Original Article

Metachronous Neoplasia and Local Recurrence after Colorectal Endoscopic Submucosal Dissection

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Several reports discussed colonoscopic surveillance after polypectomy and endoscopic mucosal resection (EMR) for colorectal polyps, but only a few reports focused on prognostic analyses, and none involved metachronous neoplasia after colorectal endoscopic submucosal dissection (ESD). We conducted the present study to assess the risk of adenoma recurrence requiring endoscopic treatment, and to establish appropriate post-ESD colonoscopic surveillance. We enrolled 116 patients who had undergone colorectal ESD at Okayama University Hospital between February 2008 and July 2014 and had been followed-up > 12 months. We retrospectively analyzed clinicopathological features of 101 lesions from 101 patients. Metachronous adenomas were detected in 21 cases (20.8%). We divided the patients into 2 groups according to the occurrence of metachronous adenomas. Our comparison of clinicopathological characteristics between these groups showed that in the metachronous adenomas group the number of synchronous adenomas at index colonoscopy was high and the rate of laterally spreading tumor-nongranular (LST-NG) was higher. A multivariate analysis indicated that the number of synchronous adenomas was significantly associated with metachronous adenomas (HR: 2.54, 95%CI: 1.04-6.52, $p < 0.05$). The colonoscopic surveillance planning after colorectal ESD should be more meticulous for patients with more synchronous adenomas.

Key words: endoscopic submucosal dissection, laterally spreading tumor, metachronous recurrence, local recurrence, post-ESD colonoscopic surveillance

Colorectal cancer is a major cause of cancer mortality worldwide, and the number of deaths from colorectal cancer is increasing [1]. Endoscopic treatment for early-stage colorectal cancer has been revealed to be effective in reducing this cancer's progression [2] and associated mortality rates [3].

Endoscopic treatment for colorectal tumors first started as snare polypectomy [4] and progressed to endoscopic mucosal resection (EMR). EMR was reported by Deyhle to be effective in the treatment of flat-type colorectal cancer [5], and the EMR technique was developed and became popular during the 1970s. EMR is considered a highly effective and minimally invasive treatment for gastrointestinal tumors, and it is still widely performed worldwide [6].

However, in some patients with colorectal cancer, the mass cannot be removed in an en bloc fashion with only one session of EMR, as in lesions ≥ 20 mm in size, lesions on flexure or on a semilunar fold (tortuous fold), and locally recurrent lesions. These lesions are incompletely resected by means of EMR [7]. The local recur-

rence rate after endoscopic piecemeal mucosal resection (EPMR) is known to be significantly higher than that of EMR [8]. En bloc resection is an important technique for the accurate pathological diagnosis of a resected specimen, and the use of en bloc resection reduces local recurrence and increases the curative resection rate.

Endoscopic submucosal dissection (ESD) was first developed for the precise resection of early gastric cancers in the 2000s [9, 10]. ESD has been adopted at several institutions for large colorectal tumors, and it was approved for governmental health insurance coverage in Japan in 2010 [8]. The ESD technique improved the curative resection rate and provided accurate histological assessments even with large tumors, difficult locations, and the presence of severe scarring.

Several guidelines for post-polypectomy colonoscopic surveillance are available, including those from the American Gastroenterological Association (AGA) [11] and the European Society of Gastrointestinal Endoscopy (ESGE) [12]. However, these guidelines mainly describe surveillance colonoscopy after EMR, and the appropriate follow-up policy after colorectal ESD has not been established.

The number of reports about treatment outcomes of colorectal ESD is increasing. Most of these reports present short-term results, such as those regarding en bloc resection, local recurrence, and complication rates [13-15]. To the best of our knowledge, our present study provides the first report about the rate of metachronous neoplasia after colorectal ESD. We conducted this study to assess the risk of not only local recurrence but also that of metachronous adenomas that require resection after colorectal ESD, and to investigate what an appropriate post-ESD colonoscopic surveillance protocol would be.

