CME/SAM

Traditional Serrated Adenoma of the Colorectum

Clinicopathologic Implications and Endoscopic Findings of the Precursor Lesions

Mi-Jung Kim, MD, PhD,[1] Eun-Jung Lee, MD,[2] Jung-Pil Suh, MD,[3] Sung-Min Chun, PhD,[4] Se-Jin Jang, MD, PhD,[4] Do Sun Kim, MD, PhD,[2] Doo Han Lee, MD, PhD,[2] Suk Hee Lee, MD, PhD,[1] and Eui Gon Youk, MD, PhD[2]

From the Departments of [1]Pathology, [2]Surgery, and [3]Internal Medicine, Daehang Hospital, Seoul, Korea, and [4]Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

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ABSTRACT

Objectives: *To investigate the clinicopathologic and endoscopic features of precursor lesions associated with traditional serrated adenomas (TSAs).*

Methods: *Mutation studies for* BRAF, KRAS, PIK3CA, *and* EGFR *and immunohistochemical staining for Ki-67 were performed on 107 TSAs from 104 patients.*

Results: *Nondysplastic hyperplastic polyp (HP) or sessile serrated adenoma/polyp (SSA/P) precursor lesions were found in 56 (52.3%) TSAs, among which 32 (57.1%) cases showed a flat-elevated lesion with a type II pit pattern during endoscopy. TSAs with an SSA/P precursor lesion were usually found in the proximal colon, while TSAs with an HP or with no precursor lesion were mainly located in the distal colon and rectum (*$P < .001$*). TSAs with a precursor lesion showed a lower frequency of conventional epithelial dysplasia and* KRAS *mutation as well as a higher frequency of* BRAF *mutation compared with those with no precursor lesion (*$P = .002$, $P < .001$, *and* $P < .001$, *respectively).*

Conclusions: *A significant proportion of HP or SSA/P precursor lesions accompanied by TSAs can be detected by endoscopy based on both their flat-elevated growth and type II pit patterns. The heterogeneity of TSAs in terms of clinicopathologic and molecular features correlated with the status or type of precursor lesions.*

Upon completion of this activity you will be able to:
- describe mucosal lesions commonly associated with traditional serrated adenomas (TSAs).
- describe endoscopic findings of nondysplastic hyperplastic polyp (HP) or sessile serrated adenoma/polyp (SSA/P) lesions accompanied with TSAs.
- discuss the clinicopathologic significance of nondysplastic HP or SSA/P precursor lesions in terms of the heterogeneity of TSAs.

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Traditional serrated adenoma (TSA) is a distinct subtype of serrated neoplasia characterized by an overall protuberant exophytic configuration, complex villous growth pattern, and peculiar columnar cells having abundant eosinophilic cytoplasm.[1-3] However, TSAs are heterogeneous in terms of their gross morphology and molecular features. The growth patterns of TSAs vary from flat elevated and sessile to pedunculated forms.[4] TSAs can show either *BRAF* or *KRAS* mutations, although the rate of mutation varies among previous studies.[5,6] In addition, some TSAs show histologic features of hyperplastic polyps (HPs) or sessile serrated adenoma/polyps (SSA/Ps) in addition to the typical area of TSAs.[6,7] Kim et al[6] have demonstrated a high prevalence of HPs or SSA/Ps associated with TSAs and have proposed the former lesions as nondysplastic precursor lesions by demonstrating the common molecular nature between both components.

The nondysplastic HP or SSA/P precursor lesions have been reported in approximately one-third of TSA samples.[5] However, the endoscopic features and clinicopathologic significance of precursor lesions accompanied by TSAs have rarely been described in large-scale studies despite the considerable rate of coexistence of the two lesions.[4,8] On the other hand, the mucosal pit patterns of TSA lesions are relatively well described.[9-11]

We performed this study to clarify the clinicopathologic significance and endoscopic features of precursor lesions accompanied by TSAs. We analyzed the results of Ki-67 immunostaining and mutation studies for *BRAF*, *KRAS*, *PIK3CA*, and *EGFR* to correlate the molecular profile with clinicopathologic findings.

Materials and Methods

Patients and Samples

Included in the present study are 107 TSAs obtained from 104 patients, all of which were retrieved from the Department of Pathology, Daehang Hospital, Seoul, Korea, between November 2011 and September 2012. The lesions were obtained by polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or transanal excision, depending on the judgment of the endoscopist (E.-J.L., J.-P.S., or E.G.Y.) during the procedure. Consultation or referral cases from other hospitals are not included in the study. Patients with familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer syndrome, or inflammatory bowel disease have been excluded. Tissue collection was approved by the institutional review board at Daehang Hospital.

Colonoscopic Evaluation

Colonoscopy was performed after standard bowel preparation. Total colonoscopies were carried out using a single-channel HD colonoscope (Olympus CF-H260AI; Olympus Optical, Tokyo, Japan). When a lesion was detected by colonoscopic examination, the surface mucus was washed away, and indigo carmine dye was spread over the lesion. The endoscopist (E.-J.L., J.-P.S., or E.G.Y.) examined the morphology of polyps for tumor size, anatomic location, gross appearance, pit pattern, and the presence of a mucous cap.

We retrospectively reviewed endoscopy images and reevaluated the mucosal pit pattern of each lesion according to Kudo's classification.[12] Briefly, type II means oval or stellar-like pits that are seen in HPs or SSA/Ps. Type III represents small tubular or roundish pits (III_S) or large tubular or roundish pits (III_L), while type IV means branch or gyrus-like crypts. Type III_L and type IV are patterns typical of conventional adenomas; a type IV pit pattern reflects the presence of a villous component. Type V, consisting of irregular (V_I) or nonstructural crypts (V_N), is characteristic of malignancy. We also evaluated if there are pinecone-like or fern-like patterns, which have been recently suggested to be characteristic of TSAs.[13,14] Laterally spreading tumor (LST) was defined as a flat lesion larger than 10 mm in diameter and extending both laterally and circumferentially rather than vertically.[15]

Histologic Evaluation

Histopathologic diagnosis of TSAs followed the criteria proposed by Torlakovic et al.[2,16] In brief, TSAs were characterized by a serrated architecture and at least a focal area with tall columnar cells having elongated nuclei and an abundant eosinophilic cytoplasm. We determined if there were features of conventional epithelial dysplasia such as extensive nuclear crowding, nuclear enlargement, loss of nuclear polarity, pseudostratification extending to the upper half of the neoplastic cell, and increased mitoses according to the architectural and cytologic criteria of the previously published studies **Image 1**.[17,18] SSA/Ps were defined by the abnormal architecture of the crypt bases, a so-called abnormal proliferation, such as the branching of crypts, dilation of the base of the crypts, and inverted T- or L-shaped crypts.[16] The diagnosis of HP was also made following the previously published histopathologic criteria.[16] The anatomic locations of polyps were recorded according to the endoscopic findings and grouped as proximal colon (up to the splenic flexure) vs distal colon and rectum combined.

Thirty cases of conventional adenoma (>1.0 cm in size) removed by the EMR or ESD procedure between September 2012 and October 2012, including eight cases with submucosal invasive adenocarcinoma (SIAC) and 20 HPs (>0.3 cm in size; 17 microvesicular and 3 goblet cell) removed by polypectomy or the EMR procedure in the same period, were used to compare histopathologic and immunohistochemical features. They were also used as a control for the mutation study. None of the control cases were obtained from the patients with TSAs.

Patients were assessed for clinicopathologic features, including age and sex, the presence or type of synchronous or metachronous polyps on follow-up by reviewing the patients' medical records, endoscopy images, and pathology reports. The slides were stained with H&E, and immunohistochemical staining for Ki-67 was performed in all cases.

Immunohistochemical Staining of Ki-67

Immunohistochemistry was manually performed using formalin-fixed, paraffin-embedded (FFPE) blocks. Sections were cut into 3-μm sections, deparaffinized in xylene, and dehydrated in descending dilutions of ethanol.

