Serrated lesions and hyperplastic (serrated) polyposis relationship with colorectal cancer: classification and surveillance recommendations

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Colorectal carcinoma (CRC) is the third most commonly diagnosed cancer and the third leading cause of cancer death in both sexes in the United States.\(^1\) However, in Central and Eastern Europe, CRC has recently become the second most common cancer, after lung cancer in men and breast cancer in women.\(^2\) In the past decade, there has been unprecedented progress in reducing the CRC incidence and death rates in the United States, mainly because the prevention and detection of CRC through screening increases the likelihood that an earlier stage of CRC will be detected, which is more likely to be cured.\(^3\)

Until the end of the previous century, there was only a 2-tiered classification of epithelial colorectal polyps: non-neoplastic hyperplastic polyps (HPs) and neoplastic adenomas (tubular, tubulovillous, villous)\(^4\) (Fig. 1). The distinctive feature of adenomas was the presence of cytologic dysplasia/intraepithelial neoplasia, and only adenomas were regarded as precursors of CRC.\(^5\) Jass\(^6\) was the first one brave enough to defy the existing opinions by proposing a revolutionary hypothesis of the relationship between HPs and CRC in 1983. The many years of intensive studies have entitled Jass et al.\(^7,8\) to propose a new theory called the HP–carcinoma sequence, contrary to the adenoma-carcinoma sequence, which was accepted many years ago.\(^5,9\) Currently, both theories are widely accepted but are considered responsible for different genetic pathways of CRC development.

SERRATED LESIONS

Since the early 1990s, HPs have been recognized as representing a heterogeneous group of polyps with a serrated morphology, and, moreover, some of them turned out to exhibit a significant risk for neoplastic progression.

Approximately 90% of CRCs start to develop from a benign polyp; however, relatively small, nonpolypoid flat and depressed lesions were described in the mid-1980s and 1990s.\(^10-12\) Because of the variable shape of CRC premalignant precursors, the word polyp has been recently superseded by the word lesion in the serrated polyp group.\(^13-15\)

There is now strong evidence that HPs and other representatives of the serrated lesions group might serve as the precursors for approximately 15% to slightly more than 20% of sporadic or nonsyndromic CRC, particularly in the proximal colon.\(^16,17\)

Serrated lesions are frequently flat or sessile, subtle, located in the proximal colon, and may be overlooked during colonoscopy by the endoscopist. Although previous studies have reported significant variation in the detection of adenomas by endoscopists, one of the first studies specifically evaluating this variation concerning serrated lesion detection was reported in 2010.\(^18\) There are numerous figures with endoscopic examples of proximal serrated lesions seen on white-light and narrow-band imaging (NBI) attached as supplementary material to the editorial on the latter report.\(^15\) On the other hand, the variability of serrated lesion diagnoses given by pathologists is still greater than expected, mainly due to frequently changing classifications and a huge amount of synonyms used in the previous literature.\(^20\) Poor interpathologist reproducibility of sessile serrated lesion diagnoses was reported in 2009 and was concerned not only with nonspecialist pathologists but with GI pathologists as well.\(^21\) Reproducibility has improved to moderate (overall \(\kappa = 0.557\)) in 2012, in the most recent study on serrated lesions performed by members of the Digestive Diseases Working Group of European Society of Pathology,\(^22\) especially when the new World Health Organization classification was introduced in 2010\(^23\), the most reproducible and discriminative criteria for each serrated polyp type were defined by these authors.\(^22\)

Major limitations of colonoscopy as a tool for preventing CRC include variable lesion detection rates responsible for missed or persistent lesions that may give rise to interval CRC.\(^24\) Cancers developing after colonoscopy are more
likely to be right sided, high microsatellite instability (MSI), and the high-level CpG island methylator phenotype, suggesting that missed serrated lesions may be a major reason for the relative failure of colonoscopy to protect against right-sided CRC.\textsuperscript{25,26} The aim of this review is to emphasize the need of close cooperation between endoscopists and pathologists to better overcome all the difficulties for our patients’ benefit.

