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Original

Accuracy of the Differential Diagnosis of Colorectal Serrated Polyps Using a Conventional Endoscope : A Prospective Study

Fumito YANAGISAWA[1)], Yutaro KUBOTA*[1)], Kazuo KONISHI[1)], Atsushi KATAGIRI[1)], Takashi MURAMOTO[1)], Toshihiro KIHARA[1)], Yuichiro YANO[1)], Masayuki TOJO[1)], Kensuke SHINMURA[1)], Kenichi KONDA[1)], Teppei TAGAWA[1)], Kentaro IIJIMA[1)], Toshihiko GOCHO[1)], Fuyuhiko YAMAMURA[2)], Toshiko YAMOCHI[3)], Masafumi TAKIMOTO[3)] and Hitoshi YOSHIDA[1)]

Abstract : Some serrated polyps (SPs) are thought to be precursors of colorectal cancers. However, the endoscopic diagnosis of sessile serrated adenoma / polyps (SSA / Ps) has been reported to have a low accuracy. The aim of this study was to clarify the ability to distinguish between SSA / Ps and non-SSA / Ps by using mucosal crypt patterns combined with endoscopic findings. In total, 457 consecutive patients who underwent endoscopic resection for colorectal polyps at the Showa University Hospital from April 2007 to December 2010 were prospectively enrolled in this study. Before treatment, mucosal crypt patterns of the lesions were classified into three types (hyperplastic, adenomatous, and mixed pattern). When the lesion had an adenomatous pattern with a cerebriform appearance or mixed pattern, it was diagnosed as a traditional serrated adenoma (TSA). If the lesion had a hyperplastic pattern and was sized 6 mm or more in the proximal colon or 10 mm or more in the distal colon, it was diagnosed as an SSA / P by the endoscopist. We analyzed 1,151 colorectal polyps in this study. Endoscopically, 117 polyps were diagnosed as SSA / Ps or hyperplastic polyps (HPs), 998 polyps were conventional adenomas, and 36 polyps were TSAs, with diagnostic accuracies of 94.7%, 94.1%, and 97.3%, respectively. Of the 117 polyps diagnosed as SSA / Ps or HPs, 59 lesions met our criteria for SSA / Ps, with a diagnostic accuracy of 70.9%. Our results indicate that the combination of mucosal crypt patterns and endoscopic findings may be useful for differentiating between SPs and non-SPs. However, additional specific endoscopic features of SSA / Ps are still needed.

Key words : sessile serrated adenoma / polyp, traditional serrated adenoma, hyperplastic polyp, conventional endoscope

Introduction

Sessile serrated adenoma / polyps (SSA / Ps) are thought to be the precursors of colorectal

[1)] *Department of Medicine, Division of Gastroenterology, Showa University School of Medicine,* 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
[2)] *Endoscopic Center, Showa University Hospital.*
[3)] *Department of Pathology, Showa University School of Medicine.*
* To whom corresponding should be addressed.

cancers (CRCs). According to the World Health Organization criteria, serrated polyps (SPs) are classified as hyperplastic polyps (HPs), SSA / Ps with or without cytological dysplasia, and traditional serrated adenomas (TSAs)[1]. Although HPs have been considered as non-neoplastic lesions without malignant potential for a long time, recent studies have demonstrated that some HPs may progress to CRCs through SSA / Ps or TSAs[2-4]. These pathways are called serrated pathways, and they involve molecular alterations such as *BRAF* and *KRAS* mutations, CpG island methylator phenotypes, and microsatellite instability[5, 6]. It is generally believed that a serrated pathway may be involved in approximately 30% of CRCs[7].

Endoscopically, SSA / Ps are often large, proximal lesions with abundant mucin secretion. However, because SSA / Ps and HPs have a similar macroscopic type (sessile or flat) and mucosal crypt pattern (type II pit pattern), several studies have reported that current endoscopic techniques have a low diagnostic accuracy for differentiating SSA / Ps from HPs[8, 9]. However, the mucosal crypt pattern of TSAs has been classified into three types, i.e., hyperplastic, cerebriform, and combined pattern[10]. Although the endoscopic diagnosis of the latter two types of TSAs is relatively easy, it is difficult to distinguish the hyperplastic type of TSAs from SSA / Ps and HPs.

