

World Journal of *Clinical Oncology*

World J Clin Oncol 2023 April 24; 14(4): 138-189



REVIEW

- 138 Immunotherapy in glioblastoma treatment: Current state and future prospects

Rocha Pinheiro SL, Lemos FFB, Marques HS, Silva Luz M, de Oliveira Silva LG, Faria Souza Mendes dos Santos C, da Costa Evangelista K, Calmon MS, Sande Loureiro M, Freire de Melo F

MINIREVIEWS

- 160 Integration of molecular testing for the personalized management of patients with diffuse large B-cell lymphoma and follicular lymphoma

Stuckey R, Luzardo Henríquez H, de la Nuez Melian H, Rivero Vera JC, Bilbao-Sieyro C, Gómez-Casares MT

- 171 Current progress on the endoscopic features of colorectal sessile serrated lesions

Wang RG, Wei L, Jiang B

ORIGINAL ARTICLE

Retrospective Cohort Study

- 179 Interaction between age and gender on survival outcomes in extramedullary multiple myeloma over the past two decades

Bangolo AI, Fwelo P, Trivedi C, Sagireddy S, Aljanaahi H, Auda A, Mohamed M, Onyeka S, Fisher M, Thapa J, Tabucanon EJ, Georgiev L, Wishart A, Kumari S, Erikson C, Bangura M, Paddy O, Madhukar R, Gomez EL, Rathod J, Naria M, Hajal B, Awadhalla M, Siegel D, Parmar H, Biran N, Vesole DH, Phull P, Weissman S

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Current progress on the endoscopic features of colorectal sessile serrated lesions

Rui-Gang Wang, Lai Wei, Bo Jiang

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Abstract

Along with the discovery and refinement of serrated pathways, the World Health Organization amended the classification of digestive system tumors in 2019, recommending the renaming of sessile serrated adenomas/polyps to sessile serrated lesions (SSLs). Given the particularity of the endoscopic appearance of SSLs, it could easily be overlooked and missed in colonoscopy screening, which is crucial for the occurrence of interval colorectal cancer. Existing literature has found that adequate bowel preparation, reasonable withdrawal time, and awareness of colorectal SSLs have improved the quality and accuracy of detection. More particularly, with the continuous advancement and development of endoscopy technology, equipment, and accessories, a potent auxiliary tool is provided for accurate observation and immediate diagnosis of SSLs. High-definition white light endoscopy, chromoendoscopy, and magnifying endoscopy have distinct roles in the detection of colorectal SSLs and are valuable in identifying the size, shape, character, risk degree, and potential malignant tendency. This article delves into the relevant factors influencing the detection rate of colorectal SSLs, reviews its characteristics under various endoscopic techniques, and expects to attract the attention of colonoscopists.

Key Words: Colorectal cancer; Sessile serrated lesions; Endoscopic features

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Core Tip: Because of its unique endoscopic patterns and behavior, sessile serrated lesions (SSLs) are easily missing during colonoscopy. SSL is a critical cause of interval colorectal cancer, so it is necessary to summarize the endoscopic features of the sessile serrated lesion to help endoscopists make a better identification and diagnosis.

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INTRODUCTION

Colorectal cancer (CRC) is a common gastrointestinal malignancy with the third-highest incidence and the second-highest mortality rate. In China, more than 550000 new cases were diagnosed and 280000 deaths took place in 2020[1], severely threatening people's lives and health. With the improvements in awareness concerning colonoscopic screening, the occurrence of interval CRC has garnered significant attention. Interval CRC refers to the CRC that is not detected during colorectal screening but discovered prior to the next recommended screening date[2]. The incidence of interval CRC is a vital indicator in assessing the quality of colonoscopic screening. Interval CRC detection in the proximal colon goes beyond being merely a test of the patient's bowel preparation since the colonoscopist's experience is also highly relevant.

