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**Serrated polyps of the colon and rectum: Remove or not?**

Sano W *et al.*Colorectal serrated polyps

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**Abstract**

In recent years, the serrated neoplasia pathway where serrated polyps arise as a colorectal cancer has gained considerable attention as a new carcinogenic pathway. Colorectal serrated polyps are histopathologically classified into hyperplastic polyps (HPs), sessile serrated lesions, and traditional serrated adenomas; in the serrated neoplasia pathway, the latter two are considered to be premalignant. In western countries, all colorectal polyps, including serrated polyps, apart from diminutive rectosigmoid HPs are removed. However, in Asian countries, the treatment strategy for colorectal serrated polyps has remained unestablished. Therefore, in this review, we described the clinicopathological features of colorectal serrated polyps and proposed to remove HPs and sessile serrated lesions ≥ 6 mm in size, and traditional serrated adenomas of any size.

**Key words**: Hyperplastic polyp; Sessile serrated adenoma/polyp; Sessile serrated lesion; Traditional serrated adenoma; Cytological dysplasia; Cryptal dysplasia

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**Core tip:** In western countries, generally all colorectal polyps are removed, including serrated polyps, except rectosigmoid hyperplastic polyps ≤ 5 mm in size. However, no treatment strategy has been developed for colorectal serrated polyps in Asian countries. Hence, in this review, we described the clinicopathological features of colorectal serrated polyps and proposed to remove hyperplastic polyps and sessile serrated lesions ≥ 6 mm in size, and traditional serrated adenomas of any size by narrow-band imaging observation.

**INTRODUCTION**

Apart from adenoma-carcinoma sequence and de novo carcinogenic pathways[1,2], the serrated neoplasia pathway where serrated polyps emerge as a colorectal cancer has been recently gaining considerable research interest as a new carcinogenic pathway. Hyperplastic polyps (HPs), sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs) are the histopathological classifications of colorectal serrated polyps[3]. Of these, SSLs and TSAs are regarded as premalignant lesions in the serrated neoplasia pathway.

SSLs had been previously described as sessile serrated adenoma/polyps[4]. They possess molecular features, such as hypermethylation of the CpG islands in the promoter regions of tumor suppressor genes (*i.e.*, the CpG island methylator phenotype-high: CIMP-high) and BRAF mutations, and they progress to either of the following colorectal cancer types: (1) Microsatellite instable colorectal cancers with MLH1 inactivation; or (2) Microsatellite stable colorectal cancers without MLH1 inactivation. Meanwhile, TSAs progress to microsatellite stable colorectal cancers through the following molecular features: (1) CIMP-high and BRAF mutations without MLH1 inactivation; or (2) KRAS mutations without any of the CIMP-high, BRAF mutations, or MLH1 inactivation[1-3,5-7].

Generally, western countries remove all colorectal polyps, including serrated polyps, apart from rectosigmoid HPs ≤ 5 mm in size. Unfortunately, Asian countries still have no treatment strategy for colorectal serrated polyps. Hence, in this review, we described the clinicopathological features of colorectal serrated polyps and proposed a treatment strategy for them.

**PREVALENCE OF COLORECTAL SERRATED POLYPS**

To clarify the prevalence of colorectal serrated polyps, particularly SSLs, we conducted a prospective study[8]. Between June 2013 and May 2014, patients aged ≥ 40 years undergoing colonoscopy for standard clinical indications at our center were prospectively enrolled. During colonoscopy, 0.05% indigo carmine dye was sprayed throughout the colorectum by using waterjet function to highlight the lesions. All detected lesions were diagnosed by high-definition magnifying narrow-band imaging (NBI) and were removed endoscopically or surgically, aside from rectosigmoid NICE (NBI international colorectal endoscopic)[9,10] or JNET (Japan NBI Expert Team)[11] type 1 lesions ≤ 5 mm in size. Regarding rectosigmoid NICE or JNET type 1 lesions measuring ≤ 5 mm, we recorded their total number by using tally counter and then removed some of them. In 315 out of 343 eligible patients, 1301 colorectal lesions were removed endoscopically or surgically. Of them, 165 HPs in 97 patients, 21 SSLs in 17 patients, and 13 TSAs in 12 patients were identified histopathologically. Furthermore, the prevalence of HPs, SSLs, and TSAs, defined as the proportion of patients with ≥ 1 HP, SSL, and TSA lesions, was 28.3%, 5.0%, and 3.5%, respectively.