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Immunohistochemical staining was carried out with mouse monoclonal anti–Ki-67 (mouse, clone 7B11, 1:100 dilution; Invitrogen, San Francisco, CA) after routine microwave antigen retrieval. Negative controls were performed by omitting the primary antibody. Slides were counterstained with Mayer hematoxylin.

DNA Extraction

A total of 107 TSA cases containing an adequate amount of tissue in the paraffin blocks were used for molecular studies. In brief, five sections of 10-μm-thick samples were used for genomic DNA extraction. Genomic DNA was extracted using the QIAamp DNA FFPE tissue kit (#56404; Qiagen, Hilden, Germany) according to the manufacturer's instructions. Among TSAs with precursor lesions or conventional epithelial dysplasia, three cases with nondysplastic SSA/Ps and four cases with conventional epithelial dysplasia were manually microdissected in each component because the two components were clearly demarcated from each other and the size of the lesions was large enough to get a sufficient amount of DNA. Microdissection was performed with great caution using the marked slide as a guide. A razor blade was used to scrape off the cells of interest into a 1.5-mL microcentrifuge tube.

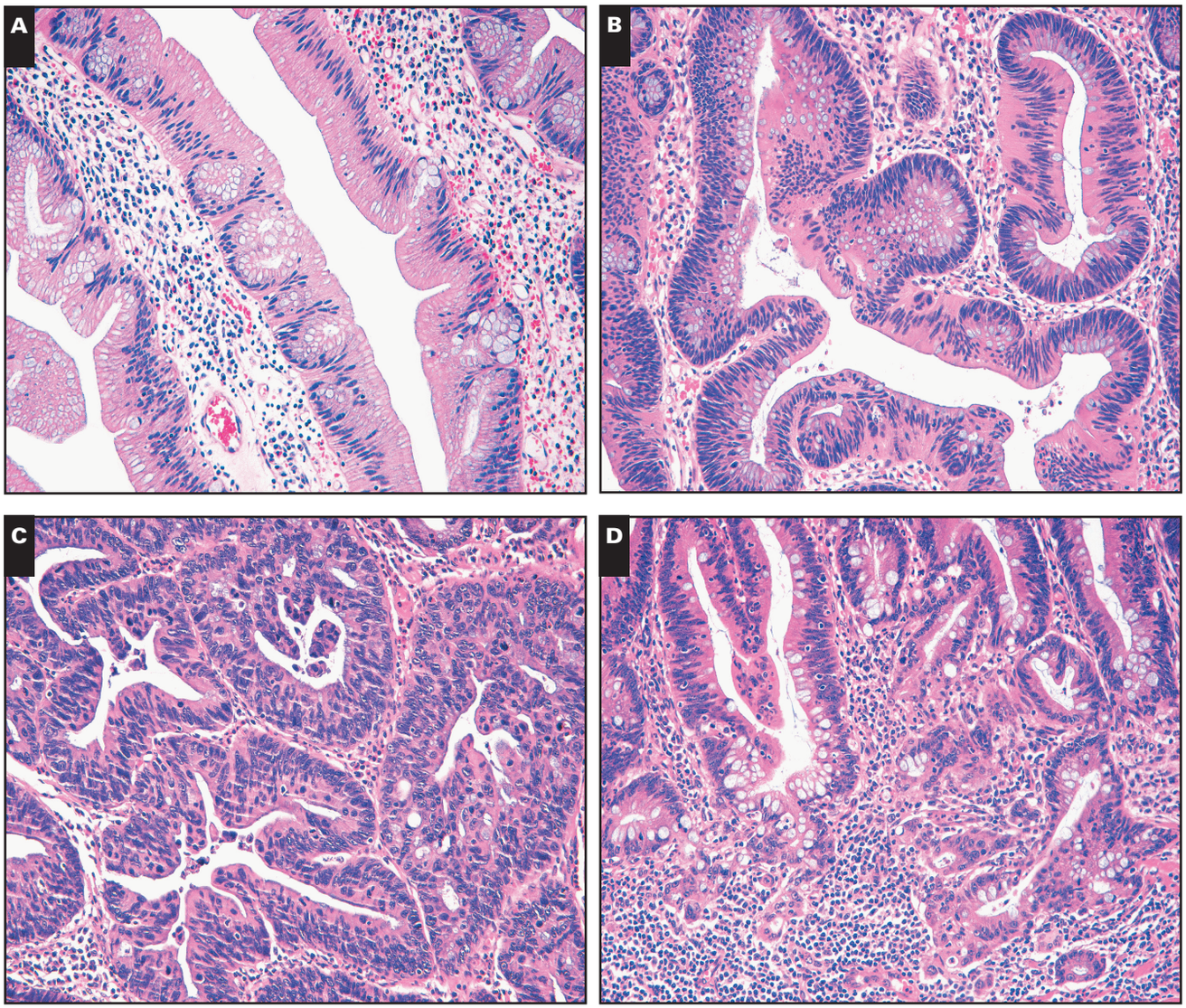

Image 1 Examples of conventional epithelial dysplasia in a traditional serrated adenoma (TSA). **A**, TSA without conventional epithelial dysplasia (H&E, ×200). **B**, TSA with conventional epithelial dysplasia showing nuclear crowding, nuclear enlargement, and pseudostratification of nuclei (H&E, ×200). **C**, TSA with extensive conventional epithelial dysplasia (intramucosal adenocarcinoma in a TSA) (H&E, ×200). **D**, TSA with submucosal invasive adenocarcinoma (H&E, ×200).

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Detection of Mutations for *KRAS*, *BRAF*, *PIK3CA*, and *EGFR* Genes Using MassArray Technology

Mutation detection was carried out using an ASAN Panel under the Sequenom MassArray technology platform with the iPLEX-Pro chemistry (Sequenom, San Diego, CA) following the manufacturer's instructions with minor modifications. In brief, specific assay pools (ASAN Panel) were designed using Assay Designer software in the MassArray Typer package (version 4.0; Sequenom). The list of genes and mutations assessed by Sequenom is presented in **Table 1**. After multiplex polymerase chain reaction (PCR) (95°C for 15 minutes; 45 cycles of incubations at 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 30 seconds; and 72°C for 3 minutes), PCR-amplified DNA was cleansed using a shrimp alkaline phosphatase mixture from the iPLEX-Prokit (cat. 10142-2; Sequenom), and primer was extended by the iPLEX chemistry, desalted using a cation exchange resin (Sequenom), and spotted onto SpectroCHIP II (Sequenom) matrix chips using a MassArray nanodispenser. Mass determination was done with the MassArray Analyzer Compact matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer. The MassArray Typer 4.0 software was used for data acquisition and analysis. Genotypes were called after cluster analysis using the default setting of a gaussian mixture model. Genotype calls were then further reviewed manually to undo any uncertain calls due to clustering artifact. Mutations for a subset of samples and targets were confirmed by Sanger sequencing **Figure 1**.