Colorectal sessile serrated lesions (SSLs) are poorly defined and pale, covered with mucus, and hardly distinguishable from the surrounding mucosa. For endoscopists who lack awareness of the features of colorectal SSLs, missing or overlooking them becomes inevitable, resulting in the incidence of interval CRCs[3]. Related research observed that the occurrence of interval CRCs three years after colonoscopy was 3.4%-9.0%[2,4].

Colorectal SSLs may proceed to CRCs through the pathways of BRAF mutation, microsatellite instability, CpG island methylation, and the deletion gene of DNA damage repair[5]. It has been exhibited that a 15%-30% incidence of CRCs occurs *via* the serrated pathway, which is known as the vital cancer pathway[5,6].

UPDATE ON THE PATHOLOGICAL CLASSIFICATION OF SERRATED LESIONS

During the previous decade, related studies have generated a more accurate description of the pathogenesis of intestinal adenocarcinoma. Population-based screening for CRCs has led to a comprehensive understanding of precancerous lesions and established a foundation for investigating the molecular pathways and biological behaviors of cancerous lesions. Accordingly, WHO renamed the sessile serrated adenoma/polyp as SSLs, as these may be flat rather than polypoid, and the association with BRAF or KRAS mutation delineates two separate neoplastic pathways.

Currently, the categorization of gastrointestinal tumors classifies serrated lesions as Hyperplastic Polyps (HP), SSL, SSL with dysplasia (SSL-D), Traditional serrated adenomas (TSA), and serrated tubular villous adenoma (STVA)[7-9].

HP is a benign lesion, and the pathological features are primarily epithelial hyperplasia in the upper 2/3 of the saphenous fossa, forming small papillae protruding into the lumen of the saphenous fossa, which then gives the luminal surface a serrated shape. Based on the cell composition and molecular genetic alterations, the two types of HP are the Microvesicular type of Hyperplastic Polyp and the Goblet Cell-rich type of Hyperplastic Polyp. Generally, the TSA is pedicled and has villous structures but is potentially malignant[10-12]. In contrast to the conventional tubulovillous adenoma, STVA usually presents histological changes in advanced adenomas, and the glands are frequently serrated when high-grade dysplasia and invasive carcinoma appear.

The histological diagnosis of SSLs necessitates the detection of at least one abnormal crypt. By way of illustration, the entire saphenous fossa is serrated and grows horizontally along the mucosal muscular layer, the basal expansion, abnormal maturation, and asymmetric proliferation, in which asymmetric proliferation causes structural changes in the entire saphenous fossa. This is the fundamental difference from the HP[8]. Moreover, SSL-D is histologically heterogeneous. Its abnormal crypt structures—being its core feature—differ from the surrounding glands like the appearance of villous structures, which are longer and more crowded, complex branching, sieve-shaped crypt, and increased or decreased serration compared with the background SSL. The morphology of SSL-Ds is often tanglesome and mixed with different subtypes, making it challenging to distinguish the degree of heterogeneous hyperplasia.

COLORECTAL SSL-RELATED RISKS

It has been widely recognized that colorectal SSLs essentially differ from HPs, both with regard to morphological and pathological characteristics analysis, and instead behave comparably to neoplastic lesions with malignant potential.

Meta-analyses have demonstrated that SSLs are associated with an increased risk of concurrent progressive tumors. Patients with larger proximal colorectal serrated lesions are at significant risk and may require closer monitoring and further completion of a colon examination[13,14]. In light of this, a population-based, case-control study from Danish revealed that having an SSL was associated with 3-fold increased odds for CRC, while having SSL-D was associated with a nearly 5-fold increased odds for CRC[15,16].

Reports have confirmed that the risk of developing CRCs in cases with SSL-D is 4.4% within a decade, which is higher than that of conventional adenoma (2.3%). This highlights a significantly increased long-term risk of CRC in patients with SSL[16]. Similarly, correlative studies have found that SSLs have a mean duration of 7-15 years before developing SSL-Ds. Then, 3.03%-12.5% of SSLs develop into CRCs 5-7 years after follow-up[17,18]. However, SSL-Ds progress to CRCs at a much faster rate, and there are reports of SSL-Ds rapidly aggravating submucosal invasive carcinomas within one or two years[19-21].

