higher than that of ESD, and significant factors associated with local recurrence were piecemeal resection, LSTs of granular type, tumor size ≥40 mm, no pre-treatment magnification, ≤10 years of experience in conventional endoscopic resection, and piecemeal resection only in ESD.[40]

Moss et al[41] suggested that EMR has the potential to be considered a first-line therapy with some advantages over alternatives such as surgery or ESD. However, tumors with scarring and those that are submucosal with severe fibrosis are reportedly difficult to treat via endoscopic resection.[20,21] It is also challenging to perform a complete resection if the recurrent lesion is a carcinoma. Moreover, in large elevated lesions suspected of being carcinomas (such as LST granular type/nodular mixed type), SM invasion may exist in the large nodule for which en bloc resection with a snare would be difficult. Furthermore, pathologic diagnosis for invasion depth and lymphovascular invasion would be difficult if a T1 carcinoma lesion was cut into pieces, and necessary additional surgical resection might not be performed. It may be a challenging task for both patients and endoscopists to follow a strict surveillance colonoscopy regimen after endoscopic resection. In fact, all 3 patients in our study who experienced local recurrence achieved histologic incomplete resection. Our data showed that only histologic complete resection is curative for large colorectal tumors.

A proportion of our patients exhibited metachronous tumors. Martinez et al[42] reported that polyp size is a risk factor for the development of interval advanced neoplasia, and that baseline polyps of 20 mm in diameter or greater carry a 19.3% increased risk of advanced neoplasia. Lieberman et al[43] reported that the risk of

TABLE 4. Continued

Time to local recurrence (month)	Size (mm)	Morphology	Histology	Treatment	Prognosis
3	3	IIa	Adenoma	Hot biopsy + APC	Alive
14	5	Is	Serrated adenoma	EMR	Alive
48	30	Is	Advanced carcinoma	Surgical resection	Alive

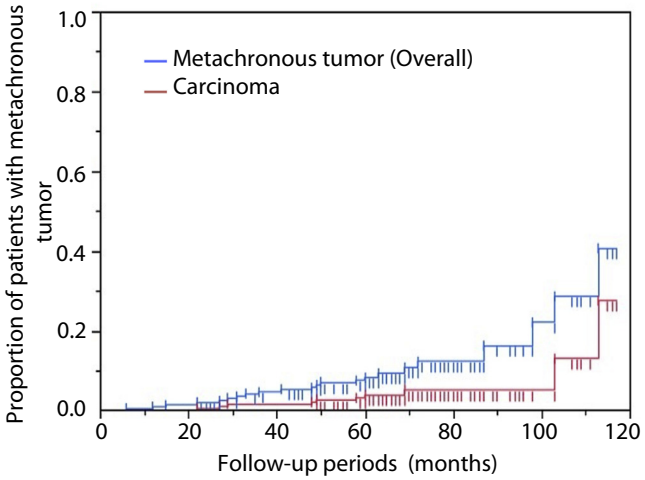

Figure 3. Metachronous tumor after ESD for superficial colorectal tumor.

advanced neoplasia after polypectomy within 5.5 years was 2.4% in their "no neoplasia" patient group and 15.5% in patients with baseline adenomas larger than 10 mm in diameter. Based on these studies, guidelines in the United States recommend 3-year surveillance intervals after removing one or more tubular adenomas larger than 10 mm in diameter.[43] According to European guidelines, patients with adenomas larger than 20 mm in diameter are at high risk, and an additional examination is recommended within 12 months to check for missed synchronous lesions before initiating the 3-year surveillance intervals.[44] However, these guidelines were based on studies incorporating polypectomy or EMR that did not include surveillance data after ESD for superficial colorectal tumors larger than 20 mm in diameter. Our results suggest that 3-year surveillance colonoscopy after ESD for superficial colorectal tumors larger than 20 mm in diameter may be sufficient with respect to detecting metachronous tumors.

Although we estimated that patients at super-high risk of metachronous tumors after endoscopic resection included those who had large superficial colorectal tumors that required ESD resection, significant risk factors were not found. Hence, a special surveillance program was deemed not to be required after ESD for superficial colorectal tumors.

There are several limitations to our study. First, it was a retrospective study performed at a single center. However, we analyzed prospectively acquired data from consecutive patients. Second, not all the patients who underwent ESD were followed; however, only 10.8% had either less than 5 years follow-up with surveillance colonoscopy after ESD for superficial colorectal tumors, or had no follow-up at all. Our follow-up rate (89.2%) was therefore relatively high. Finally, this study included patients treated since the introduction of ESD for superficial colorectal tumors, albeit without improvements in associated tools and devices. Our data show a high rate of delayed bleeding (6.3%) compared with previous reports, although only 14 patients underwent ESD under antithrombotic agents or anticoagulants. We are planning a multicenter prospective study to clarify long-term outcomes after ESD for superficial colorectal tumors.

In conclusion, the local recurrence rate after ESD for superficial colorectal tumors is very low in tumors that undergo R0 resection, and long-term outcomes are favorable if patients with non-R0 resection undergo appropriate additional surgical resection. Regarding post-ESD surveillance for superficial colorectal tumors, the possibility of local recurrence should be taken into account after piecemeal resection or histologic incomplete resection, and the likelihood of metachronous tumors should be considered.

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