### SERRATED LESIONS HISTOLOGIC CLASSIFICATION

One of the most simplified histologic classification systems of serrated lesions (previously named serrated polyps\textsuperscript{27}) includes the following entities\textsuperscript{13-15}: HP, sessile serrated lesion, traditional serrated adenoma (TSA), and mixed polyp.

Serrated lesions demonstrate serrated or “sawtoothed” features on a histologic section because of infolding of the crypt epithelium (Fig. 1B).

The diagnostic criteria and nomenclature for these lesions are not uniform and therefore somewhat confusing. In 2009, 2 histological classifications of serrated lesions were published\textsuperscript{28,29} and cited together in 2010.\textsuperscript{20} Odze and Hornick,\textsuperscript{28} according to Jass et al,\textsuperscript{30} created essential order by dividing all serrated lesions into 2 separate subgroups depending on whether dysplasia is present. Their classification is compared with the classification published by the recent World Health Organization\textsuperscript{23} in Table 1.

### HYPERPLASTIC POLYP

HPs are the most common serrated lesions, accounting for more than 75% of all serrated polyps,\textsuperscript{23} but only 10% to 12.5% of asymptomatic patients.\textsuperscript{31,32} They are common in the rectosigmoid area, where they are considered innocuous lesions. However, it was shown that all types of distal polyps, including HPs, are associated with an increased risk of proximal large serrated lesions.\textsuperscript{33} Microscopically, they...
are built from nondysplastic epithelium with infolded tufts that impart its sawtooth, serrated outline limited to the upper half of the crypt, whereas the deeper parts appear straight and tubular (Fig. 2A). The proliferative zone is restricted to the lower half of the crypt. The nuclei are small, round, and regular. HPs were further subclassified based on the mucin characteristics of lining epithelium into microvesicular HPs, goblet cell-rich HPs, and mucin-poor HP variants. Although they differ slightly in terms of distribution and molecular characteristics, currently, routine subclassification, although feasible, has not been shown to be clinically beneficial.

Features of “high-risk” HPs include multiplicity (>20), large size (>10 mm), proximal location, and a family history of CRC. It is worth emphasizing that when an endoscopist encounters a large, pale-appearing lesion suggestive of a hyperplastic one, complete resection should be pursued. If the lesion is too large for conventional polypectomy, an advanced technique such as EMR is required.

**SESSILE SERRATED LESION** *(SESSILE SERRATED ADENOMA/POLYP)*

An endoscopic and histologic diagnosis of a sessile serrated lesion (sessile serrated adenoma/polyp [SSA/P]) is often misdiagnosed as HP. One should think of SSA/P, especially if a pale-appearing lesion covered by a mucus cap is endoscopically seen. The mucus can cause the polyps to appear yellow or rust colored. One of the requirements for making the proper diagnosis of a sessile serrated lesion is resection of the entire polyp. Moreover, it may only be settled properly, providing that biopsies are not superficial or tangentially cut, and slides are prepared from a well-oriented specimen that enables an estimation of the longitudinally sectioned crypts. SSA/Ps are representative of 2 subtypes according to whether cytologic dysplasia is present (Table 1) and are placed in the separate categories of nondysplastic and dysplastic when they are called SSA/Ps with dysplasia. The main distinctive feature of a sessile serrated lesion is the presence of a disorganized and distorted crypt growth pattern with budding, branching, and basal dilation, which leads to the formation of T- or L-shaped basally located structures. Various degrees of nuclear atypia, such as vesicular, round, oval, and columnar nuclei with prominent nucleoli and mitoses in the upper half of the crypts can also be of value (Fig. 2B,C).

An SSA/P with focal cytological dysplasia, similar to that seen in a conventional adenoma, represents progression toward carcinoma. Areas of conventional adenomatous dysplasia (low- or high-grade) may be seen (Fig. 2D). Another form of dysplasia, which is referred to as serrated dysplasia with more cuboidal cells, eosinophilic cytoplasm, and more vesicular nuclei, is rarely observed. The behavior of these lesions may be more aggressive than that of a conventional adenoma.

