ENDOSCOPIC MANAGEMENT OF SESSILE SERRATED POLYPS OF THE COLON

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INTRODUCTION

The scope of this short review is to discuss the current state of practice in detection and removal of sessile serrated polyps (SSPs) during colonoscopy and the post-polypectomy management. SSPs are an important contributor to both sporadic and interval colorectal cancers.[1] The malignant pathogenesis of serrated polyps arises from a molecular pathway alternate to conventional tubular adenomas known as the serrated neoplasia pathway.[2-4] Polyp progression to cancer by this pathway can be rapid. An estimated 20% of all sporadic colorectal cancers but a significantly higher rate of interval cancers arise through the serrated neoplasia pathway.[5,6] Colorectal cancers arising from SSPs are characterised by *BRAF* gene mutation, CpG island hypermethylation in the promotor regions of tumour suppressor genes (i.e. the CpG island methylator phenotype [CIMP]), and microsatellite instability.[1] Moreover, it has been reported that interval colorectal cancers are more likely to exhibit microsatellite instability than non-interval colorectal cancers.[2] Therefore, SSPs are considered to be the most potent candidate lesions of interval colorectal cancers.

Serrated polyps can be categorised into three major subtypes including hyperplastic polyp (HP), traditional serrated adenoma (TSA), and SSP.[7] True HPs are the most common, often diminutive in size and distally located, and thought to pose little risk for further neoplastic progression. Conversely, SSPs, which account for up to 12% of all polyps in an asymptomatic average risk population, have the potential to progress toward dysplasia and malignancy.[8] The extent to which HPs of the right colon (distinct from SSPs) harbour risk for advanced neoplasia is not well defined at this time.

There are two categories of serrated polyps associated with cytological dysplasia. These include: i) SSP with cytological dysplasia and ii) TSA. TSAs were previously known by the term 'serrated adenoma' and considered a variant of conventional tubular adenomas.[4] TSAs are very rare (comprising <1% of all polyps), villiform in histology, and contain premalignant dysplastic features.

PATIENT ASSESSMENT

SSPs appear to be more common in Caucasians and women, contrary to trends seen with conventional tubular adenomas.[9-11] In addition, advanced age, tobacco use, and a higher body mass index have been reported to increase the risk of SSP presence.[12,13]

Serrated polyposis syndrome, previously known as hyperplastic polyposis syndrome, should be considered when multiple serrated polyps are present, especially if proximally located and large in size. The World Health Organization (WHO) defines serrated polyposis syndrome as fulfillment of any of the following criteria: i) at least five serrated polyps proximal to sigmoid, with two or more ≥10 mm; ii) any number of serrated polyps proximal to sigmoid colon with a first-degree relative with serrated polyposis syndrome; and iii) >20 serrated polyps of any size throughout the colon.[7] Serrated polyposis syndrome is associated with an approximately 50% lifetime risk of developing colorectal cancer.[14] Additionally, first-degree relatives of patients with serrated polyposis syndrome have also been shown to have an increased risk of colorectal cancer.

DETECTION UPON COLONOSCOPY

The endoscopic identification of SSP involves careful attention to key features. SSPs are usually

found in the proximal colon. Macroscopically these lesions are flat and can be easily missed due to their subtle appearance with poorly demarcated borders, asymmetric shape, pale colour, and mucus cap on surface.[15-17] There is wide variability in serrated detection rates between colonoscopists likely due to the relatively subtle characteristics of many of these lesions.

Kimura et al.[18] showed that *BRAF* mutation and CIMP-positive serrated lesions have a specific endoscopic pit pattern upon magnification endoscopy referred to as a Type II-O pattern. The pits of the Type II-O pattern have a round open appearance and correspond to dark spots inside the crypts in narrow-band imaging (NBI). Although Type II-O pits may not improve the detection rates of SSPs, they may be useful for distinguishing between SSPs and HPs. How this uniquely described pit pattern upon magnification endoscopy could enhance lesion recognition in typical endoscopic practice is not yet defined.

Detection of proximal serrated lesions has been shown to highly correlate with adenoma detection rates (ADR). One study found the serrated detection rate among experienced gastroenterologists to be between 0% and 2.2%, while another reported a range of 1–18% among 15 endoscopists at a single centre.[19,20] A Japanese prospective study[21] observed a SSP prevalence of at least 5%, while another study found an overall SSP prevalence of 8.1% by a single experienced colonoscopist.[8] Based on ADR targets, Kahi et al.[19] have suggested an equivalent proximal serrated detection rate of 4.5% for both men and women. While there are conflicting results on the effect of NBI compared with white light endoscopy (WLE) on serrated polyp detection, Horimatsu et al.[22] found a significantly higher rate of overall colonic polyp detection with the use of next-generation NBI.