Patients and Methods

Patients and eligibility criteria.   At our hospital, the indications for colorectal ESD are based on the Criteria of Indications for Colorectal ESD proposed by the Colon ESD Standardization Implementation Working Group in Japan [16]. These indications are: colorectal epithelial neoplasia, an endoscopically confirmed laterally spreading tumor (LST), or a polypoidal mass > 20 mm in dia.

Initially, we collected a total of 225 patients who had undergone ESD for colorectal tumors at Okayama University Hospital between February 2008 and July 2014. However, among them, 109 patients had not reached our study's minimum follow-up period of > 12 months. Further analyses in this study were thus done for the 116 patients with a follow-up period > 12 months.

Of this cohort of 116 patients, we excluded 15 patients for the following reasons: (i) residual or locally recurrent lesions after endoscopic treatment (n = 7), (ii) additional surgery after ESD (n = 2), (iii) the presence of familial adenomatous polyposis (FAP) (n = 2), serrated polyposis (n = 1), (iv) a history of surgery for advanced colorectal cancers (n = 2), and (v) a history of ulcerative colitis (n = 1) (Fig. 1).

Consequently, we retrospectively analyzed the clinicopathological features of 101 lesions from 101 patients who had undergone ESD. The analyzed parameters included the patients' gender and age, the tumor location, tumor size, macroscopic type, histological type, number of synchronous adenomas at initial colonoscopy, follow-up period after ESD, existence of local recurrence during the follow-up period, and the number of metachronous adenomas observed at colonoscopy during the follow-up period.

Three patients had 2 lesions that were simultaneously treated with ESD. We defined the larger lesion of the 2 tumors as the main lesion. In one of these patients, the 2 lesions were almost of the same size, and we considered the lesion with more malignant potential as the main lesion.

The tumor locations were classified as right colonic (from the cecum to the transverse colon), left colonic (from descending colon to sigmoid colon), or rectal. The tumor size was estimated from the endoscopic reports. The length of the major axis of resected speci-
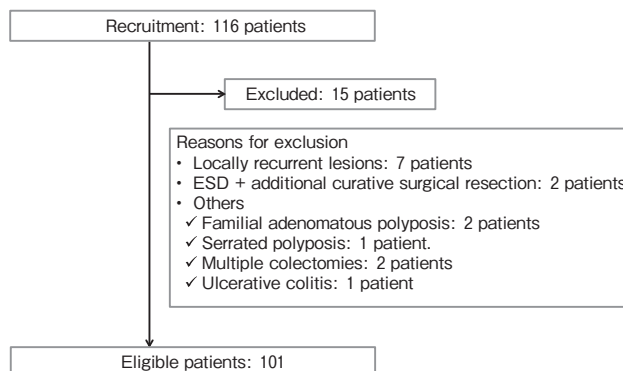

Fig. 1   Flow chart of the ESD patient enrollment.

mens, as measured by the colonoscopist, was used as the tumor size.

The macroscopic classification was based on the Paris-Japanese and Kudo classifications [8]. The tumors were classified as either laterally spreading tumor granular type (LST-G), or LST nongranular type (LST-NG). The macroscopic classifications are illustrated in Fig. 2 [8,16].

LST-Gs and LST-NGs are generally subclassified into the following subtypes: the homogenous type (LST-GH), nodular mixed type (LST-GM), flat elevated type (LST-NGF), and pseudo-depressed type (LST-NGPD) [8,16]. In our study, we did not use these subtypes, because only two patients had lesions of the LST-NGPD subtype, and if we had used this classification, the statistical analysis would have been compromised.

The histological findings were collated from the patients' pathology reports. The histological classification used was: low-grade tubular adenoma, high-grade tubular adenoma, tubulo-villous adenoma, sessile serrated adenoma/polyp, intramucosal cancer, and submucosal cancer.

We divided the 101 patients into 2 groups: the patients with metachronous adenomas at follow-up colonoscopy, and the patients without metachronous adenomas. We then conducted a subgroup analysis stratified by clinicopathological features, plus a multi-variate analysis.