FACTORS AFFECTING THE DETECTION OF COLORECTAL SSLS

As a critical influencing factor in the occurrence of interval CRCs, the detection rate of SSLs can effectively evaluate the quality of colonoscopy and assess the level of colonoscopists. A retrospective study that included more than 10000 colonoscopies found that bowel preparation, exit time, polyp diameter, and adenoma detection rate were linked to the SSL detection rate. Equally important, a multivariate analysis underlined that adenoma detection rate was an independent predictor of SSL detection rate, implying that patients who developed colorectal adenomas were at higher risk of complicating SSL[22].

Additionally, a colonoscopist's professional experience is vital to the timely and accurate detection of colorectal SSLs. Li *et al*[23] noted that different colonoscopists are independent risk factors for the detection rate of proximal colonic serrated lesions. It underscores that inexperienced colonoscopists detected serrated lesions at only 16%-83% compared with their experienced counterparts. They also found that proximal serrated polyps are more common in men over 50 years old.

ENDOSCOPIC FEATURES OF COLORECTAL SSLS

The development of an endoscopic technique delivers a reliable tool for detecting colorectal SSLs, which are not easily distinguishable from the background mucosa. To effectively prevent the incidence of interval CRCs, an early diagnosis and treatment of SSLs are crucial, thereby improving the quality of life and disease prognosis of patients.

Colorectal SSL characteristics under white light endoscopy

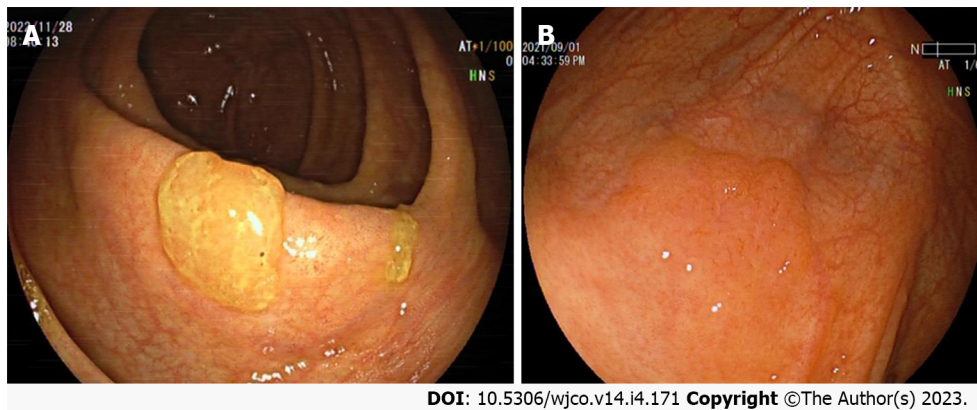
Colorectal SSL and SSL-D are prevalent in the proximal colon, usually > 5 mm in size, accounting for approximately 20%-25% of all serrated lesions. Additionally, colorectal SSLs often present with faint borders and a pale surface under white light endoscopy. Consequently, distinguishing them from the surrounding mucosa is difficult, making them prone to adverse events like missed or delayed diagnoses and incomplete resections. Most colorectal SSLs are accompanied by a mucus cap (Figure 1A), which, when flushed is not easily differentiated from HP. A further study also uncovered that inconspicuous borders and cloud-like surfaces are two independent diagnostic features of colorectal SSL in white light endoscopy[24-26]. Meanwhile, colorectal SSL-Ds are often associated with pedicled, bimodal appearance, central depression, and reddish color (Figure 1B), which can differentiate SSLs from SSL-Ds, with one of such features having a sensitivity of 97.7% and a specificity of 85.3% for the diagnosis of SSL-Ds[27].

Colorectal SSL characteristics under chromoendoscopy

Both HPs and SSLs are generally challenging and complex to identify when small (< 5 mm). To address this issue, the chromoendoscopy technique is adopted.