OPTICAL DIAGNOSIS DURING COLONOSCOPY

Hazewinkel et al.[23] derived a systematic validation of specific endoscopic features of SSP using high-resolution WLE and NBI. They determined that the presence of both an indistinctive border and cloud-like surface on high-resolution WLE led to a 77% accuracy in identifying SSP. On NBI, the presence of indistinctive borders, cloud-like surface, irregular shape, and dark spots inside the crypts were independent predictors of SSP histology in multivariate analysis. When all four characteristics were present, this led to an impressive 89% sensitivity, 96% specificity, and 93% accuracy. Furthermore, another study found that dilated and branching vessels during NBI with optical magnification can be a unique feature of SSP and improve positive predictive value.[24] These image enhanced endoscopy features hold potential promises as teachable methods in improving detection of SSP. Further work on describing how interventions might improve SSP detection is needed.

There has been attention to promote cost-effective measures in colonoscopy screening and surveillance including the utilisation of optical diagnosis in implementing a 'resect and discard' strategy for diminutive polyps.[25] The NBI International Colorectal Endoscopic (NICE) classification was developed as a tool for real-time endoscopic assessment of colorectal polyp histology.[26] However it was not designed to differentiate SSPs, but rather HPs, from adenomatous polyps. Kumar et al.[27] found that nearly one-third of SSPs were misinterpreted as HP by community gastroenterologists using the NICE classification. Sano et al.[21] observed an overall 2.7% proportion of SSP in endoscopically diagnosed HPs, with higher rates in the proximal colon and with increasing size.

Recently, IJspeert et al.[28] developed a promising new classification system for optical differentiation of adenomas, HPs, and SSP known as the Workgroup serrAted polypS and Polyposis (WASP) classification. This new classification is a stepwise approach starting with the NICE classification and then incorporating SSP features as described by Hazewinkel et al.[23] When gastroenterologists completed a short training module on the use of the WASP classification, there was a significant increase in accuracy of optical diagnosis overall as well as with SSPs specifically, and the results were sustainable after 6 months.[29]

RESECTION DURING COLONOSCOPY

The prevention of serrated pathway interval cancers requires the complete resection of premalignant lesions. Pohl et al.[30] showed a high rate of incomplete resection with serrated polyps compared with conventional adenomas in the CARE study. SSPs are hypovascular, which makes cold snare polypectomy a safe and effective method of resection for small SSP.[31,32] Endoscopic

mucosal resection (EMR) has become the widely adopted technique for resection of larger lesions. EMR involves submucosal lifting to promote a complete and safe *en bloc* resection.[33] A recent prospective multicentre study evaluated the use of dye-based conventional EMR technique for large laterally spreading lesions greater than 20 mm in size. Pellise et al.[34] found an increased risk of recurrence in conventional adenomatous lesions versus SSPs in the subgroup of 20–25 mm polyps, however the difference was not sustained in the larger subgroups. Large SSP lesions were easier to remove with a similar safety profile compared to adenomatous lesions. This study suggests that standardised dye-based EMR can be a safe and effective mode of resection for large SSPs though this can be technically challenging. Further work in defining how polypectomy techniques can be taught to ensure complete *en bloc* resection is needed.

It is our practice to carefully examine the colon for loss of vascularity and mucus cap where SSPs may be found. Upon finding an area of concern, we use NBI to identify and confirm features consistent with an SSP, as described by Hazewinkel et al.,[23] including irregular shape, cloud-like surface, and dark spots inside crypts. Small lesions (between 6 mm and 10 mm in size) are removed by cautery with a stiff snare. Once there is a high level of confidence for the presence of an SSP and the lesion is ≥1 cm in size, then a dilute indigo carmine solution is injected to create a submucosal cushion and lift the lesion. Frequently the submucosal injectate allows for improved visualisation of the margins of the lesion. With larger lesions, we may opt to use soft coagulation current (using the tip of snare or argon plasma coagulation [APC]) to liberally mark the outer borders of the lesion to ensure complete resection. We usually utilise 'endocut' for resection of these often flat lesions of the right colon to minimise complication risk. In order to minimise post-resection fragmentation of SSP margins, which would limit pathology interpretation assessment of complete resection, we remove larger SSP with retrieval nets rather than attempting retrieval through the suction channel of the colonoscope.