Direct DNA Sequencing for *KRAS* and *BRAF*

Direct DNA sequencing was performed to verify mutations in *KRAS* and *BRAF*. PCR amplification was performed using the primers in **Table 2**. The amplified DNA products were then purified using Montage centrifugal filters

Table 1
Detectable Mutations Using the MassArray Method (ASAN Panel)

Gene	Type	Exon	Mutation
EGFR	Point	Exon 18	E709A
			E709V
			E709G
			E709Q
			E709K
			V717G
			G719A
			G719C
			G719S
		Exon 19	L747S
			I759K
			D761Y
		Exon 20	S768I
			S768N
			S768T
			V769L
			R776H
			V786M
			T790M
		Exon 21	L858R
			A859T
			K860I
			L861Q
EGFR	InDel	Exon 18	del 709-710, ins D
		Exon 19	del 745-750, ins K
			del 747-753, ins S
			del 746-752, ins V
			del 747-751
			del 747-753
			del 746-750
			del 746-751, ins T
			del 747-750, ins P
			del 746-751, ins V
			del 746-751, ins A
			del 751-759, ins T
			del 751-759, ins S
			del 746-752, ins EQP
			del 752-759
			del 746-754, ins ISE
			del 753-759, ins A
			del 746-753, ins VS
			del 746-754, ins EG
			del 747-751, ins Q
			del 747-751, ins P
			del 745-752, ins KI
			del 747-752
			del 750-754
			del 753-761
			del 747-755, ins AT
			del 745-751, ins KT
			del 747-755, ins SKG
			del 749-759, ins DHD
			del 749-759, ins DTN
			del 747-750, ins KIP
			del 746-750, ins QP
EGFR	Duplication	Exon 19	dup 739-744
		Exon 20	dup 773H
KRAS	Point	Exon 2	G12A
			G12D
			G12V
			G12C
			G12R
			G12S
			G13D
			G13R
			Q61K
			Q61L
			Q61H
BRAF	Point	Exon 15	V600E
PIK3CA	Point	Exon 2	P18L
			K111E
			K111R
		Exon 10	P539R
			E542Q
			E542K
			E545A
			E545K
			Q546K
		Exon 21	T1025A
			D1029E
			D1029Y
			M1043V
			H1047L
			H1047R

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(Millipore, Bedford, MA). After purification, direct sequencing was carried out using an ABI PRISM 310 sequence analyzer (Applied Biosystems, Foster City, CA).

Statistical Analysis

Analysis of data was done using SPSS version 21.0 (SPSS, Chicago, IL). For comparing parametric distributions, a Student *t* test was used, and for frequency distributions, a χ^2 test or Fisher exact test was used. A *P* value less than .05 was considered statistically significant.

Table 2
Primer Sequences and Amplicon Size

Primer Names	Sequences	Amplicon Size, bp
BRAF V600E F	CATGAAGACCTCACAGTAAAAA	107
BRAF V600E R	CCACAAAATGGATCCAGACA	
KRAS codon 12/13 F	AGGCCTGCTGAAAATGACTG	115
KRAS codon 12/13 R	TTGGATCATATTCGTCCACAA	
KRAS codon 61 F	TGGAGAAACCTGTCTCTTGGA	98
KRAS codon 61 R	AAAGAAAGCCCTCCCCAGT	

bp, base pair.

Results

Patient Demographics and Tumor Characteristics

A total of 107 TSA cases were obtained from 104 patients. These patients included 55 men and 49 women with a mean age of 61.2 years. The mean age between patients with TSAs and control cases did not differ significantly (*P* = .793), while the male to female ratio and tumor location tended to be different in this study (*P* = .013 and *P* = .038, respectively). Most (74.8%) polyps occurred in the distal colon and rectum, while approximately one-fourth (25.2%) of cases were

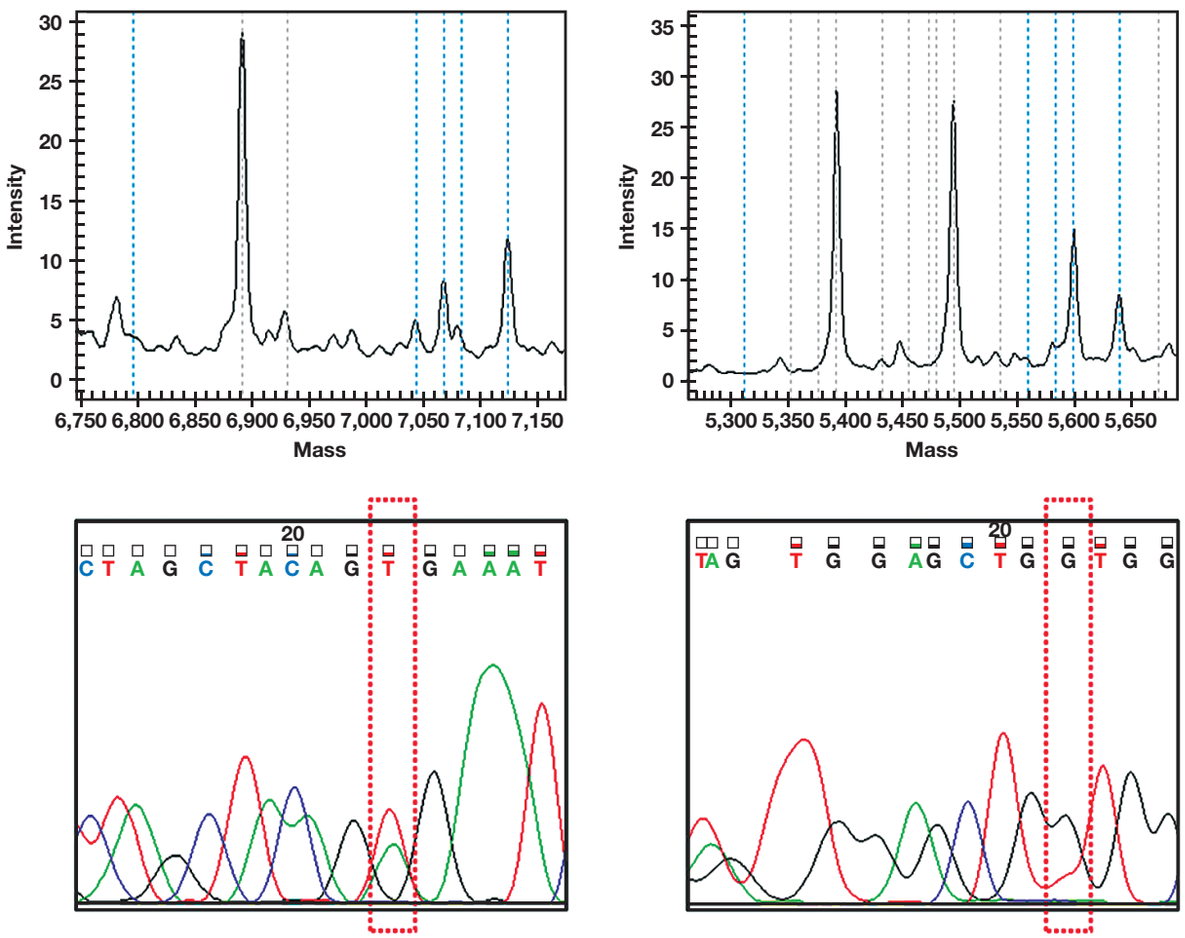

Figure 1 Mutational profiling using the Sequenom MassArray platform (Sequenom, San Diego, CA) identifies *BRAF* V600E (left column) and *KRAS* 12G>T (right column) mutations. Sanger sequencing was used to validate these findings. In each column, the mass spectrometry profile is shown demonstrating the allele called, with the corresponding Sanger sequencing trace below (red box).

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obtained from the proximal colon. The size of the polyps were variable, with a mean size of 1.3 cm (range, 0.3-5.2 cm). The mean size of TSAs was larger than that of HPs, but comparison with conventional adenomas or adenocarcinomas was not possible because of our selection criteria of control cases. The results are shown in **Table 3**.

The size of the tumor did not differ according to the tumor location ($P = .225$) but was significantly different according to the status of conventional epithelial dysplasia, which was noted in 23 (21.5%) TSA lesions. Tumors were larger in those with conventional epithelial dysplasia compared with those without (mean, 2.1 vs 1.1 cm; $P < .001$). Patients' mean age, sex, or tumor location did not differ according to the status of conventional epithelial dysplasia ($P = .235$, $P = 1.000$, and $P = .178$, respectively). The clinicopathologic features of the patients with and without conventional epithelial dysplasia are summarized in **Table 4**.

All TSA cases in this study contained a serrated architecture in at least 20% of its area as well as tall columnar cells having an abundant eosinophilic cytoplasm **Image 2D**, **Image 3E**, and **Image 4D**. The low-power picture of TSAs was somewhat variable depending on the growth pattern, the extent of peculiar tall columnar cells having an eosinophilic cytoplasm, the status of precursor lesions, and the amount of a stromal component. Ectopic crypt formation (ECF) was identified in most (79.4%) cases.