Definitions. We used the following terms in this study: *Synchronous adenoma*: Adenomatous polyps ≥6 mm detected and resected endoscopically at the same time that the main lesion was treated with ESD, or at the preoperative examination before ESD. In the Japan Gastroenterological Endoscopy Society (JGES) guidelines for colorectal ESD/EMR, resection is recommended for adenomas ≥6 mm in size [16]. Following these guidelines, all detected adenomatous polyps ≥6 mm in size were resected at our hospital. When such polyps were detected within 1 year after ESD, they were still categorized as synchronous adenomas, taking into account the risk that they had been overlooked earlier. *Metachronous adenoma*: Adenomatous polyps ≥6 mm detected and resected endoscopically at follow-up colonoscopy, ≥1 year after the ESD (not including local recurrence).

ESD procedure. All patients underwent high-quality colonoscopy (an index colonoscopy) at enrolment. All procedures were performed by 1 of 4 highly experienced board-certified endoscopists at Okayama University Hospital who had each previously performed >30 ESDs.

Conscious sedation was maintained for the entire duration of each ESD procedure by administering intravenous midazolam (2-3 mg) and pethidine hydrochloride (35-70 mg). (Opystan; Mitsubishi Tanabe Pharma,

LST Granular (LST-G)   LST non-Granular (LST-NG)

Homogenous type   Nodular mixed type   Flat elevated type   Pseudo-depressed type

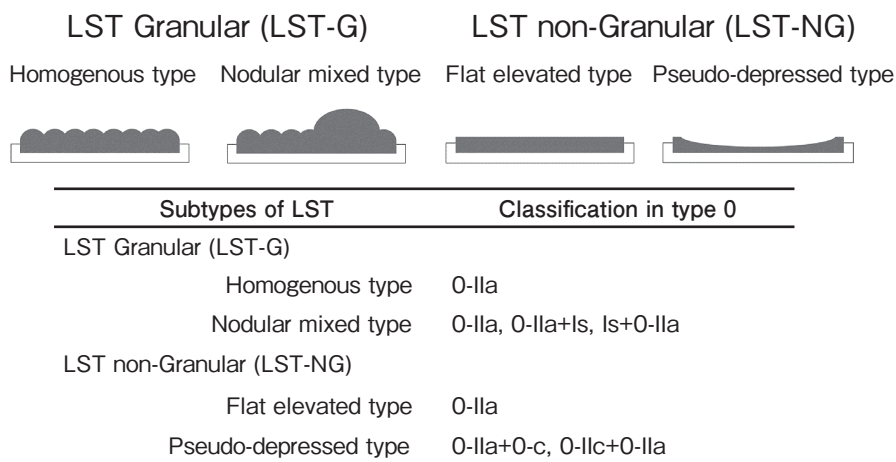| Subtypes of LST	Classification in type 0
LST Granular (LST-G)	
Homogenous type	0-IIa
Nodular mixed type	0-IIa, 0-IIa+Is, Is+0-IIa
LST non-Granular (LST-NG)	
Flat elevated type	0-IIa
Pseudo-depressed type	0-IIa+0-c, 0-IIc+0-IIa

Fig. 2   Subtypes of laterally spreading tumors (LSTs) and their correspondence in the Paris-Japanese classification. LSTs were defined as lesions > 10 mm in dia. with a low vertical axis extending laterally along the luminal wall. LSTs were classified as either granular type (LST-G) or nongranular type (LST-NG). The LST-Gs and LST-NGs were subclassified into the following subtypes: homogenous type (LST-GH), nodular mixed type (LST-GM), flat elevated type (LST-NGF), and pseudo-depressed type (LST-NGPD). The LST subclassification in relation to the macroscopic classification is shown [8,24].

Osaka, Japan). Carbon dioxide was used for insufflation. A single-channel gastroscope (GIF 260, 260J, Q240Z; Olympus, Tokyo, Japan) and a colonoscope (PCF260AI, 260J, 240ZI, and Q260AZI; Olympus) were used for the rectal and colonic ESD, respectively. Electrosurgical knives and a high-frequency automated electrosurgical generator (ICC200 or VIO300; Erbe Elektromedizin, Tübingen, Germany) in endocut or forced coagulation modes were used.