In the study of Hazewinkel *et al*[12] of 1426 patients with a median age of 60 years who underwent screening colonoscopy, the prevalence of HPs, SSLs, and TSAs was 23.8%, 4.8%, and 0.1%, respectively. In another study of 1479 patients by Carr *et al*[13], the prevalence of HPs, SSLs, and TSAs was 30%, 3.9%, and 0.7%, respectively. Abdeljawad *et al*[14] reported that the prevalence of SSLs was 8.1% in their study of 1910 patients aged ≥ 50 years who underwent screening colonoscopy. The previously reported prevalence of colorectal serrated polyps varies due to the study design and population, colonoscopy equipment and observation method, experience of the endoscopists, and the histopathological diagnostic criteria. However, SSLs, which have recently attracted attention as precursors of microsatellite instable colorectal cancers, seem not to be rare in clinical practice[14,15].

**ENDOSCOPIC FEATURES OF COLORECTAL SERRATED POLYPS**

***HP***

HPs commonly exist in the left colorectum, particularly rectosigmoid colon, and are often ≤ 5 mm in size. In white light endoscopy, they appear as discolored, flat elevated lesions (Figure 1A). In NBI endoscopy, they appear as whitish lesions (NICE or JNET type 1) without expanded, brown meshed capillary vessels (MC vessels)[16], which are seen in conventional adenomas (Figure 1B). In chromoendoscopy, Kudo type II asteroid pits are observed on the lesion surface (Figure 1C).

***SSL***

SSLs typically occur in the right colon and are slightly larger than HPs. The characteristic findings of SSLs include various endoscopic findings, such as a mucous cap in white light endoscopy[17], a red cap sign in NBI endoscopy[18], a cloud-like surface in white light or NBI endoscopy[19], dilated and branching vessels in NBI endoscopy[20], expanded crypt openings in NBI endoscopy[21], and type II open-shape (type II-O) pits in chromoendoscopy[22] (Figure 2). However, SSLs resemble HPs endoscopically, and most of them are detected as discolored, flat elevated lesions in white light endoscopy and whitish lesions (NICE or JNET type 1) in NBI endoscopy; therefore, differentiating between HPs and SSLs endoscopically in clinical practice remains often challenging.

***SSL with dysplasia***

SSL is generally accompanied with dysplasia during carcinogenesis[1-4,6]. Endoscopic morphological findings, such as large or small nodules on the surface and partial protrusion of SSLs, were useful indicators of dysplasia within SSLs, with an accuracy of 93.3% on the analysis of 326 SSLs (Figure 3)[23]. Burgess *et al*[24] also reported that the presence of any 0-Is or nodular components within SSLs was associated with dysplasia within SSLs, with 71.0% accuracy on the analysis of 207 SSLs ≥ 20 mm in size.

Regarding the pit pattern analysis of SSLs with dysplasia (SSLDs) using magnifying chromoendoscopy, Burgess *et al*[24] stated that SSLDs exhibited an adenomatous pit pattern (Kudo type III, IV, or V), with 70.6% accuracy on the analysis of 201 SSLs ≥ 20 mm in size. Moreover, Murakami *et al*[25] reported that SSLDs exhibited Kudo type III, IV, VI, or VN pit patterns in addition to a type II pit pattern, with 99.4% accuracy on the analysis of 314 SSLs. Tanaka *et al*[26] also described that SSLDs exhibited an adenomatous pit pattern (Kudo type III or IV) in addition to a type II or II-O pit pattern, with 89.4% accuracy on the analysis of 123 SSLs.

Utilizing nonmagnifying NBI observation, Tate *et al*[27] reported that a demarcated area with a neoplastic pit pattern (Kudo type III/IV or NICE type 2) was a useful indicator of dysplasia within SSLs, with 95.0% accuracy on the analysis of 141 SSLs ≥ 8 mm in size.

Thus, high-accuracy endoscopic diagnosis of SSLDs is becoming possible; however, some SSLDs do not exhibit the abovementioned characteristic endoscopic findings.