Fifty-six (52.3%) cases displayed nondysplastic HP (44 cases) or SSA/P (12 cases) precursor lesions **Image 2B**, **Image 2C**, **Image 3C**, and **Image 3D**. The precursor lesions, either HP or SSA/P, were noted not only in the

Table 3
Patient Demographics and Tumor Characteristics[a]

Parameters	TSA Group (n = 107)[b]	Control Group			*P* Value[c]
		HP (n = 20)	Conventional Adenoma (n = 22)	Adenocarcinoma (n = 8)	
Age, mean (range), y	61.2 (30-81)	60.5 (42-80)	58.9 (43-79)	62.4 (44-73)	.793
Sex, No.					.013
Female	49 (47.1)	3 (15.0)	14 (63.6)	3 (37.5)	
Male	55 (52.9)	17 (85.0)	8 (36.4)	5 (62.5)	
Polyp location					.038
Proximal	27 (25.2)	3 (15.0)	11 (50.0)	1 (12.5)	
Distal	80 (74.8)	17 (85.0)	11 (50.1)	7 (87.5)	
Gross type					.003
Pedunculated (Ip)	34 (31.8)	0	3 (13.6)	1 (12.5)	
Sessile (Is)	54 (50.5)	12 (60.0)	8 (36.4)	5 (62.5)	
Slightly elevated (IIa)	19 (17.8)	8 (40.0)	11 (50.0)	2 (25.0)	
Pit pattern[d]					<.001
II	3 (3.0)	20 (100.0)	1 (4.5)	0	
III_L	15 (14.9)	0	15 (68.2)	0	
IV, pinecone-like or fern-like	68 (67.3)	0	0	0	
V	0	0	0	6 (75.0)	
Mixed pattern					
II + III_L	0	0	2 (9.1)	0	
II + IV	0	0	1 (4.5)	0	
IV + III_L	13 (12.9)	0	2 (9.1)	0	
IV + V	1 (1.0)	0	0	0	
III_L + V	0	0	1 (4.5)	1 (12.5)	
III_L + IV + V	1 (1.0)	0	0	1 (12.5)	
Mean polyp size, cm	1.3	0.5	2.1	2.0	NA
Nondysplastic precursor lesion					NA
Present	56 (52.3)	NA	NA	NA	
Absent	51 (47.7)	NA	NA	NA	
Procedure					<.001
Polypectomy	37 (34.6)	19 (95.0)	0	0	
EMR	57 (53.3)	1 (5.0)	12 (54.5)	1 (12.5)	
ESD	12 (11.2)	0	10 (45.5)	7 (87.5)	
Transanal excision	1 (0.9)	0	0	0	
Mutation results					<.001
BRAF positive	59 (55.1)	10 (50.0)	0	0	
KRAS positive	36 (33.6)	4 (20.0)[e]	12 (54.5)	2 (25.0)	
Both negative	12 (11.2)	6 (30.0)	10 (45.5)	6 (75.0)	

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HP, hyperplastic polyp; NA, not applicable; TSA, traditional serrated adenoma.
[a] Values are presented as number (%) unless otherwise indicated.
[b] Total of 107 TSAs from 104 patients.
[c] *P* value calculated with *t* test for continuous variables and χ^2 for categorical variables.
[d] Pit pattern analysis of main TSA lesions using 101 cases.
[e] Three cases from goblet cell HP and one case from microvesicular HP.

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periphery or stalk of TSAs but also as intimately admixed forms with a typical TSA component. In 19 (17.8%) cases of TSAs, tubular adenoma (TA)–like lesions were identified **Image 4C**. The clinicopathologic features of TSAs did significantly differ according to the status of precursor lesions. In contrast to the preferential proximal location of TSAs with an SSA/P precursor, TSAs with an HP or with no precursor lesion were mainly located in the distal colon or rectum ($P < .001$). TSAs with a precursor lesion showed a lower frequency of conventional epithelial dysplasia compared with those with no precursor lesion ($P = .002$). The clinicopathologic features of TSAs according to the status of precursor conditions are summarized in **Table 5**.

Sixty-four (59.8%) and eight (7.5%) cases were accompanied by synchronous conventional adenomas and SSA/Ps, respectively. Three cases and one case were associated with synchronous and metachronous cancers, respectively.

Endoscopic Findings

Fifty-four (50.5%) cases of TSAs were sessile, while approximately one-third (31.8%) showed a pedunculated configuration. The remaining (17.8%) polyps were of a slightly elevated type. Eleven (10.3%) cases corresponded to an LST. Forty-six (43.0%) of the 107 TSAs were accompanied by a flat-elevated type II pit pattern lesion **Image 2A**, **Image 3A**, **Image 3B**, **Image 4A**, and **Image 4B**. Among 107 TSA cases, we determined the pit patterns of 101 main TSA lesions except for six cases that displayed indeterminate pit patterns. Sometimes, a type IV pit pattern coexisted with a fern-like appearance. The main TSA lesions most frequently showed a type IV pit pattern and/or a pinecone-like or fern-like appearance, contrary to conventional adenomas in which a type III_L pit pattern was most frequent. Three cases of conventional adenoma displayed a type IV pit pattern (admixed with type II or III_L pits) without a fern-like or pinecone-like appearance. There was a significant difference in pit patterns between TSA lesions and conventional adenomas ($P < .001$). Two TSA lesions with a type IV pit pattern (including one case also admixed with a type III_L pit pattern) were admixed with a type V pit pattern. As expected, all HPs showed a type II pit pattern. In the case of conventional adenomas with submucosal invasion, all showed a type V pit pattern as a basic architecture. Pit patterns of the TSA lesions and control groups are summarized in Table 3.

Comparison of Endoscopic Features With Clinicopathologic Findings

Of 46 (43.0%) TSA cases with flat-elevated lesions showing a type II pit pattern, 32 (69.6%) displayed histologically identifiable precursor lesions, and the remaining 10 (21.3%) cases were TA-like lesions accompanied by TSA lesions (Image 4C), as shown in **Table 6**. The precursor lesions were either HPs (22 cases) or SSA/Ps (10 cases) (Image 2B, Image 2C, and Image 3D). Four TSA cases with a flat-elevated lesion showing a type II pit pattern did not show any histologic evidence of either a precursor lesion or a TA-like component. With the exclusion of the above-mentioned four TSA cases and 24 TSA cases accompanied by HP or SSA/P precursor lesions without flat-elevated lesions showing a type II pit pattern, 79 (73.8%) cases showed a correlation between endoscopy images and histologic findings (Table 6).

The pits of the TA-like lesions accompanied by TSA lesions were similar to those of nondysplastic HP or SSA/P precursor lesions but tended to be dense and looked more

Table 4
Clinicopathologic Characteristics of TSAs With and Without Conventional Epithelial Dysplasia[a]

Parameters	TSA Group (n = 107)[b] Conventional Dysplasia (+) (n = 23)	Conventional Dysplasia (–) (n = 84)[c]	*P* Value[d]
Age, mean (range), y	58.8 (30-77)	61.8 (34-81)	.235
Sex			1.000
Female	11 (47.8)	38 (46.9)	
Male	12 (52.2)	43 (53.1)	
Tumor location			.178
Proximal	3 (13.0)	24 (28.6)	
Distal	20 (87.0)	60 (71.4)	
Gross type			.792
Pedunculated (Ip)	8 (34.8)	26 (31.0)	
Sessile (Is)	12 (52.2)	42 (50.0)	
Slightly elevated (IIa)	3 (13.0)	16 (19.0)	
Pit pattern[e]			.091
II	1 (4.5)	2 (2.5)	
III_L	4 (18.2)	11 (13.9)	
IV, pinecone-like, or fern-like	11 (50.0)	57 (72.2)	
V	0	0	
Mixed pattern			
IV + III_L	4 (18.2)	9 (11.4)	
IV + V	1 (4.5)	0	
III_L + IV + V	1 (4.5)	0	
Mean tumor size, cm	2.1	1.1	<.001
Nondysplastic precursor lesion			.002
Present	5 (21.7)	51 (60.7)	
Absent	18 (78.3)	33 (39.3)	
Procedure			.009
Polypectomy	3 (13.0)	34 (40.5)	
EMR	13 (56.5)	44 (52.4)	
ESD	7 (30.4)	5 (6.0)	
Transanal excision	0	1 (1.2)	
Mutation results			.438
BRAF positive	10 (43.5)	49 (58.3)	
KRAS positive	10 (43.5)	26 (31.0)	
Both negative	3 (13.0)	9 (10.7)	

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TSA, traditional serrated adenoma.
[a] Values are presented as number (%) unless otherwise indicated.
[b] Total of 107 TSAs from 104 patients.
[c] Total of 84 TSAs from 81 patients.
[d] *P* value calculated with *t* test for continuous variables and χ^2 for categorical variables.
[e] Pit pattern analysis of main TSA lesions using 101 cases (with conventional dysplasia, 22 cases; without conventional dysplasia, 79 cases).