After a submucosal injection of glycerol (Chugai Pharma, Tokyo, Japan), a circumferential incision was made in the mucosa using a B-Knife® (Xemex, Tokyo, Japan), or DualKnife® (Olympus). A mixture of glycerol containing a small amount of indigo carmine dye and sodium hyaluronate acid solution (Mucoup®; Johnson & Johnson, New Brunswick, NJ, USA) was then injected into the submucosal layer to lift the lesion. The thickened submucosal layer was incised using a B-knife®, Dual-Knife®, Mucosectom® (Pentax, Tokyo, Japan), or SB knife® (Sumitomo Bakelite, Tokyo, Japan).

Follow-up colonoscopy.   The first follow-up colonoscopy was usually performed 6 or 12 months after ESD, and once every 1-2 years thereafter to assess the presence/absence of local recurrence and metachronous adenomas. The time interval between follow-up colonoscopies was decided by each endoscopist after considering the patient's histological findings.

During the follow-up colonoscopy, the endoscopist documented the locations and sizes of all detected lesions, and categorized them as neoplastic or non-neoplastic lesions using chromoendoscopy, narrow band imaging, and magnifying chromoendoscopy.

If the lesions were identified as adenomatous polyps ≥6 mm in dia., a hot biopsy, snare polypectomy, or EMR was performed, and all resected specimens were examined histologically.

Histological assessment.   All resected specimens were retrieved, fixed in 10% buffered formalin solution, and examined histologically after hematoxylin and eosin staining. The specimens were cut longitudinally into 2-mm-wide sections that were evaluated microscopically regarding the resected margin status and tumor characteristics including size, histological type, depth of invasion, and vascular and lymphatic invasions.

All histological diagnoses were based on the World Health Organization classification system [18], and measurements of tumor invasion depth were obtained according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) [19].

Statistical analysis.   We used the Chi-square test or Fisher's exact test to compare categorical data (patient gender and age, tumor location, tumor size, macroscopic type, histological type, number of synchronous adenomas at initial colonoscopy, follow-up period after ESD, existence of local recurrence during the follow-up period, and the number of metachronous adenomas observed at colonoscopy during the follow-up period) between the 2 patient groups. In the multivariate analysis, we performed a proportional hazards test to analyze each tumor's size and macroscopic type and the number of synchronous adenomas at index colonoscopy.

The significance level was set at $p < 0.05$. The statistical analyses were performed using the JMP 10.0 software package for Windows (SAS, Cary, NC, Japan).

Results

Table 1 summarizes the 101 patients' baseline characteristics. The median follow-up period was 30.1 months (range 12-82.9 mos.). The median number of follow-up colonoscopies was 2 (range 1-5). The average patient age was 68.2 ± 10.0 years. Sixty-one patients (60.4%) were men, and the other 40 were women (39.6%).

Forty-eight lesions (47.5%) were right colonic, 25 (24.8%) were left colonic, and 28 (27.7%) were rectal. The median size of the resected tumors was 35 mm (range 15-95 mm). All lesions were categorized as LSTs. Among these, 66 lesions (65.4%) were of the LST-G type, and the other 35 lesions (34.6%) were of the LST-NG type.

The histological types of the tumors were as follows: the low-risk group (30 cases, 29.7%), all of which were of the low-grade tubular adenoma type; and the high-risk group (71 cases, 71.3%): sessile serrated adenoma/polyp, 2 cases (1.9%); high-grade tubular adenoma, 18 cases (17.8%); tubulo-villous adenoma, 12 cases (11.8%); intramucosal cancer, 33 cases (32.6%); and SM1 (submucosal invasion $< 1,000\ \mu$m from muscularis mucosae) type, 6 cases (5.9%).