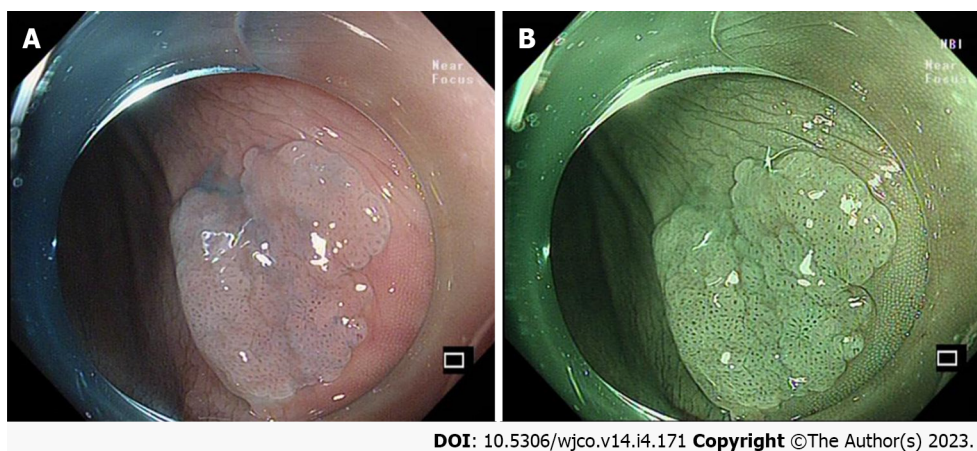
During endoscopy, chemical dyes (indigo carmine, crystalline violet, acetic acid, among several others) spray on the surface of the lesions, so the particles of the stains are deposited within the folds of the colorectal SSL lesion and surrounding mucosa. Then, the outlining of the lesion border and surface microstructure facilitates the assessment of SSL size and character.

It is important to note that acetic acid spray plays an important role in showing the borders and diameter of colorectal SSLs (Figure 2A). The surface morphology of the SSL is clearer and more easily



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Figure 1 White light endoscopic features of colorectal sessile serrated lesion cases. A: The sessile serrated lesions (SSLs) case with mucus cap under white light endoscopy; B: The borders of SSLs are not clearly distinguishable from the surrounding mucosa, and the morphology are cloud-like surface under white light. The above figure shows a case of SSL-D which has a reddish surface and a central depression.



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Figure 2 Endoscopic features of the colorectal sessile serrated lesion case after acetic acid spray. A: The border of the sessile serrated lesions (SSLs) is clearly revealed under acetic acid spray; B: The combined application of acetic acid spray and narrow band imaging can clearly show the borders and surface microstructure of SSLs, which is more conducive to endoscopic treatment.

described after acetic acid spray, and its useful in better delineation of the recurrent colorectal SSL[28-30]. In addition, it has been demonstrated that acetic acid spray can help endoscopists perform cold resection of colorectal SSLs more accurately[31] (Figure 2B).

One study classified the chromoendoscopy images of the surface glands of more than 300 SSLs and indicated that open Type II (Pit II-O) structures, compared with the conventional Pit II type glands opening pattern, were endoscopic characteristics in colorectal SSLs[24]. Moreover, the opening pattern of the Pit II-O gland is similar to that of Pit II, and the former is typically surrounded by the latter, but the former features an expanded and more rounded shape, reflecting the expansion of the SSL crypt (Figure 3).

The image enhanced endoscopy (IEE) is the most common mode of electronic staining used in colonoscopy. Narrow band imaging (NBI) is a widely used IEE, which utilizes a filter to screen the broadband spectrum of the red, blue, and green light emitted by the light source, leaving only the narrowband spectrum for the diagnosis of various digestive disorders. Linked color imaging and blue laser imaging (BLI) are the next-generation IEEs, considering that their imaging principle is founded on light absorption and reflection by the mucosa of the digestive tract. Then, the lesions appear in a different color from the surrounding tissues, yielding a clear distinction between the superficial mucosal microvasculature and microstructure. It is also worth noting that the IEE has a brighter and higher resolution and is known as the "electron chromatography" technique given that the image observed by the IEE resembles a dye-stained image.