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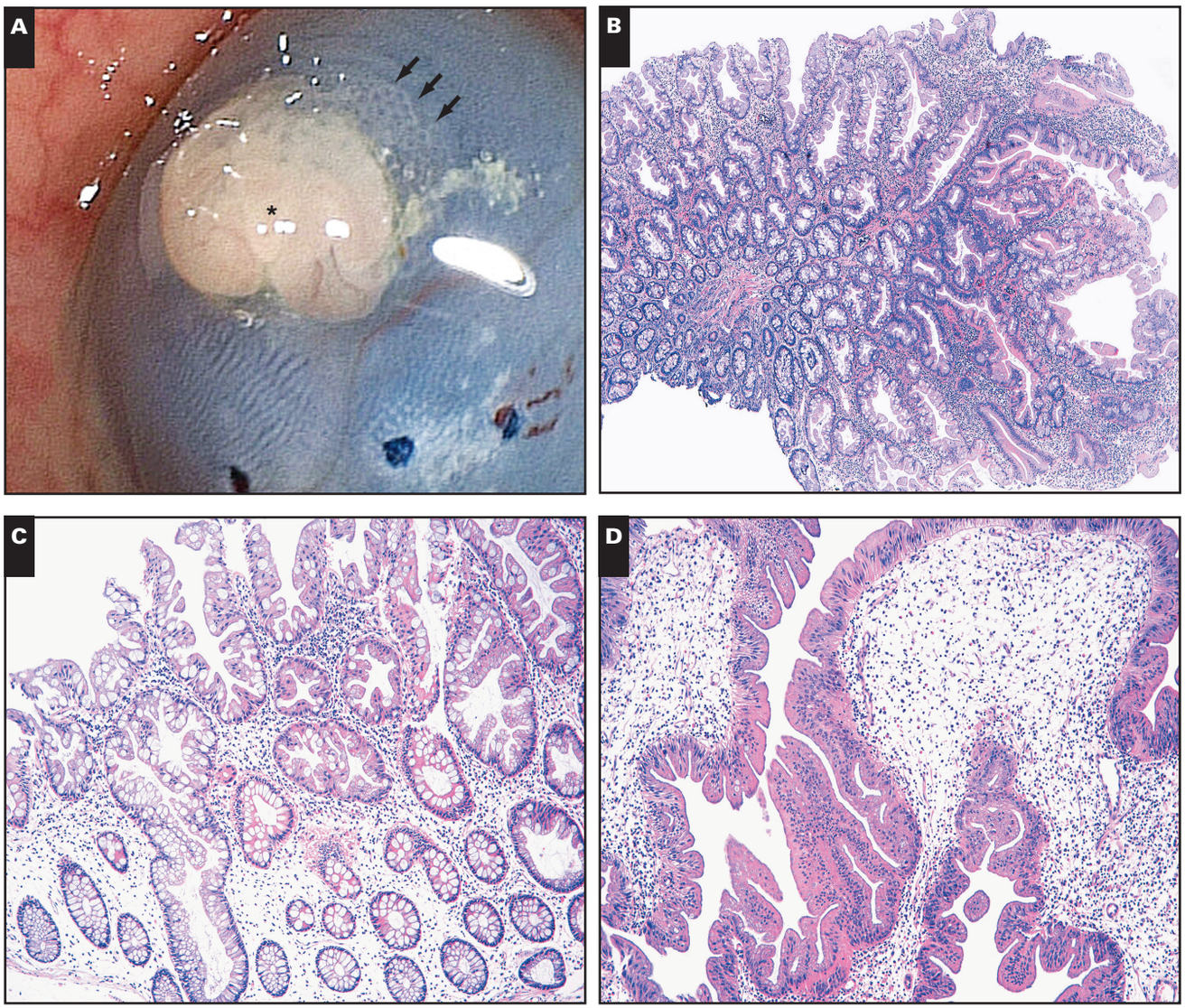

Image 2 The endoscopic appearance and histology of a traditional serrated adenoma (TSA) with a hyperplastic polyp (HP) precursor lesion. **A**, The endoscopic image shows a slightly elevated lesion with a type II pit pattern (arrows) bordering on the protruded TSA lesion (*). **B**, The low-power view of the photomicrograph shows both a TSA (right half) and an HP (left half) (H&E, ×40). **C**, The histology of the slightly elevated lesion demonstrates an HP displaying serrated architecture in the upper half of the crypts (H&E, ×100). **D**, The protruded lesion shows histologic features of a TSA characterized by prominent serration and diffuse cytoplasmic eosinophilia (H&E, ×100).

elongated, suggesting both higher cellularity and the presence of larger tubular glands. The surface of the TA-like lesions appeared to be lobulated compared with the smooth surface of HP or SSA/P precursor lesions. Ten of 12 TSA lesions with an SSA/P precursor lesion showed an endoscopically identifiable flat-elevated lesion with a type II pit pattern. Among 10 cases, six showed a mucous cap and five cases displayed an LST pattern, reflecting the presence of an underlying SSA/P precursor lesion (Images 3A and 3B).

As previously mentioned, the main TSA lesions most frequently showed a type IV pit pattern and/or a pinecone-like or fern-like appearance. Two cases displayed an admixed type V pit pattern, corresponding to a submucosal invasive serrated carcinoma. There was no significant difference in pit patterns between TSA lesions with and without conventional epithelial dysplasia ($P = .091$). Pit patterns of the main TSA lesions are summarized in Tables 3 and 4.

Comparison of Mutation Results With Clinicopathologic Findings

BRAF mutation was observed in 59 (55.1%) TSA lesions, while *KRAS* mutations were identified in 36 (33.6%) cases.