***TSA***

TSAs commonly appear in the left colorectum, similar to HPs. They appear as reddish, protruded or pedunculated lesions in white light observation and “pine cone-like” or “branch coral-like” lesions in macroscopic observation (Figure 4A and B). In NBI endoscopy, “leaf vein-like” expanded, brown capillary vessels, which differ from MC vessels seen in conventional adenomas, are identified in the large stromal area around the crypts, and TSAs appear as brownish resembling conventional adenomas (NICE or JNET type 2) (Figure 4C). In chromoendoscopy, they are characterized by type IIIH pits, which are Kudo type IIIL-like tubular pits accompanied with serration in the crypt margin, or type IVH pits, which are Kudo type IV-like villous pits accompanied with serration in the crypt margin (Figure 4D)[28].

**HISTOPATHOLOGICAL FEATURES OF COLORECTAL SERRATED POLYPS**

***HP***

On the basis of mucin type, HPs are subclassified into three types, namely, microvesicular HPs (MVHPs), goblet-cell-rich HPs, and mucin-poor HPs[2]. MVHPs and goblet-cell-rich HPs account for up to 60% and 30%, respectively, whereas mucin-poor HPs remain rare. All these HPs are histologically characterized by the elongation of the intestinal crypts, with serration of the upper part of the crypts (Figure 5A). Conversely, the lower part of the crypts is narrow, without any serration. The basal part of the crypts exhibits uniform proliferation. Meanwhile, cytological dysplasia is not seen in any HP types.

***SSL***

SSLs are histopathologically characterized by (1) crypt dilation; (2) irregularly branching crypts; and (3) horizontally arranged basal crypts (inverted T- and/or L-shaped crypts) (Figure 5B)[29,30]. The proliferation zone of the crypts often shifts from the basal part to the side of the crypts[2].

According to the Japanese Society for Cancer of the Colon and Rectum criteria established in 2011, when at least two of these three histopathological findings were found in ≥ 10% of the lesion area, the serrated polyps are diagnosed as SSLs[29,30]. However, those that do not meet the abovementioned criteria are diagnosed as HPs.

***SSLD***

Generally, cytological dysplasia arising in SSLs is divided into two types, namely, conventional adenoma-like dysplasia and serrated dysplasia (Figure 5C and D)[3,4,31,32].

Conventional adenoma-like dysplasia is histopathologically characterized by the presence of elongated cells with penicillate and hyperchromatic pseudostratified nuclei, basophilic cytoplasm, and increased mitoses, and it resembles a conventional tubular or tubulovillous adenoma cytologically. Meanwhile, serrated dysplasia is histopathologically characterized by a proliferation of cuboidal atypical cells, eosinophilic cytoplasm, enlarged round nuclei with open vesicular prominent chromatin, prominent nucleoli, and increased mitoses[3,4,31,32].

After the analysis of 326 SSLs, we also found a previously unreported type of dysplasia, termed as “cryptal dysplasia,” which is localized in the crypt base but cannot be classified as either conventional adenoma-like or serrated dysplasia (Figure 5E)[23]. Although the clinical significance of “cryptal dysplasia” remains unclear, this type was common within SSLDs and mostly coexisted with conventional adenoma-like and/or serrated dysplasia to a varied extent. Further assessment of the clinical significance of “cryptal dysplasia” is necessary to become widely recognized and be applied by endoscopists and pathologists in their diagnostic examinations.

***TSA***

TSAs are histopathologically characterized by tubulovillous or villous architecture, tall columnar cells with intensely eosinophilic cytoplasm and pencillate nuclei, slit-like serrations due to narrow slits in the deeply eosinophilic epithelium resembling normal small intestinal mucosa, and ectopic crypt formations due to the abnormal crypt development with loss of orientation toward the muscularis mucosae (Figure 5F and G)[3,7].

**MANAGEMENT OF COLORECTAL SERRATED POLYPS**

***NICE or JNET type 1 lesions including HP and SSL***

NBI observation detects both HPs and SSLs as NICE or JNET type 1 lesions. In our study, the probability of NICE or JNET type 1 lesions being SSLs significantly increased with the lesion size, with 6 mm as the boundary (≤ 5 mm: 0.7%; 6-9 mm: 29.0%; ≥ 10 mm: 70%) (Table 1)[8]. In addition, 89.1% and 10.9% of HPs were ≤ 5 and ≥ 6 mm in size, respectively, showing a pyramid-type distribution; meanwhile, 76.2% and 23.8% of SSLs were ≥ 6 and ≤ 5 mm in size, respectively, indicating an inverted pyramid-type distribution. Furthermore, HPs, particularly MVHPs, harbor genetic abnormalities, such as CIMP-high and BRAF mutations, similar to SSLs[33-35]. Thus, HPs will transition to SSLs with an increase of the lesion size, with a boundary of approximately 6 mm.

