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Title: Endoscopic diagnosis of sessile serrated adenoma/polyp with and without dysplasia/carcinoma

Dear Editor,

Thank you for your e-mail and the reviewers' comments on our manuscript. We truly appreciate the constructive suggestions and have made every attempt to revise our manuscript in accordance with the suggestions. The changes made are as follows:

*Reviewers' comments:*

**Reviewer #1 (Reviewer's code: 00069471):**

This review article deals with SSAP and its diagnosis with endoscopy. This is well written and covers various endoscopic findings including NBI magnification. Many endoscopists can learn a lot about endoscopic diagnosis of SSAP.

Reply: Thank you for your review of our manuscript.

**Reviewer #2 (Reviewer's code: 01560095):**

Major comments;

1. In "Introduction" as well as in "Conclusion", the authors emphasized the importance of detection and complete resection of SSA/P in colonoscopy. I think it would be reasonable to describe more on detection of these lesions in this MINIREVIEW.

Reply: As suggested, we added the following sentences to the "DIAGNOSIS OF SSA/P USING CONVENTIONAL WHITE-LIGHT ENDOSCOPY" section, indicated with underlined text:

However, in contrast to hyperplastic polyps, SSA/Ps are usually larger than 5 mm, frequently covered by a thin layer called a ''mucus cap'' [4, 34, 43, 44], and they are more commonly located in the proximal colon [14, 45]. Conversely, although SSA/Ps are difficult to detect because of their slightly elevated morphology, adhesion of mucus in the proximal colon can be one of the most useful clues for SSA/P detection.

Furthermore, we have added the "ENDOSCOPIC DETECTION OF SSA/P" section, indicated with underlined text:

**ENDOSCOPIC DETECTION OF SSA/P**

The detection of SSA/Ps requires careful colonoscopy. As stated above, because most SSA/Ps are slightly flat-elevated and have subtle mucosal features, SSA/Ps are difficult to detect with endoscopy, and could easily be missed. Therefore, bowel preparation must be excellent. Potential SSA/Ps are initially considered at long view and investigated at close-up view. At long view, the presence of SSA/P is suspected when there is a patch that appears nodular, reddish, covered with

mucus, and/or circled by fine debris. Then such a lesion must be approached and the mucosa washed. Finally, at close-up view, using white light and under NBI, the surface pattern and vessels are examined.

Recently, some studies [57, 58] have shown that image-enhanced endoscopy such as NBI might increase the detection of serrated lesions in the proximal colon, although the results did not reach significance. Therefore, image-enhanced endoscopy currently cannot be recommended as a detection tool for SSA/P. Additional studies assessing SSA/P detection rates with image-enhanced endoscopy are needed.

**REFERENCES**


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58. **Rex DK**, Clodfelter R, Rahmani F, Fatima H, James-Stevenson TN, Tang JC, Kim HN, McHenry L, Kahi CJ, Rogers NA, Helper DJ, Sagi SV, Kessler WR, Wo JM, Fischer M, Kwo PY. Narrow-band imaging versus white light for the detection of proximal colon serrated lesions: a randomized, controlled trial. *Gastrointest Endosc* 2016; **83**: 166–171 [PMID: 25952085 DOI: 10.1016/j.gie.2015.03.1915]


2. Since one of the main topics in this article is differentiation between SSA/P and hyperplastic polyp. I suggest the authors to discuss more on how endoscopic distinction between SSA/P and hyperplastic polyp would impact clinical practice. It is known that some hyperplastic polyps, namely MVHPs, have BRAF mutation and thus assumed to be a possible precursor in serrated pathway. Therefore, even a lesion diagnosed as a hyperplastic polyp, especially in the right side, might not be ignored as harmless.

Reply: As suggested, we added the following sentences to the "DIAGNOSIS OF SSA/P USING CONVENTIONAL WHITE-LIGHT ENDOSCOPY" section, indicated with underlined text: Generally, hyperplastic polyps are traditionally considered non-neoplastic, but SSA/Ps have malignant potential to progress to invasive carcinomas. Therefore, differentiating an SSA/P from a hyperplastic polyp is clinically important to determine the necessity of an endoscopic resection or to

provide support for a recommendation of a surveillance interval [40, 41].

In addition, it is well-known that some hyperplastic polyps such as microvesicular type of hyperplastic polyps (MVHPs) harbor BRAF mutation and are thus assumed to be a possible precursor of the serrated neoplasia pathway. Therefore, as the reviewer mentioned, when taking into account of the development and progression in this pathway, MVHPs should not be ignored as harmless. However, from the point of view of clinical practice, we disagree with the necessity of endoscopic resection of hyperplastic polyps such as MVHPs, because hyperplastic polyps only rarely progress to carcinoma. Via endoscopy, it is difficult to differentiate subtypes of hyperplastic polyps including MVHP, goblet cell-rich type of hyperplastic polyp (GCHP), and mucin-poor type of hyperplastic polyp (MPHP). In this review article, hyperplastic polyp does not mean a specific subtype of hyperplastic polyps such as MVHPs but in general means hyperplastic polyp as a non-neoplastic lesion.

Minor comments;

1. In “Introduction”, the authors mentioned as if Torlakovic et al. introduced the term “sessile serrated polyp”. I believe they proposed the term “sessile serrated adenoma” but not “sessile serrated polyp” to describe lesions currently known as “SSA/P”.

Reply: As suggested, we have amended the Introduction section as follows: Torlakovic et al. [3] described abnormal proliferations in colorectal serrated polyps that resembled hyperplastic polyps superficially, but could be distinguished histologically based on their abnormal architectural features, and they introduced the term “sessile serrated adenoma”. Currently, these polyps are categorized as sessile serrated adenoma/polyp (SSA/P) in accordance with the World Health Organization’s recommendations [4].

