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Morphological Characteristics, Classifications and Difficulties in the Use of Diagnostic Criteria for Serrated Lesions of the Large Intestine

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Abstract

Introduction Colorectal carcinoma (CRC) is the most common gastrointestinal neoplasm in the world, accounting for 15% of cancer-related deaths. This condition is related to different molecular pathways, among them the recently described serrated pathway, whose characteristic entities, serrated lesions, have undergone important changes in their names and diagnostic criteria in the past thirty years. The multiplicity of denominations and criteria over the last years may be responsible for the low interobserver concordance (IOC) described in the literature.

Objectives The present study aims to describe the evolution in classification of serrated lesions, based on the last three publications of the World Health Organization (WHO) and the reproducibility of these criteria by pathologists, based on the evaluation of the IOC.

Methods A search was conducted in the PubMed, ResearchGate and Portal Capes databases, with the following terms: *sessile serrated lesion*; *serrated lesions*; *serrated adenoma*; *interobserver concordance*; and *reproducibility*. Articles published since 1990 were researched.

Results and Discussion The classification of serrated lesions in the past thirty years showed different denominations and diagnostic criteria. The reproducibility and IOC of these criteria in the literature, based on the kappa coefficient, varied in most studies, from very poor to moderate.

Conclusions Interobserver concordance and the reproducibility of microscopic criteria may represent a limitation for the diagnosis and appropriate management of these lesions. It is necessary to investigate diagnostic tools to improve the performance of the pathologist's evaluation, for better concordance, and, consequently, adequate diagnosis and treatment.

Keywords

- Sessile serrated lesion
- serrated lesions
- serrated adenoma
- interobserver concordance
- reproducibility

Introduction

Colorectal carcinoma (CRC) is the most common gastrointestinal malignancy in the world, with ~ 150,000 new cases per year in the United States, ~ 52,000 deaths annually, and 15% of all cancer-related deaths.[1] The development of CRC is related to a combination of molecular events that include genetic and epigenetic abnormalities, traditionally

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described by two genetic pathways: the adenomatous polyposis coli (APC)/β-catenin pathway (or classic sequence pathway – adenoma/adenocarcinoma), which corresponds to up to 80% of sporadic colon tumors, and the microsatellite instability pathway, related to the loss of the DNA mismatch repair (MMR) gene function, which corresponds to 15% to 30% of the cases.[2–4] In recent decades, an alternative pathway has been described, characterized by mutations in BRAF oncogene and silencing of different groups of genes by hypermethylation of CpG regions, identified in cancers related to the (non-hereditary) MMR mutation. In contrast, KRAS and p53 mutations, common in the classic pathway, are not detected in these groups of tumors, showing a characteristic molecular profile of combination of microsatellite instability (MSI), BRAF mutation, and methylation of genes such as MLH1, p16 and MGMT.[5] With the evolution in the knowledge on the molecular biology of these lesions, it was possible to identify that they represent a group of lesions characterized mainly by glandular serrated lumens with a specific genetic signature. These entities, with distinct molecular profiles, morphologically resemble the lesions of sessile architecture and serration of glandular lumens, described by Longacre and Fenoglio-Preiser[6] in 1990, and later improved by Torlakovic and Snover[7] in 1996, and first included in World Health Organization's (WHO) Classification of Tumors,[12] also known as the WHO Blue Books, in 2000. The multiple new classifications and terminologies for these lesions later created, associated with recent information about biological behavior and treatments, have been reviewed over the last decades, and grouped in the serrated pathway of carcinogenesis.[8] The correlation between the different carcinogenesis pathways described so far and the molecular subtypes of CRC currently identified demand increasing investigation regarding the role of morphological and molecular profiles of serrated lesions and the serrated pathway in colorectal carcinogenesis.

Objectives

The objectives of the present article are to describe the evolution in the classification of serrated lesions, based on nomenclatures and microscopic criteria used in the last 3 WHO publications (of 2000,[11] 2010,[3] and 2019[9]), and to describe the reproducibility of these criteria and the pathologists' ability to make a diagnosis, over the last years, based on the intrerobserver concordance (IOC) by the kappa coefficient, according to different articles published in the literature.