Recently, it has been proposed that novel endoscopic features, such as type II open-shape (type II-O) pit pattern[11] or varicose microvascular vessels (VMVs)[12], can improve the accuracy of making a differential diagnosis between SSA / Ps and HPs. The diagnostic accuracies of a type II-O pit pattern and VMVs have been reported as 72% and 73%, respectively. Although this diagnostic performance is better than in previous reports, identifying these endoscopic features requires magnifying endoscopy. The usefulness of magnifying endoscopy is widely recognized in Japan, however it still remains controversial in western countries[13, 14]. Therefore, it is important to differentiate SSA / Ps from HPs using conventional endoscopy.

The aim of this study was to clarify the ability to distinguish between SSA / Ps and non-SSA / Ps by mucosal crypt patterns combined with endoscopic findings using a conventional endoscope.

Methods

Patients

A total of 457 consecutive, unselected patients who underwent endoscopic resection for colorectal polyps at the Showa University Hospital from April 2007 to December 2010 were prospectively enrolled in this study. Patients with familial adenomatous polyposis, hereditary non-polyposis CRC, inflammatory bowel disease, poor bowel preparation, or incomplete colonoscopy were excluded from the study.

Endoscopic examination

All patients prepared for the procedure by ingesting 2 l of a polyethylene glycol-electrolyte solution. Scopolamine butylbromide (20 mg) and midazolam (2 mg) were administered intravenously to patients who had no contraindications to these agents. A single expert endoscopist (K.K.) performed all examinations using a high-resolution video colonoscope (CF-260AI or

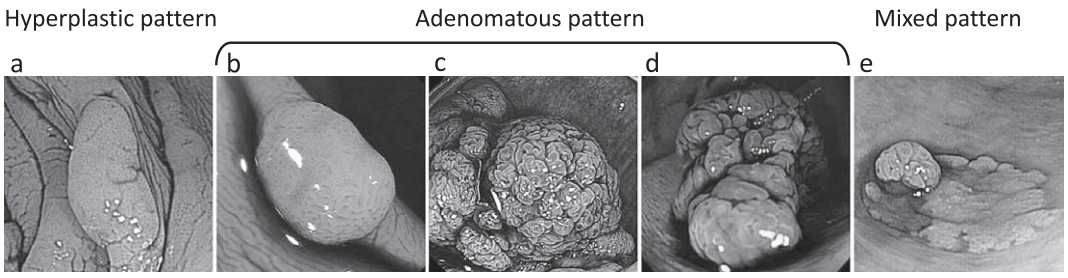

Fig. 1. Modified Kudo classification according to mucosal crypt patterns: (a) hyperplastic pattern, type II (stellar or papillary pits); (b) adenomatous pattern, type IIIL (tubular pits); (c) adenomatous pattern, type IV (branch-like or gyrus-like pits); (d) adenomatous pattern with a cerebriform (pinecone-like) appearance; and (e) mixed pattern, a combination of the two patterns (e.g., hyperplastic and adenomatous patterns)

PCF-240; Olympus Optical, Tokyo, Japan). When a lesion was seen, 5 to 10 ml of 0.2% indigo carmine dye was sprayed directly onto the lesion's surface before treatment. The size, location, and macroscopic appearance of the lesion, and the mucosal crypt pattern on the surface of the lesion were recorded. The mucosal crypt pattern of each lesion was determined according to the modified classification of Kudo *et al*[15]. Briefly, the mucosal crypt patterns were classified into three types: hyperplastic pattern, type II (stellar or papillary pits); adenomatous pattern, type III or type IV (tubular or branch-like or gyrus-like pits); and mixed pattern (combination of the hyperplastic and adenomatous patterns) (Fig. 1a-e)[3]. When the lesion had a hyperplastic pattern, it was diagnosed as an SSA/P or HP. If the lesion had an adenomatous pattern with a cerebriform (pinecone-like) appearance or mixed pattern, it was diagnosed as a TSA. Any remaining lesion that had an adenomatous pattern was diagnosed as a conventional adenoma (CAD). Furthermore, if the lesion had a hyperplastic pattern and was sized 6 mm or more in the proximal colon (cecum, ascending, and transverse colon) or sized 10 mm or more in the distal colon (descending and sigmoid colon, and rectum), it was diagnosed as an SSA/P by the endoscopist (Fig. 2).

All detected lesions with an adenomatous pattern or mixed pattern were resected endoscopically. However, we used the following criteria to determine whether lesions that exhibited a hyperplastic pattern on their surface should be removed endoscopically: (a) HPs with a typical location in the rectosigmoid area, (b) small size (usually 5 mm or less in diameter), and (c) symmetrical and uniform shape. If the lesion fulfilled the aforementioned three criteria, the endoscopist did not resect it. Other lesions with a hyperplastic pattern were resected.