At index colonoscopy, the median number of synchronous adenomas was 2 (range; 1-13), and they were found in 61 cases (61.4%). Among these cases, synchronous adenomas were detected within 1 year after ESD in 19 cases. If all 19 of these polyps are considered

Table 1   Baseline clinical and pathological characteristics of the patients who underwent ESD

	n=101
Men n, (%)	61 (60.4%)
Age (mean ± SD), years	68.2 ± 10.0
Tumor characteristics	
Location n, (%)	
Right colon	48 (47.5%)
Left colon	25 (24.8%)
Rectum	28 (27.7%)
Median tumor size (range), mm	35 (15−95)
Macroscopic type n, (%)	
LST-G	66 (65.4%)
LST-NG	35 (34.6%)
Histological type n, (%)	
Low-risk group	
Low grade tubular adenoma	30 (29.7%)
High-risk group	
SSA/P	2 (1.9%)
High grade tubular adenoma	18 (17.8%)
Tubulo-villous adenoma	12 (11.8%)
Intramucosal cancer	33 (32.6%)
SM1 cancer	6 (5.9%)
Median follow-up period (range), months	30.1 (12−82.9)
Median number of synchronous adenomas analyzed at index colonoscopy (range), months	2 (1−13)

SD, standard deviation; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type; SSA/P, sessile serrated adenoma/polyp; SM1, submucosal invasion less than 1,000 μm from muscularis mucosae.
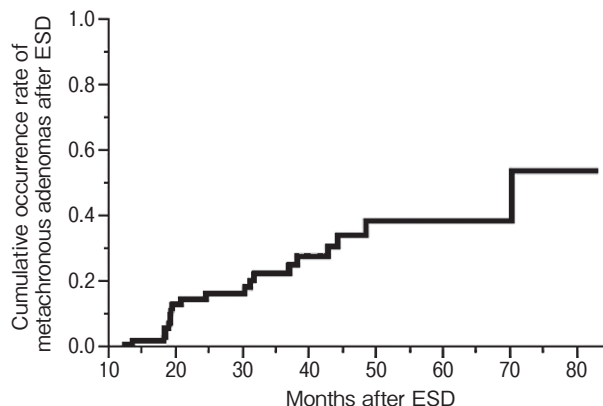

Fig. 3   Cumulative occurrence rate of metachronous adenomas after colorectal ESD. The Kaplan-Meier curve for the 101 patients treated with ESD is shown. The 3-year cumulative occurrence rate of metachronous adenomas was 23.0%, and the 5-year cumulative occurrence rate was 39.0%.

missed cases, the rate of missed adenomas was 18.8% (19/101).

Metachronous adenomas after ESD were detected in 21 cases (20.8%), whereas local recurrence was detected in only 1 case (0.99%). Fig. 3 provides the Kaplan-Meier curve for the cumulative occurrence rate of metachronous adenomas after ESD. The 3- and 5-year cumulative occurrence rates of metachronous adenomas were 23.0% and 39.0%, respectively.

Our comparison of the clinicopathological characteristics of the 2 patient groups divided according to the metachronous occurrence versus non-occurrence of adenomas revealed that in the metachronous occurrence group, the number of synchronous adenomas at index colonoscopy was significantly higher ($p=0.02$) and the rate of LST-NG was significantly higher ($p<0.01$) compared to the group without metachronous occurrence (Table 2).

The univariate analysis indicated that the following were associated with the metachronous occurrence of adenomas: tumor size <35 mm (hazard ratio [HR] 2.49, 95% confidence interval (CI) 1.03-6.57, $p=0.042$), macroscopic type (LST-NG) (HR 2.49, 95%CI 1.04-6.32, $p=0.039$), and number of synchronous adenomas (≥ 3) (HR 3.08, 95%CI 1.29-7.83, $p=0.0108$). The multivariate analysis indicated that the number of synchronous adenomas analyzed at index colonoscopy was significantly associated with metachronous adenomas (HR 2.54, 95%CI 1.04-6.52, $p<0.05$) (Table 3).

All of the recurrent tumors, including local recurrence, were treated with endoscopic resection. Curative resections were achieved in all cases.