Methods

A systematic review of articles was performed in the PubMed, ResearchGate and Portal Capes databases, using the following terms: *sessile serrated lesion*; *serrated lesions*; *serrated adenoma*; *interobserver concordance*; and *reprodutibility*. A total of 30 articles published between January 1990 and June 2020 were selected.

Results and Discussion

According to the 2019 WHO classification, intestinal serrated lesions are classified as hyperplastic polyps (HPs), serrated lesions with and without dysplasia, traditional serrated adenomas (TSAs), and unclassified serrated adenomas.[9] The nomenclature of these lesions in classifications and diagnostic criteria has undergone changes in the last three decades and, and, in order to better understand taht, it is necessary to review the definitions adopted in the first published studies. In 1990, Longacre and Fenoglio-Preiser[6] described some polyps of serrated architecture that presented characteristics common to conventional adenomas (CAs) and HPs, and named them as mixed hyperplastic/adenomatous polyps – serrated adenomas. In 1996, Torlakovic and Snover[7] described a group of serrated lesions, in a case of serrated polyposis syndrome (SPS), which showed abnormal architecture and cytological dysplasia, defined as "sessile serrated adenomas (SSAs)," currently considered precursor lesions for CRC with MSI.[8] The prevalence of SSAs was underestimated for years, corresponding from 0.1% to 14.7% of all colorectal polyps. The differentiation of these from other conventional polyps and adenomas became fundamental, since the identification of a morphological and molecular profile related to the serrated carcinogenesis pathway was described, with different prognosis, follow-up and response to treatment when compared to traditional CRCs.[9–11] For the first time in 2000, the WHO[12] described two main types of serrated lesions: HPs (metaplastic) and serrated adenomas, as well as mixed hyperplastic/adenomatous polyps. In 2010, the WHO[3] classified serrated lesions into three main categories: 1) HPs, microvesicular HPs (MVHPs), goblet cell-rich HPs (GCRHPs) and mucin-poor HPs (MPHPs); 2) sessile serrated adenomas/polyps (SSA/Ps), with and without cytological dysplasia, conventional (similar to conventional, non-serrated adenomas), or serrated (pencillate nuclei and eosinophilic cytoplasm); and 3) TSAs. The WHO classification also considered the diagnostic criteria of mixed polyps (MPs), which contain alterations of more than one type of serrated lesion, but which could represent collision lesions or a possible progression from one lesion to another, and recommended that the terminology should be used with caution.[3] In 2019, the WHO[9] published the 5th edition of its classification: 1) MVHPs and GCRHPs; 2) sessile serrated lesions (SSLs), with and without cytological dysplasia (conventional and/or serrated); 3) TSAs; and 4) unclassified serrated adenomas, described as lesions with intermediate characteristics between SSLs and TSAs, in addition to "serrated tubulo-villous adenomas". The latter category apparently replaces the previous nomenclature of "mixed polyps". The denominations adopted by the 2019 WHO classification were already recommended by the 2017 British Society of Gastroenterology's[5] position statement, which used the terms "hyperplastic polyp, sessile serrated lesions with and without dysplasia, traditional serrated adenoma, and mixed polyps". ►**Table 1** shows the main classifications of serrated lesions in the past thirty years, based on the last three WHO

Table 1 Evolution in the classification of serrated lesions

Main authors and publications	Classification of serrated lesions
Longacre and Fenoglio-Preiser[6]	• Hyperplastic polyp. • Mixed hyperplastic adenomatous polyp/serrated adenoma.
Torlakovic and Snover[7]	• Hyperplastic polyp. • Sessile serrated adenoma. • Mixed hyperplastic adenomatous polyp.
World Health Organization (WHO) 2000[12]	• Hyperplastic polyp (metaplastic). • Serrated adenoma. • Mixed polyp (hyperplastic/adenomatous).
WHO 2010[3]	• Hyperplastic polyp (microvesicular, globet cell-rich and mucin-poor). • Sessile serrated polyp/adenoma (with or without dysplasia). • Traditional serrated adenoma. • Mixed polyp.
WHO 2019[9]	• Hyperplastic polyp (microvesicular, globet cell-rich and mucin-poor). • Sessile serrated lesion. • Sessile serrated lesion with dysplasia. • Traditional serrated adenoma. • Unclassified serrated polyp.

classifications and original descriptions from Longacre and Fenoglio-Preiser[6] and Torlakovic and Snover.[7]

Current Overview of Serrated Lesions

The morphological characteristics of each serrated lesion will be addressed briefly. ►**Figure 1** and ►**Table 2** show the main histological differences between the serrated lesions.