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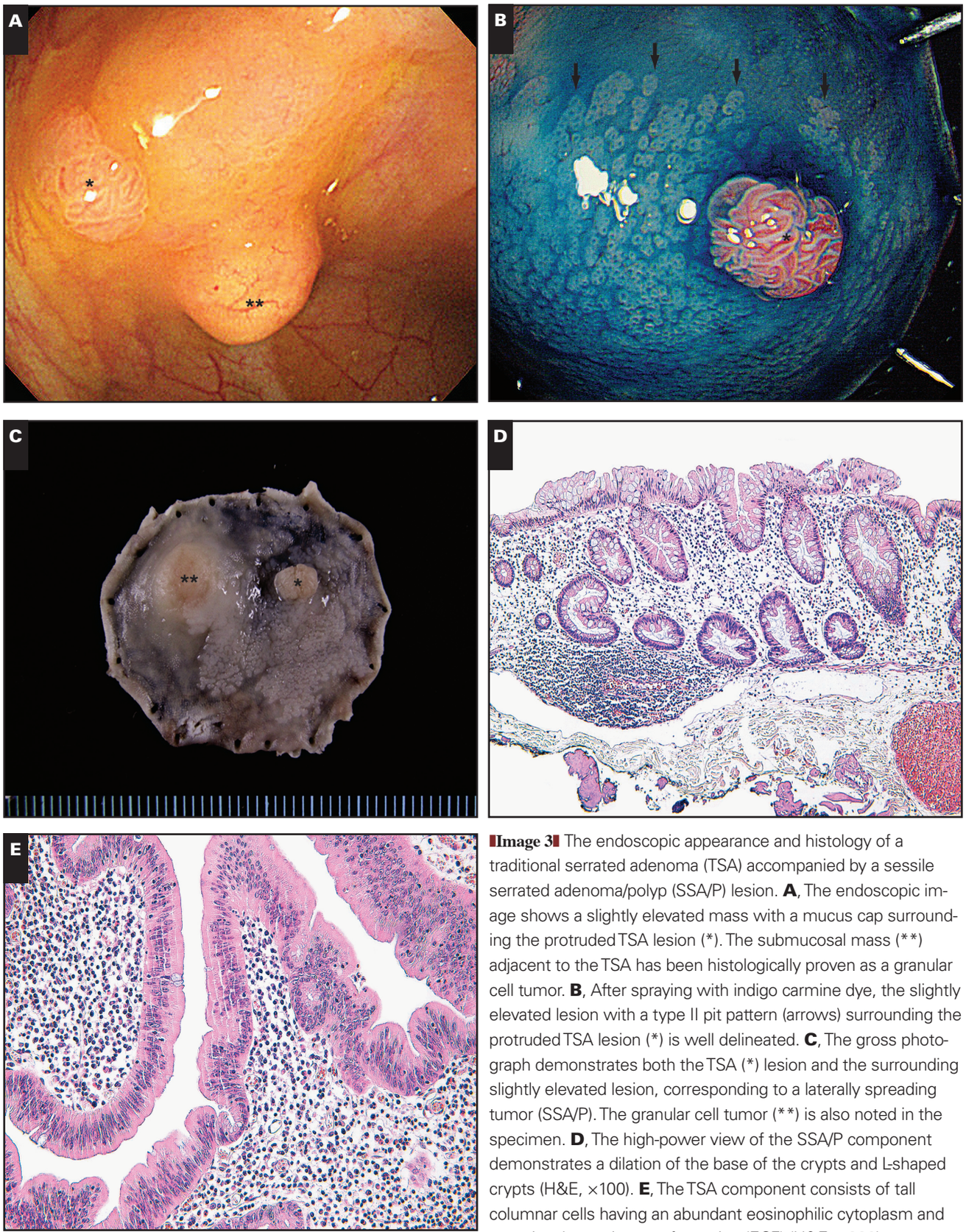

Image 3 The endoscopic appearance and histology of a traditional serrated adenoma (TSA) accompanied by a sessile serrated adenoma/polyp (SSA/P) lesion. **A**, The endoscopic image shows a slightly elevated mass with a mucus cap surrounding the protruded TSA lesion (*). The submucosal mass (**) adjacent to the TSA has been histologically proven as a granular cell tumor. **B**, After spraying with indigo carmine dye, the slightly elevated lesion with a type II pit pattern (arrows) surrounding the protruded TSA lesion (*) is well delineated. **C**, The gross photograph demonstrates both the TSA (*) lesion and the surrounding slightly elevated lesion, corresponding to a laterally spreading tumor (SSA/P). The granular cell tumor (**) is also noted in the specimen. **D**, The high-power view of the SSA/P component demonstrates a dilation of the base of the crypts and L-shaped crypts (H&E, ×100). **E**, The TSA component consists of tall columnar cells having an abundant eosinophilic cytoplasm and occasional ectopic crypt formation (ECF) (H&E, ×200).

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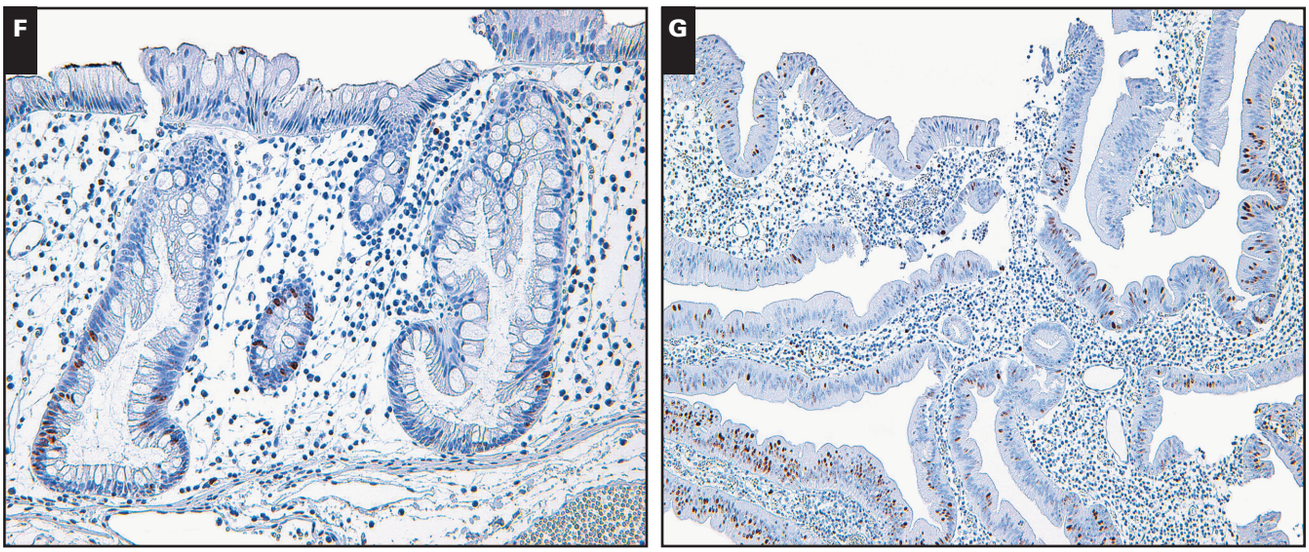

Immunohistochemistry for Ki-67 shows irregularly distributed Ki-67+ cells in the SSA/P (**F**, ×200) and preferential expression of the Ki-67+ cells in ECFs of the TSA component (**G**, ×100).

Mutations of *BRAF* and *KRAS* were mutually exclusive. Twelve (11.2%) TSA lesions showed neither *BRAF* 600E nor *KRAS* codon 12, 13, or 61 mutations. One (0.9%) case showed a *PIK3CA* mutation in addition to a *BRAF* 600E mutation. No cases showed any kind of *EGFR* mutation. Among control groups, the rates of *BRAF* and *KRAS* mutations in HPs were 50.0% and 20.0%, respectively. However, none of the conventional adenomas or SIACs displayed the *BRAF* mutation. There was a significant difference in the mutation results between TSAs and control groups ($P < .001$).

TSA cases with a precursor lesion showed a higher frequency of *BRAF* mutation (71.7%) compared with those with no precursor lesion (34.0%). The frequency of *BRAF* or *KRAS* mutations did not significantly differ between TSAs with an HP precursor and those with an SSA/P precursor ($P = 1.000$ and $P = .692$, respectively). In contrast, TSA cases with no precursor lesion displayed a significantly higher frequency of *KRAS* mutation (51.1%) compared with cases with precursor lesions (34.0%; $P < .001$). The results are summarized in Tables 3 and 5. The frequency of the *BRAF* or *KRAS* mutation did not differ depending on the status of conventional epithelial dysplasia ($P = .438$) (Table 4).

Mutation tests performed in three TSA cases with a nondysplastic SSA/P precursor component showed the same *BRAF* mutations in both components. Taken together, our findings confirm the previous observations, that both HPs and SSA/Ps represent a precursor of TSAs. The presence of TA-like lesions was associated with a higher frequency of *KRAS* and a lower frequency of *BRAF* mutations ($P = .053$ and $P = .018$, respectively).

Immunohistochemical Findings

In TSAs, Ki-67+ cells were preferentially identified in both ectopic crypts and deep crypts as well as in areas with conventional epithelial dysplasia, as previously described[2,17] **Image 3G**. However, SSA/Ps showed scattered Ki-67+ cells with an irregular and asymmetrical distribution **Image 3F**. In TA-like lesions associated with TSAs, the Ki-67+ cells were usually distributed in the lower two-thirds of the crypts, in contrast to conventional adenomas, where the Ki-67+ cells were preferentially identified in the upper zone or entire length of the crypts. The distribution of Ki-67+ cells in TA-like areas was similar to that of HPs in that proliferative zones were expanded with a regular and symmetrical pattern **Image 4E**.