If differentiating between HPs and SSLs is easy, SSLs can be removed selectively; however, it is often challenging in clinical practice. In addition, NICE or JNET type 1 lesions ≥ 6 mm in size, even if HPs, may eventually transition to SSLs if left unattended. Therefore, we propose to remove all NICE or JNET type 1 lesions ≥ 6 mm in size. In our study, most NICE or JNET type1 lesions were ≤ 5 mm, and only 1.1% of them were ≥ 6 mm in size[8]. Additionally, the prevalence of NICE or JNET type1 lesions ≥ 6 mm in size was not high at 8.5%, suggesting that the removal of all NICE or JNET type 1 lesions ≥ 6 mm in size seems feasible in clinical practice.

Meanwhile, in our study, the probability of NICE or JNET type1 lesions ≤ 5 mm in size being SSLs was only 0.7% (Table 1)[8]. In our other study, the rate of dysplasia within SSLs increased as the lesion size increased (≤ 5 mm, 0%; 6-9 mm, 6.0%; ≥ 10 mm, 13.6%) (Table 2)[23], similar to a stepwise increase of the dysplasia degree or cancer rate within conventional adenomas that occurs along with an increase in lesion size[36-38]. Thus, the probability of NICE or JNET type 1 lesions ≤ 5 mm in size being SSLs was extremely low, and even if they are SSLs, the rate of dysplasia within SSLs ≤ 5 mm in size was also extremely low, suggesting that NICE or JNET type 1 lesions ≤ 5 mm in size can be left in situ.

Western countries remove all NICE or JNET type 1 lesions ≤ 5 mm in the cecum, ascending, transverse, and descending colon. However, in our study, despite the relatively high (25.1%) prevalence of these lesions, the probability of these being SSLs was quite low (1.6%)[8]. Therefore, removing all NICE / JNET type 1 lesions ≤ 5 mm in the whole colon apart from rectosigmoid colon appears to have more disadvantages such as the probable adverse events including post-polypectomy bleeding and perforation, the burden on the endoscopists, and the time-consuming examinations, than the advantages of removing SSLs ≤ 5 mm in size. However, these lesions include HPs, which have the potential to transition to SSLs, and some SSLs. Hence, we recommend following up these lesions at appropriate intervals (*e.g.*, 5 years[39,40]) if left unattended.

***SSLD***

As mentioned, SSLs are frequently accompanied with dysplasia during carcinogenesis[1-4,6], and they may rapidly progress to carcinomas after they start to develop dysplasia within them[41]. In our study, the rate of dysplasia within SSLs increased as the lesion size also increased, and all SSLDs were ≥ 6 mm in size (Table 2)[23]. Therefore, if all SSLs ≥ 6 mm in size are removed, we could possibly remove almost all SSLDs with a high sensitivity. Given that endoscopically diagnosing SSLDs with a high accuracy is gradually becoming possible[23-27], colorectal lesions suspected of SSLDs should be removed en bloc for accurate pathological assessment and prevention of recurrent cancers due to incomplete removal.

***TSA***

In NBI endoscopy, TSAs are detected as NICE or JNET type 2 brownish lesions similar to conventional adenomas. Considering the lower prevalence[8,12,13] and similar malignant potential[42,43] (*e.g.*, cancer rate within the lesions) of TSAs compared with conventional adenomas, we propose to remove all TSAs of any size in the same fashion as conventional adenomas.

**CONCLUSION**

In this review, we described the clinicopathological features of colorectal serrated polyps and proposed a treatment strategy for them. When the removal of all conventional adenomas and cancers, which exhibit NICE or JNET types 2 and 3 on NBI observation, is added to our proposed treatment strategy, the treatment algorithm for colorectal polyps, including serrated polyps, using NBI observation is as follows (Figure 6): (1) Leave in situ NICE or JNET type 1 lesions, such as HPs and few SSLs, at ≤ 5 mm in size, (2) Remove NICE or JNET type 1 lesions, such as HPs and SSLs, at ≥ 6 mm in size, and (3) Remove NICE or JNET types 2 and 3 lesions, including SSLDs, TSAs, conventional adenomas, and cancers, of any size. This treatment algorithm for colorectal polyps is simple and seems feasible in clinical practice. We believe that this simple treatment strategy will result in the decline of colorectal cancer morbidity and mortality in Asian countries.