Hyperplastic Polyps

Hyperplastic polyps are the most commonly observed type of serrated lesion, corresponding to between 24% and 42% of all intestinal polyps, and 83% to 96% of serrated lesions.[5,10,11] They are usually small, measuring less than 5.0 cm, and with a sessile pattern, containing glands with columnar epithelium, goblet cells, and elongated and dilated crypts. They have straight crypts that extend symmetrically from the polyp surface to the muscularis mucosa, with greater luminal distension and serration in its proximal portion, without important architectural distortion, horizontal or irregular branching pattern.[11] The basal membrane may be thickened; reactive epithelial alterations and mitotic figures may be present, and should not be confused with dysplasia.[5] Currently, two morphological types of HPs are recognized. The most common is the MVHP, composed of glands with epithelial cells containing mucus, apical serration and goblet cells in lower frequency; it is more often located in the left colon and rectum, although 10% to 15% of them may be located in the right and transverse colons.[13] The second type, corresponding to one third of the total, the GCRHP, exhibits numerous goblet cells and lower apical serration, being more commonly found in the left colon and rectum. The MVHP most often has mutations in the BRAF gene, and the GCRHP may exhibit KRAS mutations, suggesting that they may be in different parts of the serrated pathway. A third type, rarely identified, described in previous publications,[3,12] the MPHP, was excluded from the 2019 WHO classification; little is known about the molecular characteristics related to this subtype, and one theory is that it would correspond to the MVHP with reactive epithelial alterations secondary to inflammation.[13]

Sessile Serrated Lesions

Sessile serrated lesions and TSAs generally have in common the serrated appearance of their crypt lumens. They are larger than HPs and, most SSLs occur in the right colon. The diagnosis is based on the distorted and disorganized pattern of the crypts, mainly in the basal portion, with serration along the whole extension of the crypt, including its base, which is dilated, and with horizontal branches forming a "J," "L" or "Inverted T" pattern. Superficial biopsies may represent a greater challenge in the differentiation from MVHPs. The crypts of the SSLs tend to be arranged parallel to the muscularis mucosa and sometimes herniated through it, not necessarily representing invasion. They show clear columnar cells with a less eosinophilic cytoplasm than those observed in TSAs. The presence of mucinous cells in the base of the crypts can lead to mucus accumulation and dialtion of the luminal gland, differently from HPs, which show narrow lumens in their bases, and proliferative cells.[4] Another important issue is whether SSLs arise de novo or originate from HPs, particularly MVHPs. The identification of most of pure SSLs at the right colon and MVHPs at the left colon support the de novo theory. However, the frequent identification of areas of MVHPs in large SSLs, associated with the presence of hypermethylation and BRAF mutations observed in $\sim$ 66% to 75% of MVHPs, and $\sim$ 85% of SSLs, suggests that SSLs may in fact represent advanced forms of MVHPs.[14] Sessile serrated lesions were defined in the 2010 WHO[3] classification as lesions presenting the aforementioned characteristics **in at least three crypts (or two adjacent crypts).** However, according to the criteria of the American Gastroenterology Association (AGA), the presence of these