### Table 1. Comparison of 2 current histopathological classifications of serrated polyps/lesions according to Odze and Hornick and Snover et al

<table>
<thead>
<tr>
<th>Odze and Hornick 2009: type and synonym</th>
<th>Snover et al: type and synonym</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Nondysplastic</td>
<td></td>
</tr>
<tr>
<td>A. Normal architecture, normal proliferation</td>
<td>Hyperplastic/metaplastic polyp</td>
</tr>
<tr>
<td></td>
<td>Microvesicular hyperplastic polyp</td>
</tr>
<tr>
<td></td>
<td>Goblet cell hyperplastic polyp</td>
</tr>
<tr>
<td>B. Abnormal architecture, abnormal proliferation</td>
<td>Sessile serrated adenoma/polyp</td>
</tr>
<tr>
<td></td>
<td>serrated polyp with abnormal proliferation</td>
</tr>
<tr>
<td>II. Dysplastic</td>
<td></td>
</tr>
<tr>
<td>A. Serrated adenoma (traditional)</td>
<td>Traditional serrated adenoma</td>
</tr>
<tr>
<td></td>
<td>serrated adenoma</td>
</tr>
<tr>
<td></td>
<td>filiform serrated adenoma</td>
</tr>
<tr>
<td>B. Sessile serrated polyp with dysplasia</td>
<td>Sessile serrated adenoma/polyp</td>
</tr>
<tr>
<td></td>
<td>with dysplasia</td>
</tr>
<tr>
<td></td>
<td>mixed hyperplastic-adenomatous polyp</td>
</tr>
<tr>
<td></td>
<td>advanced sessile serrated adenoma</td>
</tr>
<tr>
<td>C. Conventional adenoma with serrated architecture</td>
<td></td>
</tr>
</tbody>
</table>

**SESSILE SERRATED LESION** *(SESSILE SERRATED ADENOMA/POLYP)*

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SSA/P proper pathologic assessment, regardless of the presence or absence of cytologic dysplasia, is vital to determining the proper surveillance interval.

The term sessile serrated lesion should replace the previous names sessile serrated polyp or sessile serrated adenoma, used even in recently published reports. The word adenoma is the most misleading because one of the subtypes of SSA/P does not display dysplasia, which formerly was an obligatory hallmark of conventional adenomas. However, in contrast to HPs, right-sided, large (≥10 mm) sessile serrated lesions might be particularly prone to CRC progression.

A statistically significant age difference (P < .001) between patients with SSA/P with focal low-grade dysplasia, high-grade dysplasia, or carcinoma was recently found. In summary, the time course of more than 10 to 15 years between SSA/P transforming to CRC was 2 to 3 times longer than that of the conventional adenoma-carcinoma sequence, which contrasts with hitherto existing opinions on more aggressive behavior of sessile serrated lesions than that of conventional adenoma.

TRADITIONAL SERRATED ADENOMA

This lesion, first defined as a serrated adenoma, is mostly located in the rectosigmoid area but has a predisposition for larger lesions (>10 mm) involving the right side of the colon. They account for only 0.6% to 1.3% of all colorectal polyps and 1.7% of all adenomas. A relatively high proportion of CRCs (5.8%) include residual TSAs. Although endoscopically more often described as pedunculated than sessile, they were also found in 1.2% to 12.2% of the other flat or carpet-like neoplastic lesions. The prominent serrated, sawtooth epithelium with an abundant and eosinophilic cytoplasm is characterized by low- or high-grade dysplasia, with low-grade dysplasia being the most frequent. Two types of dysplasia may be observed: conventional adenoma-like type or serrated type. Premature crypts perpendicular to the longitudinal axis of the villi, called an ectopic crypt formation, are distinctive. They should be completely resected, if possible, even when presenting as benign on endoscopy.

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MIXED POLYP (SSA/P WITH DYSPLASIA)

Mixed polyps, synonymous with SSA/P with dysplasia, combine serrated and dysplastic features. The first mixed hyperplastic/adenomatous polyp with a focal adenocarcinoma was described in 1984. Since then, in
more large, especially proximally located HPs, dysplastic and even carcinomatous focal changes have been reported.\textsuperscript{44,61-64} and, on the other hand, hyperplastic areas were revealed in 9.6% of conventional adenomas\textsuperscript{47,64} (Fig. 2G,H).