**LIMITATION**

Our proposal of the treatment strategy for colorectal serrated polyps has the limitation that it is mainly based on studies of Japanese patients. Therefore, further studies are needed to evaluate the applicability of our treatment strategy in other Asian countries. We hope that in the future, treatment guidelines for colorectal serrated polyps will be established also in Asian countries, as well as surveillance guidelines based on these.

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**Footnotes**

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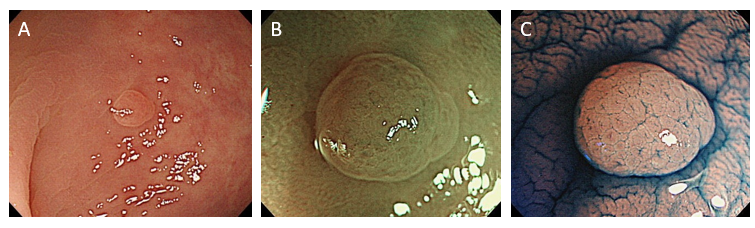
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Grade D (Fair): 0

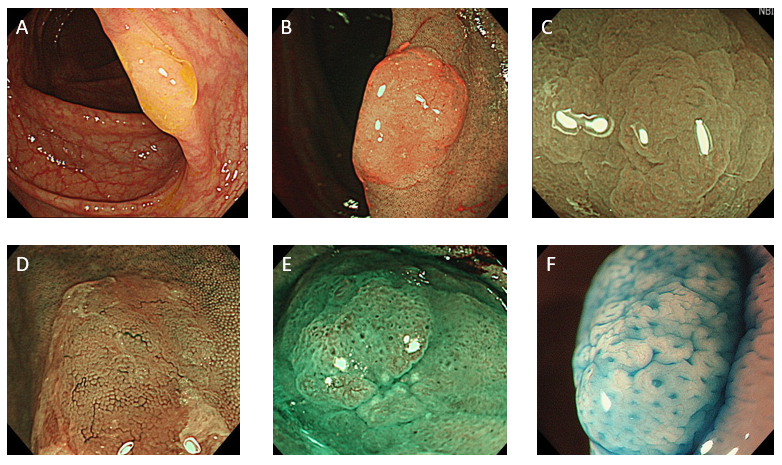
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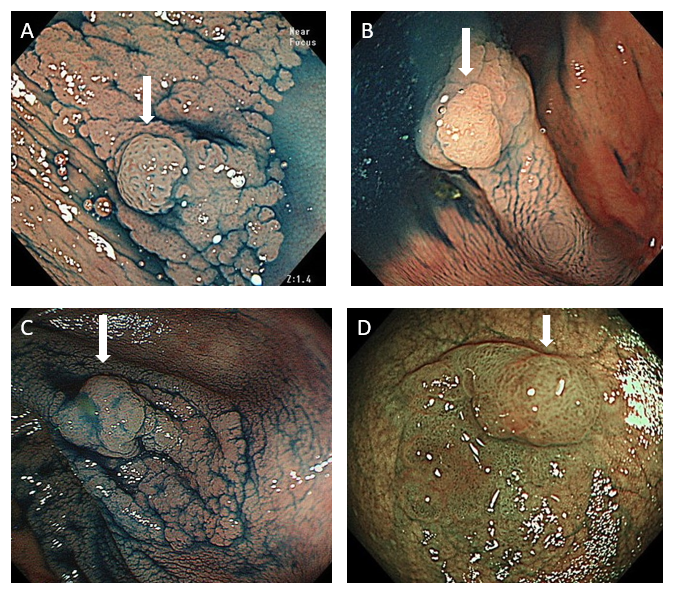
**Figure Legends**