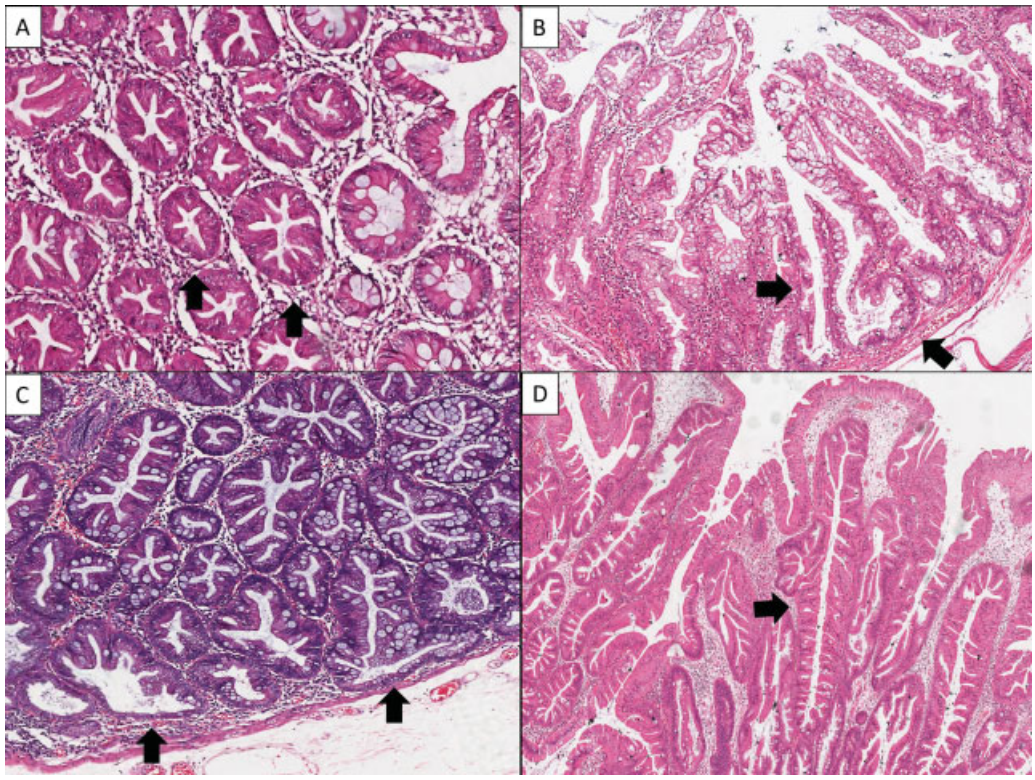

Fig. 1 (**A**) Hyperplastic polyp. Rounded glands with superficial and regular crypt serrations (arrows); (**B**) sessile serrated lesion with complete (including distal) crypt serration and characteristic lateral branching of the base of the crypt (arrows); (**C**) sessile serrated lesion with irregular (assymetric) crypt serration and lateral branching of the base of the crypt and dilatation (arrows); (**D**) traditional serrated adenoma, showing slit-like serration and eosinophilic cytoplasm. Staining method: Hematoxilin-Eosin. (Magnification: A and C – 200 X; B and D – 100 X).

alterations **in only one crypt** would be enough for the diagnosis.[13] Divergences in established criteria may justify the difficulties to make an adequate diagnosis; it is estimated that ~ 20% to 30% of lesions previously classified as HPs currently correspond to SSLs and TSAs, as observed in studies[4,8,15] on the reclassification of these lesions. The 2019 WHO classification[9] considers a minimum criterion "**the presence of at least one serrated crypt containing**

Table 2 Serrated lesions and main and minor histological characteristics

Serrated lesions	Main histological characteristics	Minor histological characteristics
Hyperplastic polyps	• Proliferative zone confined to crypt base. • Proximal crypt serration. • Straight crypts, without distortion. • More than one type of epitelial cell according to the polyp type.	• Localized basement membrane thickening. • Individual crypt branching may eventually exist. • Small, round and basally-located nuclei.
Traditional serrated adenoma	• Eosinophilic cytoplasm and pencillate nuclei. • Formation of ectopic crypt. • Villous architecture. • Slit-like serration.	• Flat-type traditional serrated adenoma may show a few or no formation of ectopic crypts. • A few globet cells may be present, except in the mucin-rich type, in which they are predominant. • In up to 50% of the cases, a serrated precursor may be found.
Sessile serrated lesions	• Assymetric crypt dilation and/or branching. • Luminal crypt serration throughout the entire extension, including its base. • Horizontal branching of the base of the crypt in J, L or inverted-T pattern. • Crypt herniation through the muscularis mucosa.	• Microvesicular and globet cells. • Proliferative zone in the middle and base of the crypt. • Most lesions do not exhibit epithelial dysplasia.