2. In “DIAGNOSIS OF SSA/P USING MAGNIFYING CHROMOENDOSCOPY” (page 11), the authors describe SSA/Ps as nonneoplastic lesions just like hyperplastic polyps. I believe there has been considerable debate whether SSA/Ps are neoplastic or not, however, since the authors try to

stress the importance of differentiating SSA/Ps from hyperplastic polyps in this entire manuscript, it might confuse readers.

Reply: As suggested, we have amended the sentences in the "DIAGNOSIS OF SSA/P USING MAGNIFYING CHROMOENDOSCOPY" section as follows: As previously explained [54–56], magnifying colonoscopy is useful for differentiating between neoplastic and nonneoplastic lesions, and for assessing early colorectal cancers' depths of invasion. Both hyperplastic polyps and SSA/Ps have type II pit patterns. Recently, the type II-open pit pattern has been described as a hallmark of SSA/Ps (sensitivity: 66%; specificity: 97%) [35].

3. In "ENDOSCOPIC DIAGNOSIS OF SSA/P WITH DYSPLASIA/CARCINOMA" (page12), the authors mentioned that "a mucus cap was found in almost all of the serrated lesions". I don't agree with this since most of hyperplastic polyps are not covered with mucus cap. Actually, the authors themselves suggested a mucus cap is a characteristic of SSA/P.

Reply: As suggested, we have amended the sentences in the "ENDOSCOPIC DIAGNOSIS OF SSA/P WITH DYSPLASIA/CARCINOMA" section as follows: Macroscopically, a mucus cap was found in almost all of the SSA/P lesions, including the SSA/Ps with and without dysplasia or carcinoma, in our study [39], suggesting that a mucus cap may be one of the strongest markers of an SSA/P.

**Reviewer #3 (Reviewer's code: 02542422):**

This is a well-summarized minireview about the endoscopic diagnosis of sessile serrated adenoma/polyp with and without dysplasia/carcinoma. However, I think that the definition of SSA with dysplasia is misunderstood. Please refer Bettington's inclusion criteria described below.[1] "For inclusion, cases were required to show (1) a component of ordinary SSA at the edge of the lesion comprising at least three crypts, one of which must show SSA-type histology; (2) abrupt transition from ordinary SSA to overt cytological dysplasia or carcinoma within one tissue fragment and (3) exclusion of cases representing TSA arising in an SSA.[2] These criteria were used to ensure the series represented a homogenous group. Criteria one was designed to guarantee origin in an

SSA, criteria two to ensure the dysplasia or carcinoma was arising in the SSA of interest rather than being from a separate conventional adenoma collected in the same specimen jar and criteria three to exclude the phenomenon of TSA arising in an SSA.[3,4] TSA arising in an SSA can be easily misdiagnosed as SSAD but is a separate entity with distinct clinicopathological and biological features, thus requiring exclusion from the current study."[2] References) 1. Bettington M, Walker N, Rosty C, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut. 2017;66:97-106 2. Bettington ML, Walker NI, Rosty C, et al. A clinicopathological and molecular analysis of 200 traditional serrated adenomas. Mod Pathol 2015;28:414–27. 3. Kim M-J, Lee E-J, Suh J-P, et al. Traditional serrated adenoma of the colorectum: clinicopathologic implications and endoscopic findings of the precursor lesions. Am J Clin Pathol 2013;140:898–911. 4. Kim KM, Lee EJ, Kim YH, et al. KRAS mutations in traditional serrated adenomas from Korea herald an aggressive phenotype. Am J Surg Pathol 2010;34:667–75.

Reply: We appreciate your suggestion. As suggested, Figure 5 apparently looks like traditional serrated adenoma (TSA) arising in a SSA/P. In order to avoid misunderstandings, we replaced the original images with those of the other representative case of SSA/P with dysplasia in Figure 5. Furthermore, we amended the following sentences in the Figure legends: Figure 5. Endoscopic images of a sessile serrated adenoma/polyp (SSA/P) with high-grade cytologic dysplasia in a representative case. (A), (B), and (C) A conventional endoscopic view using white-light imaging. (A) An endoscopic image shows a pale-color, flat-elevated lesion covered with mucus at the ascending colon (arrows). (B) The lesion is covered with mucus cap. (C) After washing the target lesion to sufficiently remove mucus, a flat-elevated lesion that had a 13-mm diameter and a dome-shaped double elevation can be clearly seen. The dome-shaped area is slightly red-colored. (D) and (E) Magnifying chromoendoscopic views using crystal violet staining. (D) A type II-open pit pattern is partly evident in the edge of the lesion (arrows). (E) Type $V_I$-mild pit pattern consisting of areas with irregular pits can be observed at the dome-shaped area. We endoscopically diagnosed the lesion as an SSA/P with cytologic dysplasia, and achieved an en bloc resection by performing an endoscopic mucosal resection. (F), (G), and (H) Histopathologic findings with hematoxylin-eosin staining of the resected specimen. (G) Crypts with a serrated architecture exhibit irregularly dilated crypts, irregularly branching crypts, and horizontally arranged basal crypts, corresponding to SSA/P. (H) A high-power view shows conventional adenomatous high-grade

dysplasia with cytological atypia and architectural dysplasia in the dome-shaped area. The lesion was pathologically consistent with an SSA/P with high-grade cytologic dysplasia.

We have responded to Reviewers' comments in good faith and changed the original text in accordance with their suggestions. We would appreciate further slight change by editors where deemed necessary. Thank you for your kind patience in evaluating our paper.

Sincerely,

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