Varied histologic components, such as HP, traditional serrated adenoma, or conventional adenoma, might be intermingled in SSA/P with dysplasia.\textsuperscript{50,65} The term mixed polyp is recently discouraged because it does not convey the concept that combined features represent progression of SSA/P to carcinoma.\textsuperscript{23,55}

**HYPERPLASTIC/SERRATED POLYPOSY**

Hyperplastic polyposis was first described as a metaplastic polyposis more than 30 years ago\textsuperscript{66} with the suggestion that at least 100 polyps should be sufficient to mimic familial adenomatous polyposis. The authors claimed that hyperplastic polyposis has no pathologic significance, is not a precancerous lesion, and does not have an observed familial distribution. However, subsequent reports have shown relatively low polyp numbers, large HPs, a family history, and an association of hyperplastic polyposis with CRC.\textsuperscript{67-71}

The criteria for the diagnosis of hyperplastic polyposis, recently renamed serrated polyposis,\textsuperscript{56} published by the World Health Organization\textsuperscript{23} and the National Comprehensive Cancer Network (NCCN)\textsuperscript{72-74} are as follows: 1. At least 5 histologically diagnosed HPs proximal to the sigmoid colon, of which 2 are larger than 10 mm in diameter, or 2. Any number of HPs occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic/serrated polyposis (HPSP), or 3. More than 20 HPs of any size but distributed throughout the colon.

HPSP is a rare entity, with an overall incidence of 1 in 100,000.\textsuperscript{75,76} However, because of an erroneous interpretation of an abstract on hyperplastic polyposis published in 2001,\textsuperscript{77} its highly exaggerated prevalence of 1 in 3000 in the general population was cited\textsuperscript{78,79} but, fortunately, this was recently explained.\textsuperscript{80} Review of the available literature from 1977 to the end of 2009 showed that in the period of 33 years, only 308 HPSP cases (9 per year) were described.\textsuperscript{80}

Patients with untreated HPSP are reported to be at a substantially increased risk of CRC, varying from 0% to more than 50% but persistently reported as greater than 50%. Admittedly, CRC was diagnosed in 122 of 308 HPSP patients (39.6%) described until 2009\textsuperscript{80} but a preliminary analysis of 41 of 124 of these HPSP patients reported as of 2004 showed that this rate might depend on the method of patient selection.\textsuperscript{81} CRC rates were as follows: 1. 1 of 15 asymptomatic individuals (6.6%) in whom CRC and/or HPSP were discovered during colonoscopy-based screening program • 26 of 57 patients (45.6%) whose CRC and/or HPSP were found incidentally at diagnostic colonoscopy because of different clinical symptoms such as acute large bowel obstruction, diffuse abdominal pain or discomfort, weight loss, increase in bowel movements or moderate obstruction, severe anemia, and rectal bleeding or melena episodes

- 14 of 17 colectomy or hemicolectomy specimens (82.3%) removed from patients who had biopsy-proven invasive CRC in whom HPSP was discovered coincidentally with CRC during pathologic gross examination

The last value concerning CRC/HPSP rate in colectomy specimens was confirmed in another study.\textsuperscript{82}

Thus, the overall high CRC prevalence in HPSP is probably somewhat exaggerated and does not correspond to facts. However, although HPSP is considered rare, it may be underrecognized, largely because most patients are asymptomatic unless HPSP is associated with malignancy.

Moreover, analysis of the association between CRC and HPSP does not prove that cancers originate exclusively in an HP.\textsuperscript{16} Another coexisting polyp with dysplastic elements, such as traditional serrated polyph, mixed polyph, and conventional adenoma, increases the risk of CRC and might be the likely origin of CRC.\textsuperscript{59,83-86}

The existence of 2 clinical variants of HPSP was described\textsuperscript{23,87,88}: 1. Type 1: serrated adenomatous polyposis with a mixture of mutiple and large sessile serrated lesions, TSAs, mixed polyps, HPs, and even conventional adenomas, which are associated with a significant risk of CRC.\textsuperscript{59} 2. Type 2: HPSP comprising numerous small (usually ≤5 mm), classic HPs with little risk of malignancy.\textsuperscript{66,71}