unequivocal architectural distortions". Sessile serrated lesions may exhibit nuclear and cytoplasmic atypia similar to that of low- and high-grade dysplasia observed in CAs; in these situations, well-defined areas of cytological dysplasia are often identified in SSLs without dysplasia. These areas are almost always related to the loss of immunoexpression of MHL1 due to the inactivation of the gene, common in the MSI pathway, but unusual in the classic carcinogenesis scheme[15]; at the same time, foci of dysplasia retain the BRAF gene mutation observed in the remainder of the SSL. The identification of dysplasia is considered a marker of progression to CRC, associated with rapid increase in size. In addition, the focus of dysplasia in SSLs with malignant transformation is often identified, and identification of SSLs with cytological dysplasia in polyps of individuals without a history of CRC is infrequent.[13,15]

More than one type of dysplasia is described in SSLs; however, the importance of differentiation and graduation is still an issue to be defined. The most common type, conventional dysplasia (similar to that of adenomas), is characterized by the presence of elongated cells with pseudostratified and hyperchromatic nuclei, amphophilic cytoplasm, and increased number of mitoses. Although graduation into low and high grades is performed in CAs, the importance of the graduation of SSL dysplasia is not clear, and the recommendation is to consider lesions with cytological dysplasia as a polyp of greater risk (advanced), with management similar to that of high grade adenomas.[16] A second, less described type of dysplasia is the "serrated dysplasia," rarely observed in SSLs, characterized by the proliferation of more cuboidal atypical cells, with eosinophilic cytoplasm, increased nuclear size with vesicular chromatin and prominent nucleolus, as well as an increased number of mitoses; this pattern is considered by some authors a marker of tumor progression.[13]

Traditional Serrated Adenoma

The third type of serrated polyp is the TSA, which usually exhibits a protuberant exophytic configuration, villous architectural pattern with rounded ends, coated by large numbers of columnar cells with eosinophilic cytoplasm, and elongated and pseudostratified nuclei. A usual characteristic is the presence of so-called "ectopic crypts," whose formation seems to be related to the loss of their normal anchorage to the muscularis mucosa. Both types of dysplasia can be found in TSAs; however, it is discussed whether the serrated pattern represents a real dysplastic alteration or a metaplastic one, since it differs from the cytological and architectural pattern of conventional dysplasia. The overall prevalence of this type of condition is of 0.6%.[4,13] With neoplastic progression, TSAs are believed to have increased levels of cytological atypia prior to the development of carcinoma. There is no consensus regarding the identification or graduation of dysplasia in TSAs, and the recommendation is that should be graded similarly to CAs (low and high grades). A recent study[8] showed that 25% of the TSAs studied had high-grade dysplasia, and 8% presented intramucous carcinomas. The risk of malignancy in TSAs and the time of progression are yet to be defined.[13,17] The molecular profile described for TSAs exhibits great heterogeneity, which can be partially attributed to the confusing terminology and difficulty in diagnosing serrated lesions.[15] The data available suggest that TSAs are not part of the serrated pathway, at least regarding SSLs, since they do not always present MLH1 hypermethylation and BRAF mutations, and may also exhibit KRAS and p53 mutations. Despite all these controversies, it is believed that they are better managed, in terms of follow-up and treatment, such as tubular adenomas of the same size.[13]

Non-classifiable Serrated Adenoma

This was a category introduced in the 2019 WHO classification,[9] with the purpose of including serrated polyps of difficult distinction, especially TSAs and SSLs with dysplasia. The newly described serrated tubullo-villous adenoma (TVA) is also included in this group.[9] Possibly, given the uncertainty regarding the characteristics of this group of lesions, the microscopic criteria for this category were not described in this edition.