Discussion

In the National Polyp Study (NPS) conducted in the United States, Winawer *et al.* reported that colorectal cancer can be prevented by the endoscopic removal of adenomatous polyps [2]. In another study, Zauber *et al.* reported that the endoscopic removal of adenomatous polyps can prevent death from colorectal cancer [3].

The AGA and ESGE issued their own guidelines for surveillance after endoscopic treatment for colorectal adenoma, and each of these entities' guidelines recommend that all adenomas should be removed at the initial examination. Most of the cases examined in these guidelines were related to snare polypectomy and EMR, with only a few cases of colorectal ESD examined [11,12].

Table 2   Comparison between clinicopathological characteristics of the groups according to metachronous occurrence of adenomas

	With Metachronous adenomas	Without Metachronous adenomas	
	n=21 (%)	n=80 (%)	p value
Male sex n, (%)	14 (66.7)	47 (58.7)	0.51
Age (mean ± SD), years	69.0 ± 7.6	68.0 ± 10.6	0.73
Tumor characteristics			
Location n, (%)			
Right colon	11 (52.4)	37 (46.3)	0.62
Left colon+Rectum	10 (47.6)	43 (53.7)	
Median tumor size (range), mm	30 (15–62)	37 (15–95)	0.06
Macroscopic type n, (%)			
LST-G	8 (38.1)	58 (72.5)	<0.01
LST-NG	13 (61.9)	22 (27.5)	
Histological type n, (%)			
High-risk group	17 (80.9)	54 (67.5)	0.23
Low-risk group	4 (19.1)	26 (32.5)	
Median follow-up period (range), months	20 (12–70)	23 (12–83)	0.88
Median number of synchronous adenomas analyzed at index colonoscopy (range), n	3 (1–9)	2 (1–13)	0.02

SD, standard deviation; LST-G, granular laterally spreading tumor; LST-NG, non-granular laterally spreading tumor.

Table 3   Results of univariate and multivariate analyses for metachronous occurrence of adenomas

Characteristics	Univariate analysis			Multivariate analysis		
	H.R.	95%C.I.	p value	H.R.	95%C.I.	p value
Sex						
Femal						
Male	0.97	0.40–2.56	0.95			
Age						
	1.03	0.98–1.09	0.24			
Tumor location						
Right colon						
Left colon + Rectum	0.80	0.33–1.91	0.62			
Tumor size (median = 35 mm)						
≥35 mm						
<35 mm	2.49	1.03–6.57	0.04	1.86	0.74–5.09	0.19
Macroscopic type						
LST-G						
LST-NG	2.49	1.04–6.32	0.04	1.71	0.68–4.55	0.25
Histological type						
Low-risk group						
High-risk group	1.91	0.70–6.65	0.22			
Number of synchronous adenomas analyzed at index colonoscopy						
<2						
≥3	3.08	1.29–7.83	0.01	2.54	1.04–6.52	0.04

LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type; C.I., 95% confidence interval; H.R., hazard ratio.

The JSCCR published its own guidelines for the treatment and follow-up of colorectal cancer. In its guidelines concerning the follow-up strategy after endoscopic resection, mainly local recurrence is described, and metachronous lesions of the colon are not extensively described [19].

ESD allows clinicians to freely determine the horizontal cutting line, and to visually confirm the vertical cutting line in the submucosal layer, so that large lesions can be resected en bloc fashion with certainty. As mentioned in the Introduction, the local recurrence rate after ESD has been much lower than that after EMR. The recommendations regarding surveillance plans after colorectal ESD should thus be reviewed and updated.

There are few previous reports about surveillance after colorectal ESD or studies focusing on large (≥ 20 mm dia.) colorectal lesions, and thus our present findings will be useful in the context of establishing appropriate post-ESD colonoscopic surveillance.

Although there are slight differences among the studies, the rates of local recurrence for en bloc resection with EMR and piecemeal resection were reported as 4.0% (0-17.9%) and 17.0% (4.8-31.4%), respectively [8]. The latter rate is significantly higher than the former. In our study, the local recurrence rate was 0.99% (1/101), which does not differ from the previous reports about colorectal ESD (0-11%) [8].