In 2010, the risk of CRC developing in HPSP was reported by Boparai et al\textsuperscript{78,82} in 77 patients during follow-up and in 347 HPSP first-degree relatives. These were the most numerous groups ever studied compared with the follow-up of only 43 of 308 HPSP patients and only 29 of 308 HPSP patients whose first-degree relatives were screened in the available literature concerning HPSP published during the period 1977 through 2009.\textsuperscript{80,87,89-91}

**JASS SYNDROME**

Jass et al\textsuperscript{92} and Jeevratnam et al\textsuperscript{93} were the first to describe a variant of familial serrated neoplasia, referred to as Jass syndrome.\textsuperscript{94} A familial clustering of CRC was identified later in a group of 11 MSI-variable CRC families described in 2005 by Young et al,\textsuperscript{95} in whom there was evidence that the genetic predisposition to autosomal dominant CRC was linked to the serrated pathway and led to the name serrated pathway syndrome (SPS).\textsuperscript{95,96} These families comprise affected individuals across several generations, with 2 to 4 relatives with CRC and 6 of 11 families fulfilling the Amsterdam I criteria. CRC was accompanied by sparse serrated lesions, conventional adenomas,
and, only occasionally, with 2 of 42 subjects (4.8%) in the 11 SPS families who met the criteria of HPSP. The authors distinguish this disorder from “conventional” HPSP, which also follows the serrated pathway, but essential lesions of HPSP constitute more or less numerous serrated polyps that eventually might be precursors of CRC in the future. Moreover, there is weaker familial clustering. Thus, SPS and HPSP are 2 separate syndromes in which the BRAF mutation and methylations co-occur within CRC and serrated precursor lesions. It is worth stressing that although more than half of SPS families fulfilled the Amsterdam I criteria, several studies have suggested that the BRAF mutation is very rare in Lynch syndrome tumors, further delineating SPS as a separate entity.97,98

Genomic regions associated with Jass syndrome presented evidence of a chromosome 2q32.2-q33.3 linkage.94 The spectrum of serrated neoplasia may also implicate the subset of sporadic CRC with high levels of MSI with widespread CpG island methylator phenotype and somatic BRAF mutations.

Three settings exemplifying serrated neoplasia either in the form of syndromes or sporadic CRC are presented in Figure 3 according to Young and Jass.96

SERRATED PATHWAY TO CRC

Two slightly overlapping categories of serrated carcinoma pathways were proposed in 2009, depending on whether carcinoma arises from pre-existing SSA/P or TSA.29 Most frequently this pathway appears to begin with a mutation of the BRAF gene, which is present in the majority of SSA/Ps and commonly in microvesicular HPs.23,29,99 SSA/P is prone to hypermethylation of cytosine residues within CpG islands (CpG island methylator phenotype) associated with a loss of gene expression. CRC patients with hMLH1 methylation acquire defective DNA mismatch repair and progress via the high MSI pathway.23,29

Several types of serrated polyps, including goblet cell-rich HPs and TSAs more often contain KRAS rather than BRAF mutations. TSAs may progress to low MSI or microsatellite stable serrated carcinoma.23,29

The most simplified serrated polyp–carcinoma sequence may be as follows: HP → sessile serrated lesion → sessile serrated lesion with dysplasia (mixed polyp) → TSA → carcinoma.17,40,62,100-102

Schematic representation of the development of sporadic CRC with MSI via methylation of the MLH1 gene is presented in Figure 4.

NEW ENDOSCOPIC IMAGING MODALITIES

Over the past 10 years, significant progress in colonoscopy imaging was made with the development of new strategies, such as pancolonic chromoendoscopy, NBI, and ultrahigh magnification systems, including optical magnification and confocal laser endomicroscopy. These new options allow physicians to evaluate small lesions.