Reproducibility and Interobserver Agreement in the Histopathological Diagnosis of Serrated Lesions

The detection of serrated lesions depends mainly on the examiner" experience; approximately half of the lesions in the proximal colon go unnoticed during the endoscopic examination, which contributes to the lower detection rates of proximal colon cancers compared with distal lesions.[16] The surveillance and treatment of serrated lesions, within each histological type, diverge from those of conventional adenomas, based on the 2012 consensus recommendations of the American Society of Gastrointestinal Endoscopy (ASGE), the AGA, and the American College of Gastroenterology (ACG). In general, serrated lesions larger than 10 mm and/or presenting cytological dysplasia, as well as TSAs, have a surveillance periodicity of 3 years, lower than that of tubular adenomas with low-grade dysplasia.[16] Despite the existing recommendations, the strategies for the surveillance of serrated lesions can only be adequately used after the proper histological diagnosis. However, the literature[14,18–22] highlights a great difficulty related to the adoption and interpretation by the pathologists of the criteria for the classification of serrated lesions. Part of this difficulty is probably related to the different denominations applied, as well as to the subjectivity of the existing histological criteria. Moreover, each type of polyp has peculiarities, which lead to confusion between one or more histological types (not necessarily only with serrated polyps). The related studies addressing this issue consider two main points: the percentage of HP reclassifications to SSA, MP, SSA/P and TSA, and the IOC or intraobserver concordance based on the kappa coefficient, according to the classifications, denominations and criteria presented in the 2000[12] and 2010[3] WHO classifications (depending on the year of the paper). As an example, a study[20] conducted in 2014 shows that 41 (20.5%) among 200 polyps (serrated and conventional) presented discordant diagnoses, and that the use of the 2010 WHO[3] classification, led to a reduction in the diagnosis of SSA/Ps and an increase

in the detection of HPs, due to the adoption of more rigid criteria. Currently, with the change in diagnostic criteria for "only one crypt" containing the histological characteristics of SSLs, this will probably lead to new IOC profiles, even though there does not seem to be yet a published study on this topic.

One of the most cited studies was performed in 2007.[22] In it, an online quiz was conducted with microphotographs of 20 lesions and 168 observers from different countries, for which 4 diagnoses were admitted (HP, TVA, SSA and TSA). The denominations most used by the participants were investigated, resulting in more than 19 different terms used, such as: *serrated polyp with anomalous proliferation*, *traditional mixed serrated adenoma*, *sessile serrated adenoma*, *hyperplastic-adenomatous mixed polyp*, among others.[22] It also should be pointed out from this study that the mean agreement percentage was $\sim$ 48%, with SSAs being more confused with HPs and TSAs, and TSAs more confused with TVAs. It is noteworthy that 9.4% of the participants claimed to have never used the term *serrated adenoma* as a diagnosis.

Another frequently cited study[23] was conducted in 2009, containing 40 HPs diagnosed in 2001 by pathologists with no experience in gastrointestinal-tract pathology (GITP). It was proposed that the cases were reviewed by 3 GITP specialists in 2007, based on the current knowledge of that time (probably aligned with the guidelines later published in 2010 by the WHO[3]). The authors demonstrated that $\sim$ 30% to 85% of HPs were reclassified as SSAs, with a kappa coefficient of 0.16 (very poor or poor agreement).

In 2009, a study[18] described a general agreement of 42% and a kappa coefficient of 0.49 (moderate) for all types of polyps, and 0.38 (fair) for SSAs and 0.53 (moderate) for HPs. However, this study does not distinguished between TSAs and SSA/Ps. Compared with this study, another one from 2008[21] presented an almost perfect IOC (kappa coefficient $>$ 0.80) for the diagnosis of TSAs; however, it did not include in its case series CAs or MPs, which probably reduced the possibility of disagreement among observers; the kappa values were also obtained for the other categories, which ranged from 0.45 to 0.47 for SSAs; from 0.42 to 0.52 for HPs; and from 0.46 to 0.58 for all lesions in general (moderate agreement).

In 2013, 2 studies[24,25] described the review and reclassification of cases previously diagnosed as HPs in the right colon from 2009 to 2012, using, however, the criteria of the AGA,[13] (minimum of 1 crypt containing the characteristic histological changes), currently adopted in the 2019 WHO classification.[3] The studies found a percentage reclassification range, in each year, of 30% to 64% of cases (average of 42% over the 4 years), mainly for the diagnosis of SSA/Ps; as an example, in 2009, there was no record of diagnosis of any SSA/P, and 66 HPs in the right colon. Of these, 30% of the cases were reclassified as SSA/Ps, and 1%, as TSAs. The percentage of reclassification of SSA/Ps observed was of up to 5% of the cases, suggesting that the greatest difficulty lied in the differentiation of HPs from SSLs, not the contrary. The kappa value was not calculated in these studies.[24,25]