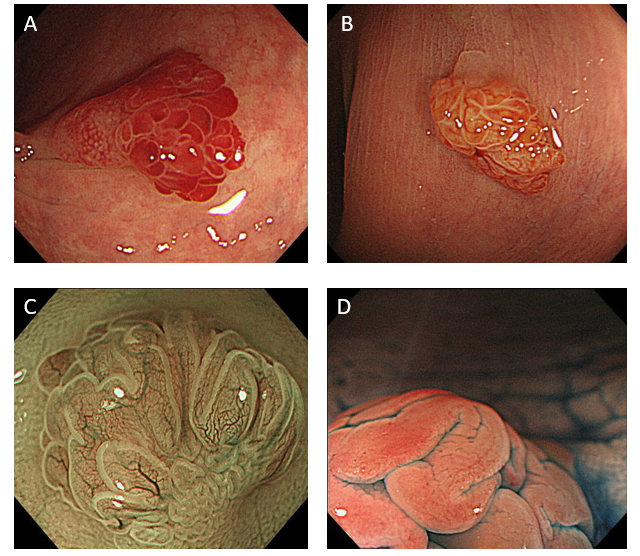
**Figure 1 Example of hyperplastic polyps.** A: White light endoscopic view. A slightly discolored, flat elevated lesion measuring 3 mm in size was detected in the sigmoid colon; B: Narrow-band imaging endoscopic view. The lesion was detected as a whitish lesion without expanded, brown meshed capillary vessels, which are seen in conventional adenomas; C: Chromoendoscopic view. Kudo type II asteroid pits were identified on the lesion surface.



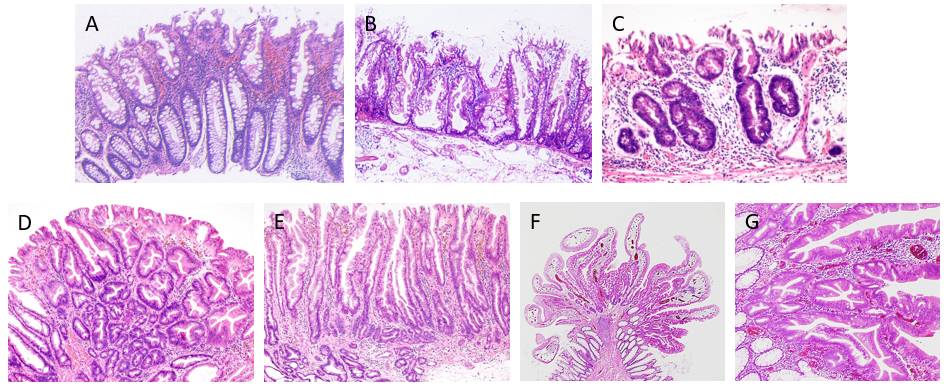
**Figure 2 Endoscopic features of sessile serrated lesions.** A: Mucous cap (white light endoscopy); B: Red cap sign [narrow-band imaging (NBI) endoscopy]; C: Cloud-like surface (white light or NBI endoscopy); D: Dilated and branching vessels (NBI endoscopy); E: Expanded crypt openings (NBI endoscopy); F: Type II open-shape pits (chromoendoscopy).



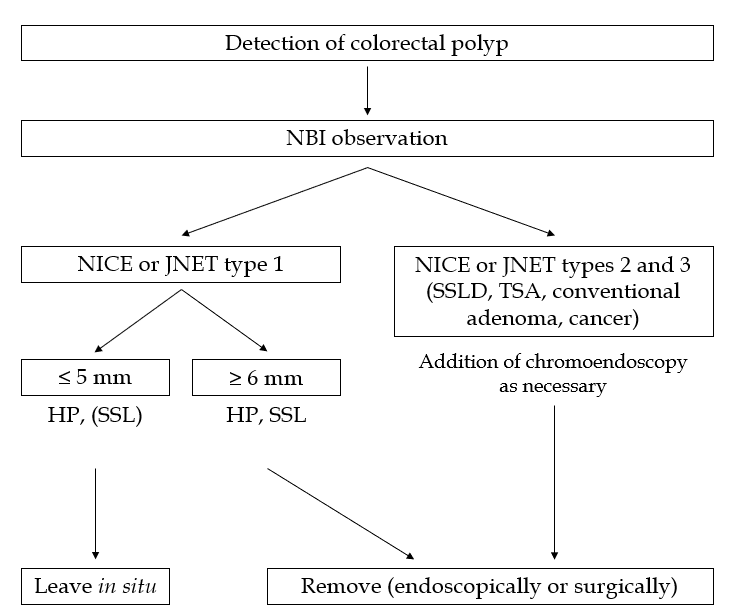
**Figure 3 Endoscopic features of sessile serrated lesion with dysplasia.** A: Small nodule on the lesion surface (arrow); B: Small nodule on the lesion surface (arrow); C: Large nodule on the lesion surface (arrow); D: Partial protrusion of the lesion (arrow).