Figure 3. The diagram of 3 settings exemplifying serrated neoplasia according to Young and Jass.96 A, Hyperplastic/serrated polyposis (HPSP) where numerous serrated polyps develop and in which synchronous cancers may be present. B, serrated pathway syndrome (SPS), which is a multicase and multigeneration colorectal carcinoma (CRC) predisposition associated with few advanced serrated polyps. C, Sporadic CpG island methylator phenotype (CIMP) CRC where no evidence of a family history is apparent. HPP, hyperplastic polyp.
and immediately decide whether to remove them. Comparing chroendoendoscopy with standard colonoscopy has shown a statistically significant increase in the overall detection rate for polypoid and flat adenomas as well as serrated lesions (\( P < .001 \)). Serrated lesions have a distinct endoscopic appearance and are more difficult to detect than conventional adenomas. The most common serrated lesion is a diminutive left-sided, pale sessile HP. Larger serrated lesions are typically similar in color to the surrounding mucosa. They are covered by a tenacious mucous cap, causing the polyps to appear yellow, green, or rust-colored and appear red on NBI. Several studies have shown that NBI can predict polyp histology in real-time with good accuracy and allows prediction of the correct colonoscopy surveillance interval in 86% to 94% patients. NBI is of particular value for the detection of serrated polyps, which represent the overall majority of polyps in HPSP: polyp miss rates of high-resolution endoscopy and NBI were 36% and 10%, respectively (\( P < .001 \)).

Probe-based confocal laser endomicroscopy is an emerging tool for in vivo imaging that may enable the endoscopist to interpret the mucosa at a subcellular resolution (the “pit or crypt pattern”), which is a key structural feature similar to a microscopic diagnosis. The Miami classification system for normal and pathological states using probe-based confocal laser endomicroscopy was recently published. This system allows the differentiation of neoplastic lesions from HPs based on a dark, irregularly thickened epithelial layer characteristic of epithelial dysplasia.

**SURVEILLANCE RECOMMENDATIONS**

Serrated lesions are acknowledged as precursors of CRC and require complete removal, especially when they are proximally located or, if in the rectosigmoid, they are larger than 5 mm. The main goal of screening and surveillance for CRC is preventing and reducing cancer mortality by detecting and removing precancerous growths and cancers at earlier, more treatable stages. It has been confirmed that a screening colonoscopy has the potential to prevent approximately 65% of CRC cases and is the most sensitive method and the most valuable tool to satisfy the requirements of screening.

In the United States, since 1998, the CRC incidence rate and death rate have been decreasing by 3.0% and 2.8% in men and by 2.3% and 2.6% in women per year, respectively, as a result of CRC screening. For every 1% increase in the number of colonoscopies conducted, there was a 3% decrease in the CRC death rate.

A system for colonoscopic surveillance after adenoma removal, which is obligatory in the European Union, was recently published and is shown in Table 2. The surveillance strategy varies according to the low-, intermediate-, and high-risk group, depending on the number and size of the adenomas and whether an advanced adenoma was present at the baseline colonoscopy. The NCCN guidelines include surveillance of all serrated lesions, except HPs, to the rules obligatory to adenomas.

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**Figure 4.** Schematic representation of the serrated pathway to high microsatellite instability (MSI-H) colorectal carcinoma modified according to the World Health Organization. The sequential pathway involves slow and rapid steps. The origin of sessile serrated adenoma/polyp (SSA/P) remains debatable; it is possible that an SSA/P arises directly from normal mucosa or from a preexisting microvesicular hyperplastic polyp, hence, the arrows for these steps are dotted. CIMP, CpG island methylator phenotype.
Most recommendations published to date about surveillance after polypectomy primarily considered adenomas, carcinomas, and HPs but ignored the other representative serrated lesions. Nevertheless, it is generally acknowledged that the presence of large (≥ 10 mm) serrated lesion increases the risk of CRC, but proximal and protruding large serrated lesions are the greatest risks for proximal CRC (odds ratio 5.36 and 9.0, respectively). The recent guidelines for screening of serrated lesions, according to the European Union and the NCCN, are provided in Table 3. Colonoscopic surveillance after the removal of isolated HPs is not specifically recommended by European, American, and NCCN guidelines. However, most
gastroenterologists would favor a complete polypectomy for the so-called high-risk HPs, which may contain focal dysplasia or TSA fragments (mixed polyps). Surveillance should then be performed as it is for conventional adenomas.

The NCCN guidelines indicate that, contrary to HPs, sessile serrated lesions should be managed in the same way as conventional adenomas. This approach has been confirmed in a study of lesions termed advanced serrated neoplasia to which, apart from TSAs and mixed polyps, sessile serrated lesion was introduced, suggesting a screening strategy identical to that for conventional adenomas.