Two other studies[19,20] show important data on this topic: the first of them, from 2014,[20] evaluated 200 lesions with diagnoses of CA, SSA, HP and MP. The general IOC was moderate to good (kappa: 0.56 and 0.68), but the agreement in the use of cytological and architectural criteria for diagnosis was analyzed, with large variations and low levels, especially between the SSA and TSA criteria, such as crypt inversion (kappa: 0.25) and crypt dilation (kappa: 0.38), formation of ectopic crypts (kappa: 0.25) and eosinophilic cytoplasm (kappa: 0.06). Variations in diagnosis were also calculated in different scenarios: A (before the disclosure of the diagnostic criteria), B (after the disclosure of age, gender and location of the lesion) and C (after the disclosure of the consensus on criteria). The greatest change observed in the diagnosis of SSAs and HPs occurred mainly in scenario C, associated with greater difficulty in the application of semiquantitative criteria, situations that had already been addressed in another study,[24] in which the use of criteria such as **one or two crypts** for the diagnosis seem to lead to significant changes in the trend of one or another diagnosis. Another study,[19] performed in 2012 with 70 cases and conducted in two stages, one before the consensus discussion and another after the definition of criteria based on the 2010 WHO classification,[3] showed an agreement of 0.318 and 0.557 (fair to moderate) for each stage respectively. It is noteworthy that, after the definition of criteria, the agreement regarding the diagnosis of HPs, SSLs and TSAs increased from 0.415, 0.301 and 0.433 to 0.977, 0.912 and 0.845 respectively; the global kappa coefficient, however, remained 0.557, possibly due to the very poor agreement regarding MPs (0.158), which even decreased after the disclosure of the criteria. Moreover, it is important to say that there were no cases of CA in this study,[19] which could possibly reduce the chance of misdiagnosis with MPs and serrated adenomas with dysplasia (in this study considered equivalent to SSL with dysplasia). This study[19] also evaluated the concordance between histological criteria, similarly to the previously mentioned 2014 study,[20] in which serrated superficial crypts (kappa coefficient: 0.97), serrated superficial epithelium (0.83), mitoses in the basal portion (0.79), goblet cells in the superficial crypts (0.77), and dilation in the superficial portion of the crypts (0.72) showed higher levels of agreement. The criteria with better discrimination capacity for each diagnostic category were: serration, dilatation and goblet cells in the superficial crypts in HP; horizontal dilatation of basal crypts and vesicular nuclei with nucleoli in SSA; and formation of ectopic crypts, cytoplasmic eosinophilia, pseudostratification, hyperchromasia, and nuclear elongation in TSA. Thus, it is suggested that architectural criteria present greater discriminatory capacity for HP and SSA, and cytological criteria contribute more to the diagnosis of TSA.

Finally, a 2015 study[26] showed 27 HPs reclassified as SSAs (SSLs and TSAs) among 310 polyps studied, resulting in a total of 31 SSAs, from 3 SSAs initially identified, and a kappa coefficient of 0.102 (very poor agreement). Over the years, other studies[27,28] have shown similar results. ►**Table 3** summarizes the main studies on the subject in the literature.

Considering all of these studies, it was possible to observe that those including lesions other than serrated ones, such as

Table 3 Interobserver variability in different series

Authors	Number of cases	Interobserver concordance
Baldin et al.,[26] 2015 **Rau et al.,[20] 2014**	$n = 310$ (HP/SSA/CA) $n = 200$ (HP/ SSA/TSA/MP/CA/OL)	Very poor Fair to good
Gill et al.,[24] 2013	$n = 797$ (HP/SSA)	30% to 64% of HPs reclassified as SSAs, over 4 years (kappa not calculated)
Ensari et al.,[19] 2012	$n = 70$ (HP/SSA/TSA/MP)	Good (in general) and very good for HP, SSA and TSA
Gunia et al.,[27] 2011	$n = 19$ (SSA/TSA/ IP)	Poor to fair
Bustamante-Balén et al.,[28] 2009	$n = 195$ (HP/SSA)	Very poor
Wong et al.,[18] 2009	$n = 60$ (HP/SSA/MP/CA/OL)	Poor
Khalid et al.,[23] 2009	$n = 40$ (HP/SSA)	Very poor
Farris et al.,[21] 2008	$n = 185$ (HP/SSA/TSA)	Good

CA, conventional adenoma; HP, hyperplastic polyp; IP, inflammatory polyp; MP, mixed polyp; OL, other lesions; SSA, sessile serrated adenoma; TSA, traditional serrated adenoma.