Histological diagnosis

All resected specimens were reviewed by a senior pathologist (T.Y.) blinded to the endoscopic findings. Histological diagnoses of TSA and SSA/P were based on the definitions established by Longacre *et al*[16] and Torlakovic *et al*[17], respectively. Serrated lesions that exhibited more than two different histological components (e.g., HP or CAD) were defined as mixed serrated polyps (MSPs). MSPs and non-neoplastic polyps were excluded from this analysis.

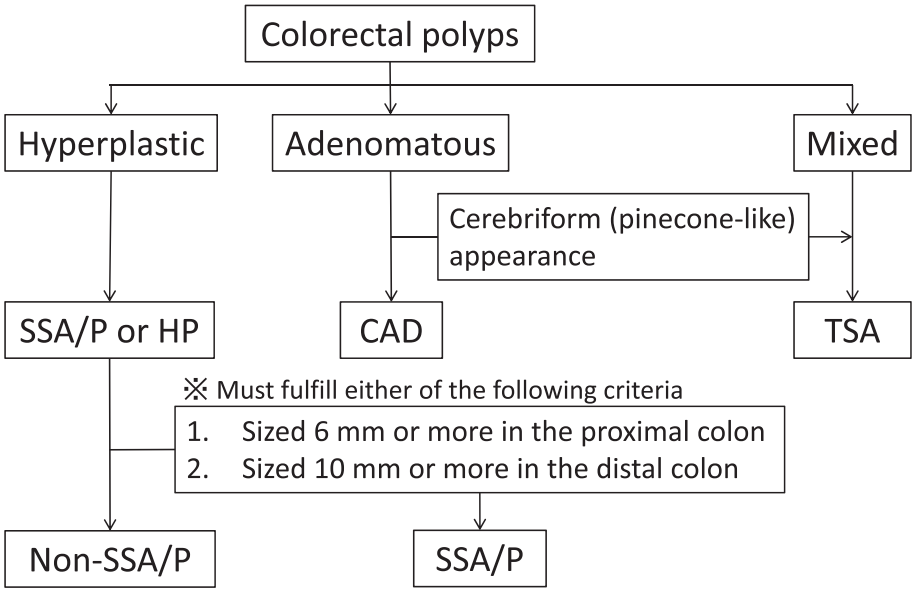

Fig. 2. Diagnostic flow chart
CAD, conventional adenoma (includes early cancer); TSA, traditional serrated adenoma; SSA / P, sessile serrated adenoma / polyp; HP, hyperplastic polyp.

Data and statistical analyses

Median values and ranges were calculated. Continuous variables (age and tumor size) were analyzed using the Wilcoxon test. Categorical variables were compared between tumor groups using the χ^2 or Fisher exact test when testing small samples. All tests were two-sided, and $P < 0.05$ was considered significant. In addition, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of our criteria for the differential diagnosis were calculated. All statistical analyses were performed using JMP, version 12 (SAS Institute, Cary, NC, USA).

Results

Clinicopathological features of the evaluated lesions

We resected 1,190 colorectal polyps in 457 patients in this study. Of the 1,190 polyps, 32 non-neoplastic polyps and 7 MSPs were excluded from this study. The remaining 1,151 polyps from 447 patients were finally evaluated. Clinicopathological features of the evaluated polyps are shown in Table 1. Of the 447 analyzed patients, 291 (65.1%) were men, and their median age was 67 years (range, 30–87 years). There were 617 polyps (53.6%) located in the proximal colon and 534 polyps (46.4%) located in the distal colon. Macroscopically, there were 926 (80.5%) protruded and 225 (19.5%) superficial lesions. The median lesion size was 7 mm (range, 2–60 mm). Histologically, there were 80 HPs (7.0%), 36 SSAPs (3.1%), 33 TSAs (2.9%), and 1,002 CADs (86.7%). CADs included 66 mucosal cancers and 13 submucosal cancers.

Table 1. Clinicopathological features of 1,151 polyps in 447 patients

Age, median (range), y	67 (30-87)
Sex, n	
male	291 (65.1%)
female	156 (34.9%)
Size, median (range), mm	7 (2-60)
Location, n	
proximal	617 (53.6%)
distal	534 (46.4%)
Macroscopic type, n	
protruded	926 (80.5%)
superficial	225 (19.5%)
Pathology, n	
hyperplastic polyp	80 (7.0%)
SSA / P	36 (3.1%)
TSA	33 (2.9%)
CAD (includes early cancer)	1,002 (86.7%)

SSA / P, sessile serrated adenoma / polyp ; TSA, traditional serrated adenoma ; CAD, conventional adenoma.