The latest recommendations for surveillance of serrated lesions, based on an expert panel consensus, were reported by Rex et al in September 2012 and are provided in Table 4. Considering the paucity of postpolypectomy observational studies, the authors suggest that the levels of evidence available to support these recommendations are of low or very low quality. However, an extensive literature review enabled the authors to draw conclusions on different surveillance intervals depending not only on polyp histology, but size, number, and location as well. Simultaneously with previously mentioned recommendations, the other guidelines for colonoscopy surveillance of both adenomas and serrated lesions have

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**TABLE 3. Guidelines for colorectal carcinoma colonoscopy screening and surveillance after the removal of serrated lesions according to the European Union and National Comprehensive Cancer Network recommendations, and the risk of malignant transformation**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Risk of colorectal carcinoma</th>
<th>Interval for control*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyp</td>
<td>None</td>
<td>No indication for follow-up</td>
</tr>
<tr>
<td>Sessile serrated lesion</td>
<td>Slightly increased, but exact data are missing</td>
<td>5 or 3 or 1 y</td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td>Increased</td>
<td>5 or 3 or 1 y</td>
</tr>
<tr>
<td>Mixed polyp</td>
<td>Increased, but exact data are not available</td>
<td>5 or 3 or 1 y</td>
</tr>
</tbody>
</table>

*The stated intervals for control apply to completely removed lesions. If the removal is incomplete or done in a piecemeal technique, a control examination including endoscopy and biopsy should be performed after 2 to 6 months.

†Time, depending on the risk group (low-, intermediate-, or high-risk group) typical for adenomas (according to Table 2).

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**TABLE 4. One of the most recent consensus surveillance interval guideline after endoscopic resection of serrated lesions**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Size, mm</th>
<th>No.</th>
<th>Location</th>
<th>Interval, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP</td>
<td>&lt;10</td>
<td>Any number</td>
<td>Rectosigmoid</td>
<td>10†</td>
</tr>
<tr>
<td>HP</td>
<td>≤5</td>
<td>≤3</td>
<td>Proximal to sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>HP</td>
<td>Any</td>
<td>≥4</td>
<td>Proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>HP</td>
<td>&gt;5</td>
<td>≥1</td>
<td>Proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10</td>
<td>&lt;3</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>≥10</td>
<td>≤3</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10</td>
<td>≥2</td>
<td>Any</td>
<td>1-3†</td>
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<tr>
<td>SSA/P with dysplasia</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td>1-3†</td>
</tr>
</tbody>
</table>

HP, Hyperplastic polyp; SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma.

*The interval recommendations presented here represent a consensus based on low-quality or very low-quality evidence.

†Patients with more than 20 HPs in the rectosigmoid meet the World Health Organization definition of serrated polyposis if there are additional serrated lesions proximal to the sigmoid.

‡Some panel members follow a policy of 5 years if there are multiple HPs 6 to 9 mm in size in the rectosigmoid.

 Patients with 2 serrated polyps ≥10 mm in the proximal colon meet the World Health Organization criteria for serrated polyposis if 3 additional serrated lesions of any size proximal to the sigmoid are identified.

SSA/P with cytological dysplasia is a more advanced lesion than SSA/P. Depending on the size of the lesion, the confidence in complete endoscopic resection, and other associated lesions, intervals shorter than 3 years may be appropriate.
been reported by the U.S. Multi-Society Task Force on Colorectal Cancer\textsuperscript{126} and are presented in Table 5.

Undoubtedly, both sets of guidelines are of great value for providing long-anticipated specific and accurately ordered recommendations for surveillance and screening intervals; nonetheless, there are slight differences between them. The data concerning all serrated lesions included in Table 4 are more precise than those in Table 5. First, in the latter, there is no information on surveillance time intervals for HPs located proximal to the sigmoid or those based on the size and number of HPs, SSPs, and TSAs. The differences between both recommendations for serrated lesion surveillance are summarized more exactly in Table 6.