Furthermore, the NBI pattern enhances the visibility of colorectal SSLs with a mucus cap and gives it a concentrated red color that contrasts more prominently with the background mucosa[32] (Figure 4A). Also, both the NBI and BLI generally feature small black spots within the glandular opening of SSLs (Figure 4B), which is a critical histological feature within dependent diagnostic value that aids the endoscopist to differentiate SSLs from HPs during colonoscopy[25,33]. It has been confirmed that

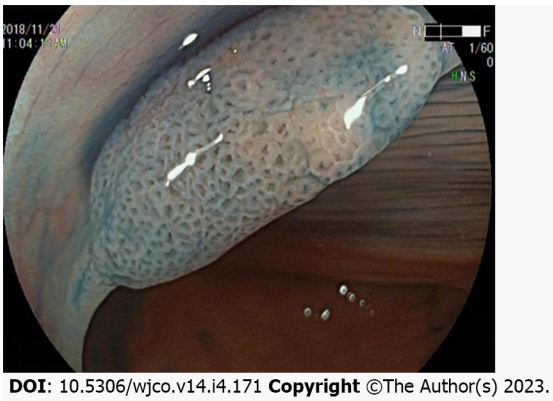


Figure 3 Endoscopic features of the colorectal sessile serrated lesion case after indigo carmine spray. The opening pattern of the Pit II-O gland, features an expanded and more rounded shape, dilation of the colorectal sessile serrated lesion surface crypt.

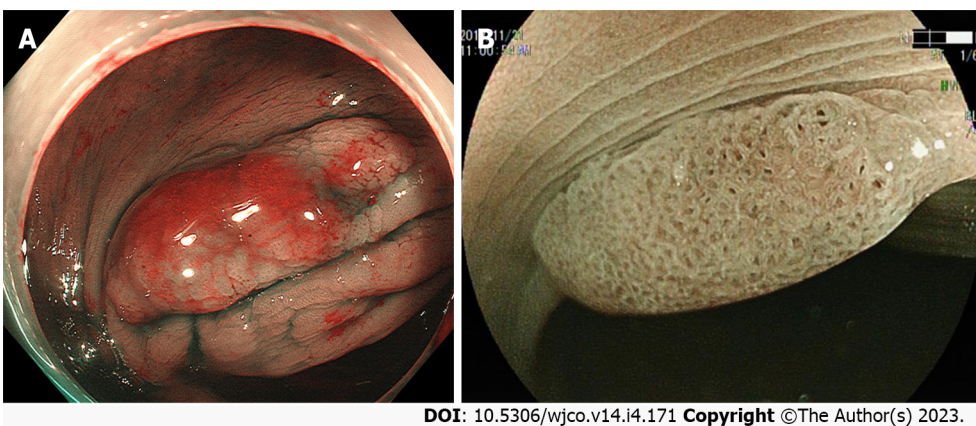


Figure 4 Endoscopic features of colorectal sessile serrated lesion cases under narrow band imaging mode. A: The mucus cap of sessile serrated lesions (SSLs) shows a brick-red appearance under narrow band imaging (NBI); B: The expansion of the surface crypt in the SSLs shows a black spot under NBI.

dilated and branching vessels in NBI endoscopy differs from the vascular surrounding superficial mucosal glands, and irregular capillaries may be observed at sites of colorectal SSL that show dysplasia [3,34,35].

Additional research showed that the multivariate analysis of the location (proximal colon), size (≥ 10 mm), glandular opening, and microvascular morphology of the serrated lesions exhibited more than 90% positive diagnosis of the SSL, which was 2.3 times more advantageous than its single factor diagnosis[36,37].