Discussion

Since recognition by Longacre and Fenoglio-Preiser in 1990,[1] TSAs have been defined as a distinct form of serrated polyp with a serrated architecture in association with adenomatous changes. However, the diagnosis of TSAs in a daily practice is not always easy because the clinicopathologic manifestation of TSA is heterogeneous in terms of its gross appearance and anatomic distribution.[4,6] In addition, the histologic features of TSA can vary depending on the extent of peculiar tall columnar cells having an eosinophilic cytoplasm, the presence of precursor lesions, and the amount of stroma. There is also a controversy over dysplasia in TSAs according to the change in its concept. TSAs were often regarded as lesions having at least low-grade dysplasia since TSAs were originally defined as a polyp with a serrated architecture and

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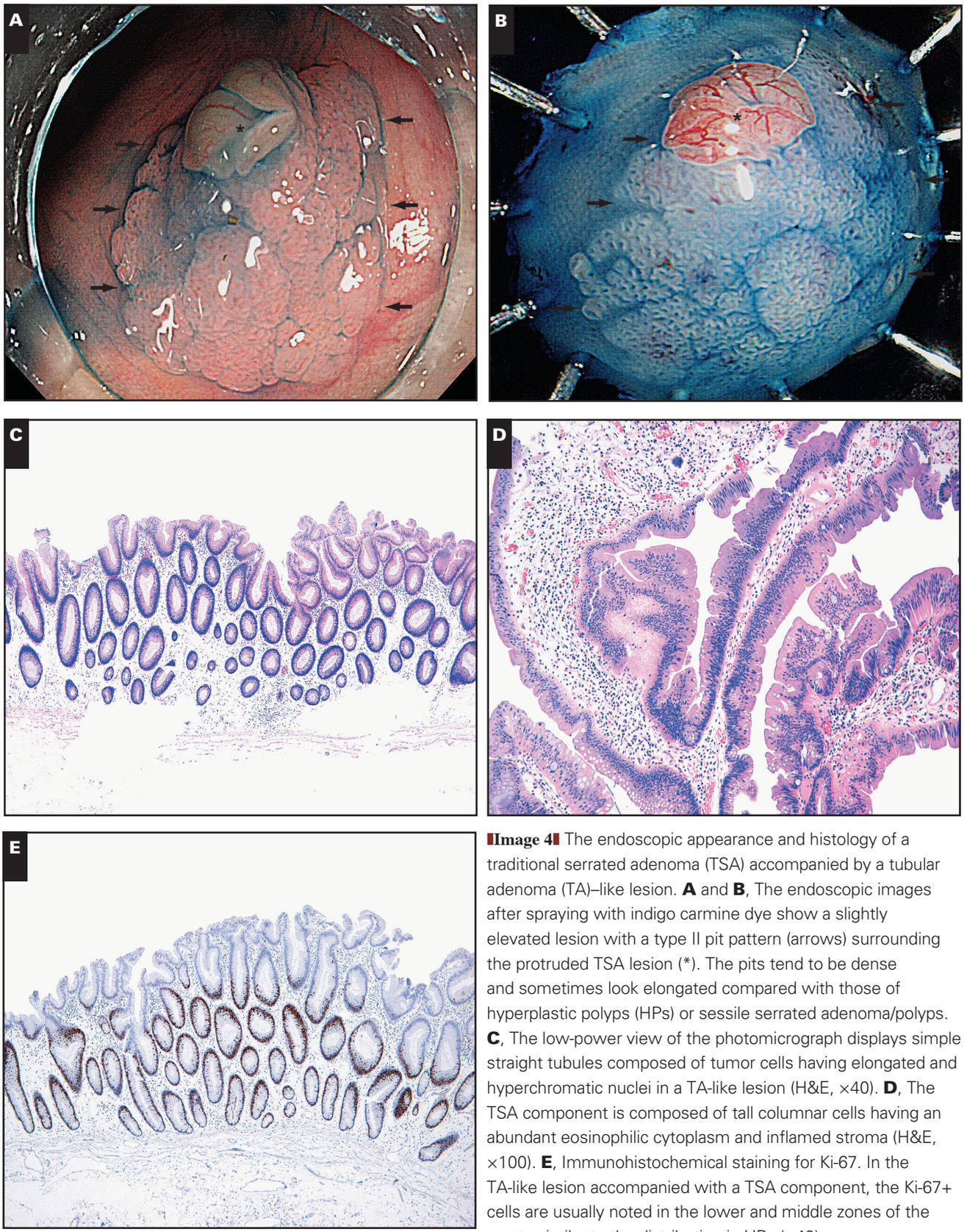

Image 4 The endoscopic appearance and histology of a traditional serrated adenoma (TSA) accompanied by a tubular adenoma (TA)–like lesion. **A** and **B**, The endoscopic images after spraying with indigo carmine dye show a slightly elevated lesion with a type II pit pattern (arrows) surrounding the protruded TSA lesion (*). The pits tend to be dense and sometimes look elongated compared with those of hyperplastic polyps (HPs) or sessile serrated adenoma/polyps. **C**, The low-power view of the photomicrograph displays simple straight tubules composed of tumor cells having elongated and hyperchromatic nuclei in a TA-like lesion (H&E, ×40). **D**, The TSA component is composed of tall columnar cells having an abundant eosinophilic cytoplasm and inflamed stroma (H&E, ×100). **E**, Immunohistochemical staining for Ki-67. In the TA-like lesion accompanied with a TSA component, the Ki-67+ cells are usually noted in the lower and middle zones of the crypts similar to the distribution in HPs (×40).

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Table 5
Clinicopathologic Characteristics of TSAs According to the Status of Precursor Conditions[a]

Parameters	HP (n = 44)	SSA/P (n = 12)	No HP or SSA/P Precursor Lesions (n = 51)	*P* Value[b]
Patient age, mean, y	60.8	57.8	62.3	.395
Sex (M:F)	1.6:1	1:1	1:1.1	.368
Tumor location				<.001
Proximal	8 (18.2)	9 (75.0)	9 (17.6)	
Distal	36 (81.8)	3 (25.0)	42 (82.4)	
Tumor size, mean, cm	1.2	1.7	1.4	.136
Conventional epithelial dysplasia				.003
Absent	41 (93.2)	10 (83.3)	33 (64.7)	
Present	3 (6.8)	2 (16.7)	18 (35.3)	
Mutation results				.002
BRAF	32 (72.7)	9 (75.0)	18 (35.3)	
KRAS	7 (15.9)	3 (25.0)	26 (51.0)	
Both negative	5 (11.4)	0	7 (13.7)	

HP, hyperplastic polyp; SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma.
[a] Values are presented as number (%) unless otherwise indicated.
[b] *P* value calculated with *t* test for continuous variables and χ^2 for categorical variables.

adenomatous cytologic changes. The peculiar cell lining the villous structure of TSAs has an elongated pencillate nucleus and was often referred to as a dysplastic cell. However, low proliferative activity of such cells, as determined by mitotic count or Ki-67 staining, raised a question as to whether this cell type represents true dysplasia or a type of "metaplasia" or "senescence."[2,3] At the present time, there is no consensus on the identification and grading of dysplasia in TSAs.[19] Therefore, we evaluated if there are features of conventional-type dysplasia in TSA lesions, and its rate (21.5%) in this study was similar to that of the previous study.[17]

In some TSA cases, HPs or SSA/Ps coexist in a typical TSA area, and such polyps are classified as a mixed serrated polyp. Although the mixed polyps might represent a collision tumor, those polyps seem to represent serrated polyps in the progression phase of the serrated neoplasia pathway; more specifically, TSAs progressed from precursor lesions.[8] Both our results and the previous reports support the latter opinion by demonstrating the same molecular profile between the two components.[6] The presence of ECF is important in the diagnosis of TSAs, but it does not seem to be mandatory because not all TSAs showed ECF in this study.