PATHOLOGIC IDENTIFICATION

Beyond the challenges of SSP detection and resection is the appropriate pathologic identification and classification of these lesions, which has implications on timing of follow-up colonoscopy. SSPs are termed histologically from the jaggedness created by in-folding of the crypt endothelium leading to a saw-tooth appearance. The most important histologic features used to define SSPs are the presence of inverted T or L-shaped crypt bases along with hyperserration and columnar dilatation extending into the lower third of the crypts.[4] This abnormal crypt architecture and irregular proliferation differentiate it from typical HPs. TSAs can be recognised by its villiform histology, eosinophilic cytoplasm, and ectopic crypt formation.

Several studies have reported only fair-to-moderate inter-observer concordance among pathologists in distinguishing SSPs from typical HPs.[20,35-37] One study found that large right-sided HPs were reclassified as SSPs in 30–85% of cases upon pathology reinterpretation.[35] Given this variation in interpretation between pathologists, some experts recommend that all serrated lesions ≥10 mm found in the proximal colon be considered SSPs.[38] There is often less misidentification between SSPs and TSAs.[39]

FOLLOW-UP RECOMMENDATIONS

Patients with serrated polyps are at increased risk for synchronous advanced neoplasia and development of neoplasia during surveillance. Large serrated polyps are strongly and independently associated with synchronous advanced neoplasia[13,40] and the risk of colorectal cancer, specifically cancer in the proximal colon.[41] In a meta-analysis, the pooled odds ratio (OR) of synchronous advanced neoplasia for patients with proximal serrated polyps was 2.77 (95% confidence interval [CI]: 1.71–4.46) and with large serrated polyps the OR was 4.10 (95% CI: 2.69–6.26).[42]

There is limited data on the risk of advanced neoplasia on follow-up or surveillance colonoscopy. Schreiner et al.[13] found that patients with advanced adenomas and a concurrent non-dysplastic serrated lesion at baseline have a higher rate of neoplasia and advanced neoplasia compared with patients with advanced adenomas alone. The correlation between proximal large serrated polyps with the occurrence of proximal neoplasia and colorectal cancer suggests a potential common genetic and epigenetic change in the normal colonic mucosa leading to a field defect.[41]

Given the above findings, the US Multi-Society Task Force (USMSTF) first incorporated guidance on post-polypectomy surveillance of serrated lesions in 2012.[43,44] SSPs without cytological dysplasia are, in general, to be managed similarly to conventional tubular adenomas. A 3-year surveillance interval is suggested in patients with high-risk factors including ≥10 mm in size or more than one to two in number. Patients with low-risk SSPs (one to two polyps, each less than 10 mm in size) are recommended a 5-year surveillance interval. The presence of cytological dysplasia confers a more rapid malignant potential and thus should be followed for 1–3 years. A TSA should have an interval colonoscopy every 3 years per USMSTF, or every 3–5 years depending on size per expert consensus. Patients with SSP should be followed annually. Follow-up colonoscopy is generally recommended at a shortened interval (<1 year) if there is any concern about completeness of resection of any neoplastic lesion or poor bowel preparation obscuring visibility.

It is important to recognise that these recommendations were developed based on limited available evidence and that further surveillance studies are much needed. Our group has shown evidence to support a shorter surveillance interval in patients with 'low-risk' SSPs as their risk for development of advanced neoplasia is greater than that observed with low-risk conventional tubular adenomas.[45]

FUTURE DIRECTIONS

In summary, SSPs have gained increasing recognition as an important contributor to interval colorectal cancers. In current endoscopic practice, there is wide variation in reported detection rates of SSPs. Further investigation should be pursued to improve endoscopic detection, complete and safe resection, and determine optimal management and surveillance intervals. Future studies to determine biomarkers for premalignant serrated lesions may also lead to better clinical outcomes. While there are multiple studies demonstrating improved ADRs with implementation of ADR monitoring programmes, correlate results in serrated detection rates are currently not well-described.[29,46] We recommend that colonoscopists begin to monitor their SSP detection rates as an initial first step to improving detection. Teachable methodologies and interventions to improve SSP detection and removal are important areas of further study.

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