Differential diagnosis of SSA / P or HP, CAD, and TSA by the mucosal crypt pattern

The mucosal crypt patterns of 1,151 polyps were classified as hyperplastic pattern (117), adenomatous pattern (1,019), and mixed pattern (15). Of the 1,019 polyps with an adenomatous pattern, 21 had a cerebriform appearance. Finally, 117 polyps were diagnosed as SSA / Ps or HPs, 998 polyps as CADs, and 36 polyps as TSAs (Fig. 2).

The diagnostic performance of the mucosal crypt pattern is shown in Table 2. The diagnostic accuracies of SSA / Ps or HPs, CADs, and TSAs were 94.7%, 94.1%, and 97.3%, respectively. Although almost all the other diagnostic performances were also good, the sensitivity and PPV of TSAs were insufficient (57.6% and 52.8%, respectively).

Differential diagnosis of SSA / Ps and non-SSA / Ps

Of the 117 polyps with a hyperplastic pattern, 59 polyps (50.4%) met our criteria for a SSA / P (Fig. 3). The accuracy, sensitivity, specificity, PPV, and NPV of an SSA / P were 70.9%, 85.7%, 64.6%, 50.8%, and 91.4%, respectively (Table 3). Table 4 shows the clinicopathological features of the 35 SSA / Ps and 82 non-SSA / Ps. The non-SSA / Ps were histologically HPs (51), CADs (19), and TSAs (12). SSA / Ps were significantly larger than non-SSA / Ps (median size 10 vs. 6 mm ; $P < 0.01$). Macroscopically, superficial lesions were more frequently found in patients with SSA / Ps than in those with HPs (71.4% vs. 45.1% ; $P = 0.01$). Compared with non-SSA / Ps, SSA / Ps tended to be found more frequently in the proximal than distal colon (71.4% vs. 53.7% ; $P = 0.07$).

Table 2. Differential diagnosis of an SSA / P or HP, CAD, and TSA

		Pathological diagnosis				Diagnostic performance				
		SSA/P or HP	CAD	TSA	Total	Sensitivity	Specificity	PPV	NPV	Accuracy
Endoscopic diagnosis	SSA/P or HP	86	19	12	117	74.1%	97.0%	73.5%	97.1%	94.7%
	CAD	30	966	2	998	96.4%	78.5%	96.8%	76.5%	94.1%
	TSA	0	17	19	36	57.6%	98.5%	52.8%	98.8%	97.3%
	Total	116	1,002	33	1,156					

SSA / P, sessile serrated adenoma / polyp ; HP, hyperplastic polyp ; CAD, conventional adenoma (includes early cancer) ; TSA, traditional serrated adenoma ; PPV, positive predictive value ; NPV, negative predictive value.

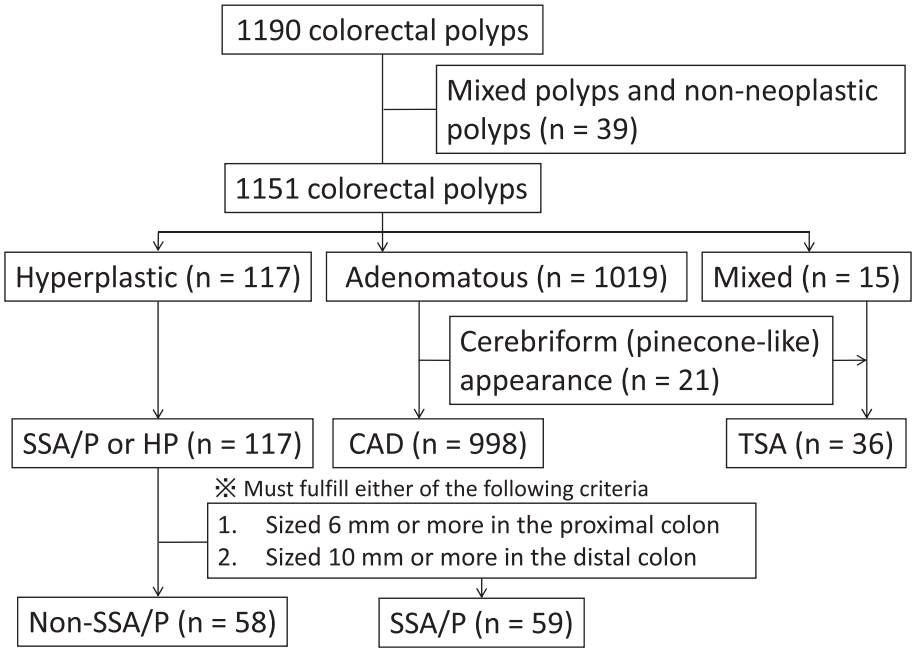

Fig. 3. Study algorithm
CAD, conventional adenoma (includes early cancer) ; TSA, traditional serrated adenoma ; SSA / P, sessile serrated adenoma / polyp ; HP, hyperplastic polyp.