In accordance with the study by Kim et al,[6] nondysplastic precursor lesions such as HPs or SSA/Ps were identified in a considerable proportion of TSA cases. The proportion of the precursor lesions (56 cases, 52.3%) in the present study is somewhat higher than that of the previous study because we included cases in which precursor lesions are intimately admixed with typical TSA areas in addition to TSA cases accompanied by a precursor lesion in the stalk or periphery of the polyp. In the former case, the precursor lesions might be hard to detect during endoscopy. We found that more than half of precursor lesions (57.1%) can be detected as a flat-elevated lesion with a type II pit pattern during endoscopy, particularly in cases located in the stalk or periphery of the TSA lesion. Yano et al[8] described this kind of mucosal crypt pattern as a hyperplastic pattern. However, this so-called hyperplastic pattern is a terminology that represents diverse serrated lesions such as HPs, SSA/Ps, or even TSAs. Therefore, the terminology can create confusion to clinicians. On a retrospective review of endoscopy image findings, four TSA cases with a slightly elevated lesion showing a type II pit pattern did not show any histologic evidence of either a precursor lesion or a TA-like component. It seems that those lesions were incompletely removed during the endoscopic procedure. Therefore, we suppose that increased awareness of such lesions could facilitate the rate of their detection and complete removal. Accordingly, one of 107 TSA cases in our study was a recurrent polyp that occurred after an incomplete removal at an outside hospital three years ago, which was eventually eradicated by ESD at our hospital. The polyp consisted of a small amount of residual TSA and a predominant TA-like lesion in the periphery, suggesting a possibility of incomplete removal of the lesions. In this study, we also attempted to evaluate the pit patterns of the main TSA lesions and found that a pinecone-like or fern-like appearance seemed to be specific for TSA lesions, as in previous studies.[12,13] However, the number of control cases (particularly conventional adenomas) was too small to permit conclusive results to be drawn.

Table 6
Correlation of Endoscopic and Histologic Findings of TSAs

	Histologic Findings			
		Precursor Lesions (n = 56)		
Endoscopic Findings (Type II Pit Pattern)	No Precursor Lesion (n = 41)	HP (n = 44)	SSA/P (n = 12)	TA-Like Lesions (n = 10)
No. not identified (n = 61)	37	22	2	0
No. identified (n = 46)	4	22	10	10

HP, hyperplastic polyp; SSA/P, sessile serrated adenoma/polyp; TA, tubular adenoma; TSA, traditional serrated adenoma.

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In agreement with Kim et al,[6] TSAs with a precursor lesion showed a significantly higher frequency of *BRAF* mutations and a lower frequency of *KRAS* mutations compared with TSAs not associated with a precursor lesion ($P < .001$ and $P < .001$, respectively). These observations suggest that the activating mutation in the *BRAF* gene plays an important role in the initiation of TSAs from a precursor lesion. In our study, we used the Sequenom MassArray technique to profile mutations for *BRAF*, *KRAS*, *PIK3CA*, and *EGFR* genes. We and others have previously demonstrated that the sensitivity of mass spectrometric methods is superior to traditional Sanger sequencing, where the aberration should be present in approximately 20% of the DNA and is highly concordant with Sanger sequencing.[20,21] In this study, *BRAF* and *KRAS* mutations were present in 55.1% and 33.6% of cases, respectively. In total, *BRAF* or *KRAS* mutations were identified in 88.7% of TSAs—a higher rate of mutations than that of previous studies.[6,16] Similar to colorectal cancers, activating mutations such as in-frame deletions, duplication, or amino acid substitutions in exons 18, 19, 20, and 21 in an *EGFR* catalytic domain seem to be absent or rare in TSAs because none of 107 TSA cases showed *EGFR* mutations in our study.[22] *EGFR* phosphorylation status reflecting the level of receptor utilization by tumor cells might play an important role in the serrated neoplasia pathway.[23] We also have confirmed that the activating *PIK3CA* mutation is a rare phenomenon in TSAs.

TSAs with a precursor lesion showed a lower frequency of conventional epithelial dysplasia in our study ($P = .002$). We suppose that the fundamental pathogenetic difference of whether TSAs originate from a nondysplastic precursor lesion seems to affect the tumor progression timeline and results in a difference in the status of dysplasia of tumors. Similarly, the status or type of the precursor lesion seems to be associated with the anatomic distribution of TSAs. TSAs with a precursor SSA/P more frequently involved the proximal colon, while TSAs with a precursor HP or with no precursor lesion affected the distal colon and rectum more frequently in this study ($P < .001$). Therefore, the inherent pathogenetic difference of where TSAs are derived from seems to be associated with the heterogeneity of tumors such as anatomic location, morphology, and malignant potential as well as mutation status.

TSAs, particularly those located in the proximal colon, are considered to originate from a SSA/P precursor lesion because TSAs with an SSA/P precursor lesion more frequently involve the proximal colon ($P < .001$). SSA/Ps and TSAs are regarded as not completely different lesions, and a histologic transition from SSA/P to TSA can occur.[6,24] Accordingly, three TSA cases with a nondysplastic SSA/P component in this study showed the same *BRAF* mutations in both components, suggesting a common genetic nature. In addition, two-thirds of TSA cases with an SSA/P component showed endoscopic features such as a flat-elevated or sessile growth pattern and/or a mucous cap, reflecting the presence of an underlying SSA/P component. Therefore, endoscopists should not overlook features suggesting the presence of SSA/Ps, particularly in cases of proximally located TSAs.

We observed that approximately 17.8% of TSAs were accompanied by a TA-like lesion. On endoscopic findings, TA-like lesions were seen as a flat-elevated lesion with a type II (sometimes transitioning into a type III_L) pit pattern. The significance of these lesions has not yet been clarified as to whether those lesions simply represent an admixed conventional adenoma component or a precursor lesion.[25] On the other hand, Torlakovic et al[2] described such lesions showing a flat growth pattern as a "flat" TSA. Such lesions might represent a morphologic spectrum of TSAs that can be identified during a cellular process of proliferation-differentiation or tumor progression. Filiform TSAs seem to represent the extreme end of the full differentiation or senescence of TSAs.[26]

Another possibility is that TA-like lesions in TSAs are a dysplastic lesion that progresses from an underlying HP in the vicinity of a TSA. We observed that histologic features of TA-like lesions were somewhat different from those of conventional adenomas in that architectural complexity, such as crypt branching and villosity, was rarely noted in TA-like lesions. Serrated architecture was also minimal (<5%) or absent; we consider these histologic findings to correlate with the endoscopic features of such lesions. In addition, the distribution of Ki-67+ cells in the TA-like lesion was similar to that of HPs in that the proliferative zones were expanded with a regular and symmetrical pattern[2] (Image 4E). Proliferation as investigated by Ki-67 staining was mainly noted in the lower and middle zones of crypts. On the contrary, the Ki-67+ cells in conventional adenomas were distributed in a diffuse and irregular pattern with a preferential expression in the upper zone or entire length of crypts similar to the results of previous studies (data not shown).[2,27]

In conclusion, we demonstrate here that precursor lesions are not uncommon in TSAs, and the molecular and clinicopathologic features of TSAs, such as anatomic distribution, morphology, and malignant potential, are significantly associated with the status or type of precursor lesions. Our results also suggest that a significant proportion of HP or SSA/P precursor lesions accompanied by TSAs can be detected by endoscopy based on both their flat-elevated growth and type II pit patterns. Similar to the multistep process of colorectal carcinogenesis, it is possible that most TSAs develop from a nondysplastic precursor lesion via the multistep tumorigenesis pathway.

Address reprint requests to Dr Kim: Dept of Pathology, Daehang Hospital, 481-10 BangBae3-dong, Seocho-gu, 137-820, Seoul, South Korea; mjkimdoc@gmail.com.

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