The general approach to HPSP is a colonoscopy with a polypectomy until all polyps 5 mm or larger are removed, and a surveillance colonoscopy is recommended either every year\textsuperscript{126,127} or 1 to 3 years, depending on the number and size of the polyps.\textsuperscript{71-74,83,89} Surgical options should be considered if colonoscopic management becomes technically difficult or ineffective or if dysplasia is diagnosed.\textsuperscript{23,128} Screening colonoscopies should also be offered to first-degree relatives of patients with HPSP.\textsuperscript{72-74,82,89,129} Properly managed patients with HPSPs appear to have a very good prognosis.

### SUMMARY

A comprehensive review of the histological classification and genetics of serrated colorectal lesions and their relationship with CRC is presented. Sessile serrated lesions might be precursors in approximately one third of CRC cases. The criteria for the diagnosis of HPSP, its incidence, and relationship with CRC are provided and thoroughly discussed.

The most recent guidelines for colonoscopy surveillance after screening and polypectomy concerning both serrated lesions and conventional adenomas presented by expert panels are provided.
TABLE 6. The differences between recommendations for serrated lesions surveillance intervals in Tables 4,55 and 5,126

<table>
<thead>
<tr>
<th></th>
<th>Interval, y</th>
<th>Table 5 (Lieberman et al126) Interval, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP &lt;10 mm in rectum or sigmoid, any no.</td>
<td>10</td>
<td>HP &lt; 10 mm in rectum or sigmoid 10</td>
</tr>
<tr>
<td>HP ≤ 5mm, no. &lt; 3, proximal to sigmoid</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>HP any size or &gt; 5 mm, no. ≥ 4 or ≥ 1, proximal to sigmoid</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>SSA/P &lt; 10 mm, no. &lt; 3</td>
<td>5</td>
<td>SSA/P with dysplasia 5</td>
</tr>
<tr>
<td>SSA/P with dysplasia any size, any no.</td>
<td>1 – 3*</td>
<td>SSA/P with dysplasia 3</td>
</tr>
<tr>
<td>TSA &lt; 10mm, no. &lt; 3</td>
<td>5</td>
<td>TSA independently on the size and no. 3</td>
</tr>
<tr>
<td>TSA ≥ 10 mm or &lt; 10 mm, no. 1 or ≤ 3</td>
<td>3</td>
<td>TSA independently on the size and no. 3</td>
</tr>
<tr>
<td>Serrated polyposis syndrome</td>
<td>NA</td>
<td>Serrated polyposis syndrome 1</td>
</tr>
</tbody>
</table>

HP, Hyperplastic poly; NA, not applied; SSA/P, sessile serrated adenoma/polyp; SSP, sessile serrated polyp with no dysplasia; TSA, traditional serrated adenoma.
*SSA/P with cytological dysplasia is a more advanced lesion than SSA/P. Depending on the size of the lesion, the confidence in complete endoscopic resection, and other associated lesions, intervals shorter than 3 years may be appropriate.19

FUTURE ISSUES

Guidelines for colonoscopy surveillance intervals for serrated lesions represent opinions based on the low quality of evidence. They are likely to change as higher-quality evidence becomes available. Future research on more numerous groups of serrated lesions with longer follow-up may allow modification of these recommendations, recognizing the unique CRC risks and growth rates of large HPs versus SSA/Ps and versus TSAs.

Identification of the molecular mechanisms underlying serrated lesion progression is mandatory to explain why some serrated lesions remain indolent for an undefined period of time, whereas others progress rapidly to invasive CRC.

A thorough analysis of hitherto-existing opinions on high CRC prevalence in HPSP is necessary. It is important to judge with great caution results of previous studies on the relationship of CRC with HPSP. Prospective studies in asymptomatic individuals, as well as in their first-degree relatives, are needed to better quantify the risk of CRC in patients with HPSP.

Regarding the terminology issues, it would be advisable to completely eliminate the term adenoma from histological classification of sessile serrated lesions (eg, sessile serrated adenomas). This word should only be used for TSAs and for dysplastic precursor lesions of non-CpG island methylator phenotype carcinomas, that is, conventional adenomas predominantly arising along the adenoma-carcinoma pathway initiated with APC mutations.

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Serrated lesions and hyperplastic (serrated) polyposis relationship with colorectal cancer