Table 3. Differential diagnosis between an SSA / P and non-SSA / P

		Pathological diagnosis			Diagnostic performance				
		SSA/P	Non-SSA/P	Total	Sensitivity	Specificity	PPV	NPV	Accuracy
Endoscopic diagnosis	SSA/P	30	29	59	85.7%	64.6%	50.8%	91.4%	70.9%
	Non-SSA/P	5	53	58					
	Total	35	82	117					

SSA / P, sessile serrated adenoma / polyp ; PPV, positive predictive value ; NPV, negative predictive value.

Table 4. Clinicopathological features of lesions with a hyperplastic pattern

	SSA / P n = 35	Non-SSA / P n = 82	*P*-value
Age, median (range), y	64 (32-75)	64 (36-83)	0.18
Sex, n			
male	22 (62.9%)	67 (81.7%)	0.04
female	13 (37.1%)	15 (18.3%)	
Size, median (range), mm	10 (6-25)	6 (2-18)	< 0.01
Location, n			
proximal	25 (71.4%)	44 (53.7%)	0.07
distal	10 (28.6%)	38 (46.3%)	
Macroscopic type, n			
protruded	10 (28.6%)	45 (54.9%)	0.01
superficial	25 (71.4%)	37 (45.1%)	

SSA / P, sessile serrated adenoma / polyp.

Discussion

Saiki *et al* reported that the frequencies of HPs, SSA / Ps, and TSAs in a Japanese population were 5.3%, 3.0%, and 0.6% of all resected colorectal polyps in a retrospective analysis[18]. Compared with their data, the frequency of TSAs in our study was slightly higher, but the frequencies of HPs and SSA / Ps were similar. We speculate that the different frequencies of TSAs are due to the study design and endoscopist, because our study had a prospective design and a single expert endoscopist performed all procedures.

Using the mucosal crypt pattern to differentiate between SSA / Ps or HPs, CADs, and TSAs, gave diagnostic accuracies of more than 90%; however, the sensitivity and PPV of TSAs were insufficient (Table 2). There are two possible reasons why these values were insufficient. First, among the 36 TSAs diagnosed using the mucosal crypt pattern, 17 (47.2%) were pathologically diagnosed as CADs. This result indicates that it is difficult to differentiate TSAs from CADs based on the mucosal crypt pattern. However, this does not affect the decision to perform endoscopic resection, considering their malignant potential for colon carcinogenesis. Second, of the 117 lesions that exhibited a hyperplastic pattern, there were 12 TSAs (10.3%). This finding suggests that the hyperplastic type of TSA is difficult to diagnose. In particular, of these TSAs with a hyperplastic crypt pattern, 6 lesions were less than 10 mm in diameter and had a superficial appearance. These lesions may be the cause of interval cancer; therefore, the diagnosis of these hyperplastic type TSAs needs to be investigated further.

We attempted to diagnose SSA / Ps in lesions with a hyperplastic pattern. The criteria that combine the tumor location and size are simple. The accuracy, sensitivity, and NPV of our criteria were similar to those using a type II-O pit pattern (11) or VMVs (12), but the specificity and PPV were insufficient. Although 59 polyps fulfilled our criteria for SSA / Ps, 29 polyps

were diagnosed as non-SSA / Ps. Our results suggest that it is difficult to detect the specific pathological features of SSA / Ps using a conventional endoscope, since we need to assess the findings of crypt distortion in the crypt base. When we compared SSA / Ps to non-SSA / Ps with a hyperplastic pattern, SSA / Ps were more often located in the proximal colon, had a superficial appearance, and were larger than non-SSA / Ps. These results are similar to those reported previously[4, 19–22].

In summary, our results indicate that the combination of mucosal crypt patterns and the endoscopic appearance may be useful for differentiating colorectal polyps. However, regarding the clinical application of the endoscopic findings, additional endoscopic characteristics that are more specific for SSA / Ps will need to be identified in the future.

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Competing interests

The authors declare no competing interests.

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