**Figure 4 Endoscopic features of traditional serrated adenoma.** A: White light endoscopic view; B: White light endoscopic view; C: Narrow-band imaging endoscopic view exhibiting “leaf vein-like” expanded, brown capillary vessels; D: Chromoendoscopic view exhibiting type IVH pits.



**Figure 5 Histopathological features of colorectal serrated polyp.** A: Microscopic view of hyperplastic polyp; B: Microscopic view of sessile serrated lesion (SSL); C: Microscopic view of SSL with dysplasia (SSLD) (conventional adenoma-like dysplasia); D: Microscopic view of SSLD (serrated dysplasia); E: Microscopic view of SSLD (“cryptal dysplasia”); F: Microscopic view of traditional serrated adenoma exhibiting papillary growth; G: Microscopic view of traditional serrated adenoma. 1:100μm.



**Figure 6 Proposal of treatment algorithm for colorectal polyps.** NBI: Narrow-band imaging; NICE: Narrow-band imaging international colorectal endoscopic; JNET: Japan narrow-band imaging expert team; HP: hyperplastic polyp; SSL: Sessile serrated lesion; SSLD: Sessile serrated lesion with dysplasia; TSA: Traditional serrated adenoma.

**Table 1 Probability of narrow-band imaging international colorectal endoscopic or Japan narrow-band imaging expert team type 1 lesions being sessile serrated lesions, % (95%CI)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Size** | **Right colon** | **Left colorectum** | **Total** |
| ≤ 5 mm | 1.8 (0.2-6.2) | 0.5 (0.1-1.4) | 0.7 (0.2-1.5) |
| 6-9 mm | 43.8 (19.8-70.1) | 13.3 (1.7-40.5) | 29.0b (14.2-48.0) |
| ≥ 10 mm | 85.7 (42.1-99.6) | 33.3 (0.8-90.6) | 70a,b (34.8-93.3) |
| Total | 10.9d (6.3-17.4) | 0.9 (0.3-2.0) | 2.7 (1.7-4.0) |

We histopathologically analyzed 792 narrow-band imaging international colorectal endoscopic or Japan narrow-band imaging expert team type 1 lesions. The overall probability of narrow-band imaging international colorectal endoscopic or Japan narrow-band imaging expert team type 1 lesions being sessile serrated lesions was 2.7% (21/792). This probability significantly increased as the lesion size also increased (≤ 5 mm: 0.7%; 6-9 mm: 29.0%; ≥ 10 mm: 70%) and was significantly higher in the right colon than in the left colorectum (10.9% *vs* 0.9%). a*P* < 0.05 *vs* 6-9 mm, b*P* < 0.01 *vs* ≤ 5 mm, and d*P* < 0.01 *vs* left colorectum, the *χ*2 test or Fisher’s exact test.

**Table 2 Rate of dysplasia within sessile serrated lesions, % (95%CI)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Size** | **Right colon** | **Left colorectum** | **Total** |
| ≤ 5 mm | 0 (0-5.0) | 0 (0-25.9) | 0 (0-4.2) |
| 6-9 mm | 5.9 (2.2-12.5) | 6.3 (0.2-30.2) | 6.0a (2.4-11.9) |
| ≥ 10 mm | 14.1 (8.6-21.3) | 8.3 (0.2-38.5) | 13.6b,c (8.4-20.4) |
| Total | 8.3 (5.4-12.1) | 5.3 (0.6-17.7) | 8.0 (5.3-11.5) |

We histopathologically analyzed 326 sessile serrated lesions. The overall rate of dysplasia (conventional adenoma-like dysplasia and/or serrated dysplasia) within sessile serrated lesions was 8.0% (26/326). This rate significantly increased as the lesion size increased (≤ 5 mm: 0%; 6-9 mm: 6.0%; ≥ 10 mm: 13.6%) but exhibited no significant difference between the right colon and left colorectum. a*P* < 0.05 *vs* ≤ 5 mm, b*P* < 0.01 *vs* ≤ 5 mm, and c*P* < 0.05 *vs* 6-9 mm, the *χ*2 test or Fisher’s exact test.