CAs, and lesions of other nature (inflammatory, reactive or normal mucosa lesions), showed higher levels of reclassification and lower IOC. This data suggests that when the study included a lower variety of lesions or restricted evaluation criteria, the chances of discordances in the evaluation were reduced. For example, CAs usually do not pose great diagnostic difficulty regarding HPs and SSLs; however, they can be easylly mistaken for TSAs, which are rare lesions with a frequency $\sim$ 1%,[22,24,25] whose difficulty to diagnose may not be clear if there is not a representative number of TSAs in the study.

A condition little addressed in reclassification studies of serrated polyps, but frequent in the pathologist routine, is the difficulty that sometimes exists to differentiate an HP from a reactive lesion. A possible explanation might be the presence of microscopic features of crypt hyperplasia and polypoid aspect observed in colonoscopies, in reactional or inflammatory lesions, acting as a confounding factor. Another possibility that could justify it, is the lack of recognition of the neoplastic potential of HPs by pathologists, as a lesion of the serrated carcinogenesis pathway, who might tend to opt for this diagnosis at the time of evaluation of a suspected lesion (both on colonoscopy and microscopic analysis) in case of doubt, since they may consider it as an innocuous or without carcinogenic potential.

Finally, the great variation in the rates of diagnostic agreement for SSLs and TSAs reflects the magnitude of the problem regarding the diagnosis of these lesions, which end up being confused with each other and with other colorectal polyps. Regarding HPs, it is recognized that they are the main simulators of SSLs, and that, in the past, most SSLs were diagnosed as HPs or MPs.[20,21,23,24] Although there are not many reports in the literature about the diagnostic difficulty in differentiating between CAs with SSLs and HPs, it is worth mentioning the perception by the pathologists that SSLs and TSAs are lesions with dysplasia, probably due to previous denominations as *serrated adenomas* and *mixed polyps*, when in fact the presence of dysplasia in these lesions is not so frequent, corresponding only to $\sim$ 5% of cases of SSL, for example.[21] Moreover, the presence of hyperplastic changes in the crypts of conventional adenomas is not infrequent, often leading the pathologist to resort to the old term "hyperplastic-adenomatous mixed polyp". This term, which was no longer used since the 2010 WHO classification[3] as a specific type of serrated lesion, apparently came to be considered again in the new classification,[9] under the term *non-classified serrated polyp*, whose frequency and minimum microscopic criteria have not yet been defined.

Conclusions

The recognition of the role of serrated lesions in colorectal carcinogenesis and its implications in the screening, follow-up and treatment of these lesions are limited, due to the current difficulty in defining and reproducing the main microscopic diagnostic criteria.[29,30] Besides that, the multiple terms applied in recent decades, sometimes confusing, compromise the evaluation of the diagnostic reproducibility and IOC. Although the first descriptions of this condition date from 1990, in the last 3 WHO classifications,[3,9,12] the described levels of diagnostic disagreement still range from 30% to 80%, according to the main studies. This is an alarming fact that reflects the need to investigate within each institution the percentages of agreement, as well as the need to seek ways to standardize criteria and reduce subjectivity, aiming at better diagnostic quality. Despite all the advances in the knowledge of the molecular biology and carcinogenesis pathways of these lesions, there is no consensus on the use of one or more markers (immunohistochemical or molecular) that could play a defining role in the diagnosis of this condition. Studies[8,9] with antibodies not used in the daily routine of immunohistochemistry, such as BRAF and Anexin A10, as well as molecular methods not often available (such as, methylation assays), still require further investigation. It is also essential to investigate diagnostic tools that can evaluate which of the microscopic criteria already described show better performance in the diagnosis, as well as greater reproducibility, to play a decisive role in diagnostic conclusion.

Conflict of Interests

The authors have no conflict of interests to declare.

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