Colorectal SSL characteristics under magnified endoscopy

In identifying neoplastic and non-neoplastic lesions, the value of magnified endoscopy combined with chromoscopy has been extensively evident. Close observation of the surface pattern of lesions with a specific combination can effectively predict its pathological characteristics and even the depth of invasion. Relevant literature has demonstrated that Type II-O glands can be used as an indicator to differentiate between SSLs and HPs. The Pit II-O glands also suggest histological variation in the morphology of colorectal SSL glands, significantly boosting the accuracy of diagnosing SSLs[38]. For large colorectal SSLs, magnified endoscopic findings of not only Type II-O glands but also those possibly mixed with Types IIIL, IV, Vi, and Vn glands at the same time often prompt SSL-Ds or cancers [24,27] (Figure 5A).

Magnified endoscopy combined with IEE can further develop the visualization of microvessels (Figure 5B). The varicose microvessels, running through the deep layer of mucosa, on the lesion surface of colorectal SSL, differ from those around the mucosal glands[37]. A similar study in China pointed out a statistical difference between magnified endoscopy and chromic endoscopy for varicose microvessels in predicting colorectal SSLs and HPs[35].

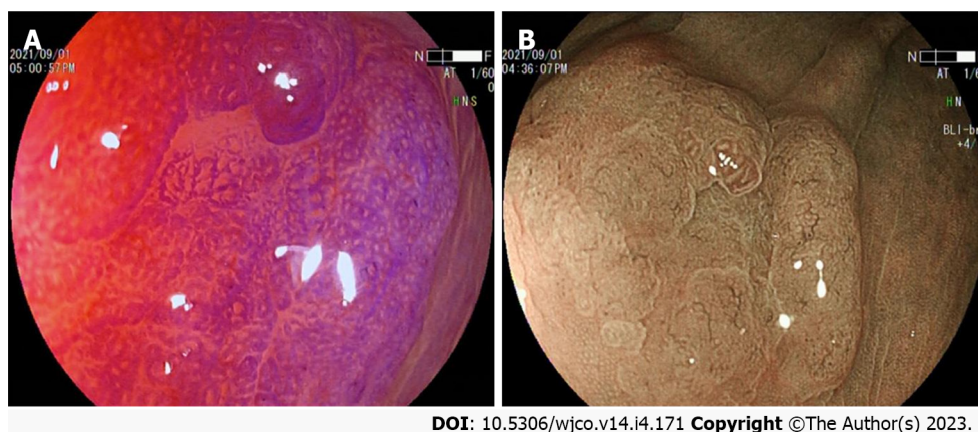


Figure 5 Endoscopic features of the colorectal sessile serrated lesion case under chromoscopy combined with magnified endoscopy. A: Crystalline violet spray makes the surface glandular structure of colorectal sessile serrated lesions (SSLs) more visible, and combined with magnified endoscopic observation is useful for inferring the pathological characteristics of the lesion; B: Blue light imaging combined with magnified endoscopic observation of the microstructure of the SSL surface revealed that the SSL-D case have a Pit III and/or Pit IV type of glandular duct opening pattern based on Pit II-O, and varicose microvessels on the surface of the lesion are found.

CONCLUSION

Colorectal SSL is potentially malignant and has a higher risk of malignancy than conventional tubular adenomas, thereby making an immediate diagnosis or early detection in colonoscopic screening especially important. However, the current diagnosis of SSLs in screening colonoscopy is undeniably insufficiently high and often depends on the histopathological diagnosis post-biopsy or resection. With advances in endoscopy equipment and imaging techniques, we have witnessed the role of cytoendoscopy in diagnosing gastrointestinal tract tumors[39]. In the future, we hope to discover a more objective and accurate factor in order to characterize the endoscopic presentation of colorectal SSLs, which can swiftly and efficiently identify lesions, reduce missed or delayed diagnoses, and effectively decrease the incidence of interval CRCs.

For colorectal SSLs, good bowel preparation is the foundation, and the endoscopist's knowledge and experience play an essential role. Ultimately, combining all the predictive factors in colonoscopy screening to generate an immediate diagnosis can improve the detection rate.

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