On the other hand, in the present study the 5-year cumulative occurrence rate of metachronous adenomas after colorectal ESD was 39.0%, which was much higher than the local recurrence rate. This metachronous recurrence rate was relatively lower than that described in previous reports [20]. The main reason for this difference would be that the median follow-up period in our study was 30.1 months, which was shorter than that in the other studies, such as the NPS [2].

In previous investigations, the risk factors for metachronous adenomas after endoscopic treatment for colorectal adenoma or early colorectal cancer included the size and pathological findings of the main lesion at the index colonoscopy, the number of synchronous adenomas, male gender, right hemi-colonic location, and older age [21]. In our study, only the number of synchronous adenomas analyzed at the index colonoscopy represented a significant risk factor for metachronous adenomas.

Although our analyses revealed no significant differ-ences between the different pathologies, metachronous adenomas tended to occur more in the high-risk histology group. This finding may change with the accumulation of future cases.

The results from our study were different from those of previous reports about surveillance after polypectomy with regard to the size of the main lesion. Lesions that were not resectable by conventional EMR were included in our study; in addition, LST-NGPDs (which have a high frequency of submucosal invasion, even as small tumors [8]) were also included. Consequently, the impact of tumor size on the occurrence of metachronous adenomas was reduced in our study compared to previous reports.

The NPS showed that the first post-polypectomy surveillance could be deferred for 3 years [2], and guidelines published by a gastrointestinal consortium in 1997 recommended that the first follow-up surveillance should be performed 3 years after polypectomy for most patients. In 2003, these guidelines were updated, and a stratification at index colonoscopy into low risk and high risk for metachronous adenomas was suggested [22].

The Japan Polyp Study also showed that the first post-polypectomy surveillance could be deferred for 3 years in patients who have undergone complete colonoscopies for the control of colorectal cancer twice, with removal of all detected polyps [23, 24]. In 2014, the JGES guidelines for colorectal ESD/EMR were published [16]. These guidelines state that no optimal examination interval for the detection of metachronous colorectal tumors has been established, but that a colonoscopy should be carried out within 3 years after endoscopic treatment.

On the other hand, Oka et al. reported that in their multicenter retrospective cohort study, 51% of the metachronous index lesions (defined as large adenomatous polyps ≥ 10 mm, intramucosal cancer, and invasive cancer) were newly detected within 3 years, and that metachronous submucosal invasive cancer was detected in seven cases in the first 12 months [20], denoting that a certain number of these index lesions were missed at the index colonoscopy.

In our study, the median follow-up period of the patients in whom metachronous adenomas were detected was 20 months (range 12-70 months.). Pathologically, most of the metachronous lesions were adenomas, with some intramucosal adenocarcinomas as the most aggressive type. As mentioned above, local recurrence

was detected in only 1 patient (0.99%). Curative endoscopic resections were achieved for all metachronous adenomas and locally recurrent lesions. Based on these results, performing a follow-up colonoscopy at 20 months after colorectal ESD seems reasonable.

Most of the prior reports about colorectal ESD focused on short-term results, such as the rate of local recurrence [14,15,17]. However, the rate of local recurrence of ESD cases has been very low in comparison to that of EMR or EPMR cases, and the metachronous recurrence rate has been relatively higher than the local recurrence rate. Accordingly, more attention should be given to metachronous adenomas rather than local recurrences when performing follow-up colonoscopies for patients after ESD.

This study has several limitations. It was a retrospective, single-institution analysis. Data about the patients' lifestyle and comorbidities as hypertension, diabetes mellitus and hyperlipidemia were not collected. In addition, submucosal invasive cancers requiring surgical intervention were not included.

In conclusion, with regard to the tumor recurrence risk after colorectal ESD, more attention should be given to metachronous adenomas occurring at other sites rather than local recurrences. Colonoscopic surveillance after colorectal ESD should be performed within 20 months after colorectal ESD, and more attention should be given to patients in whom the number of synchronous adenomas is 3 or more. Prospective randomized studies enrolling a larger number of cases should be conducted to test our present findings.

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