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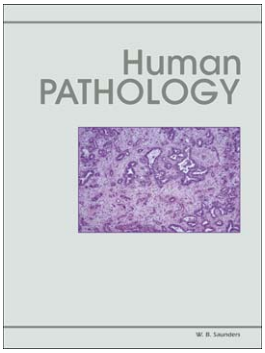

Traditional Serrated Adenoma: an update

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Progress in Pathology:

Traditional Serrated Adenoma: an update

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Abstract

Although recognized 25 years ago, the traditional serrated adenoma (TSA) remains an ongoing source of diagnostic and biological debate. Recent research has greatly improved our understanding of the morphological and molecular aspects of these polyps. In particular, the recognition of ectopic crypt foci (ECFs) in combination with typical cytology and slit-like serrations improves diagnostic reproducibility. Awareness that many TSAs particularly, *BRAF* mutated TSAs, arise in precursor micro vesicular hyper plastic polyps (MVHPs) and sessile serrated adenomas (SSAs) can aid in making this diagnosis and should not be confused with an SSA with dysplasia (SSAD). At a molecular level, TSAs can be divided into two groups based on their *BRAF* or *KRAS* mutation status. The development of overt cytological dysplasia is accompanied by *TP53* mutation, Wnt pathway activation and in some cases, silencing of *CDKN2A*. Importantly, however, mismatch repair enzyme function is retained.

Thus, the TSA is an important precursor of aggressive molecular subtypes of colorectal carcinoma.

KEY WORDS: Serrated polyp, traditional serrated adenoma, CIMP, *KRAS, BRAF.*

Introduction and History

In 1984, Urbanski and colleagues described an adenocarcinoma arising within an unusual colonic polyp [1]. This polyp was characterized by a "mixed morphology" of hyper plastic and adenomatous areas. While not using the term "serrated polyp", this perhaps is the first description of a polyp with a serrated luminal profile and harboring conventional adenomatous dysplasia [1]. The authors of this paper described the serrated areas as: "papillary infolding, with cells exhibiting strong cytoplasmic eosinophilia, goblet cell dystrophy, and varying degrees of dysplasia" [1].

The traditional serrated adenoma (TSA) was first reported by Longacre and Fenoglio-Preiser in 1990 under the more generic label of serrated adenoma [2]. They described a polyp with admixed features of hyperplastic polyp and conventional adenoma. Many had a distinctive cytology, characterised by abundant eosinophilic cytoplasm and centrally placed, pencillate nuclei. This polyp was subsequently confused with subsets of sessile serrated adenomas (SSA), sessile serrated adenomas with dysplasia (SSAD) and tubulovillous adenomas (TVA) with architectural serration. Much of the confusion was removed in 2003 when Torlakovic and Snover published their seminal paper describing the histological features of the SSA [3]. At the same time they designated the original 'serrated adenoma' as the traditional serrated adenoma to better separate it from the newly described SSA. Subsequently, they have addressed key diagnostic features of the TSA, with a particular focus on the importance of ectopic crypt formations or foci (ECF) [4]. The 4th edition of the WHO Classification of Tumours of the Digestive Tract emphasizes protuberant and viliform growth and ECFs in the diagnosis, reflecting the findings of these important papers [5].

Our understanding of the molecular biology of TSAs has also continued to evolve. MAP kinase pathway activation is established as a critical early

(probably initiating) event and occurs by either activating *BRAF* or *KRAS* mutation [6-9]. The CpG island methylator phenotype (CIMP) then develops in a subset of TSAs as a direct result of these initial mutations [10,11]. Interrogation of the histological and molecular events that occur as these polyps progress towards carcinoma has been more limited, but a few recent papers have enhanced our understanding of this process [6,7,12]. In this review we aim to highlight advances in the clinicopathological and molecular understanding of the TSA that have occurred since the publication of the 4th edition of the WHO classification of tumors of the gastrointestinal tract [5] and to frame this in a manner helpful to the practicing pathologist. In particular, we will address the issues of diagnostic features, precursor polyps, dysplasia in the context of a TSA and the molecular subtypes of carcinoma
expected to arise from these lesions.

Clinicopathological and endoscopic features

Traditional serrated adenomas are rare polyps, comprising 0.56-1.9% of all colorectal polyps [2,13-16]. The mean size at diagnosis ranges from 9-14mm, there is no obvious gender predilection and they are mostly distal and protuberant [6-9,14,16]. The mean age at diagnosis tends to be in the sixth or seventh decade. The endoscopic appearances of the TSA have not been extensively investigated, but a pine-cone like appearance has been described [17]. Using magnification chromoendoscopy they have a fern-like or stellate pit pattern [18]. Macroscopically TSAs can be either sessile or protuberant [18]. Proximal cases are more likely to be sessile than distal lesions[6].

Due to their rarity, current surveillance guidelines for TSAs are based on limited evidence. At present the US multi society-task force on colorectal cancer recommends a three-year surveillance interval after a diagnosis of a TSA [19].

Diagnostic criteria and guidelines – recent advances and distinction from other polyps

There have been considerable recent advances in the histological diagnosis of the TSA (see Figure 1 for a morphologic comparison of serrated polyps and the diagnostic features of TSA). In 2008, ECFs gained attention as a feature helpful to identify TSAs and to distinguish them from SSAs[4]. ECFs are recognized as epithelial buds with their bases not anchored to seated on the muscularis mucosae and are found along the sides of the villous projections of the polyp (Fig 1G). Some have regarded these ECFs are the proliferation zone of TSAs, but the Ki-67 proliferation in these foci are not always high. More recently, it has been recognized that a subset of TVAs also harbor ECFs [20,21]. In addition, some TSAs, in particular small polyps, do not show ECFs [6,8]. Several recent publications have re-emphasized the striking similarity between the TSA and the normal small bowel epithelium as a critical component of the diagnosis [6,20-22]. In particular the characteristic cytological appearance of the TSA and the presence of a distinctive form of serration are very useful clues to making the diagnosis. The typical cell of the TSA is one with plentiful, intensely eosinophilic cytoplasm and centrally placed, palisaded, penicillate nuclei. These cells are so characteristic of the TSA that outside of the setting of the very rare goblet cell rich variant, it is very difficult to justify this diagnosis if they are not the predominant component. Conversely, although small patches of cells with these features can be seen frequently in other polyp types, it is very unusual to see a polyp comprised predominantly of these cells that does not qualify to be diagnosed as a TSA. In tight association with this cytology are the characteristic epithelial serrations. These have been described variously as ‘slit-like’ or ‘table-top’ but essentially describe the same feature [6,21]. Although the classic TSA cytology can be seen on its own, slit –like serrations essentially always accompany the

eosinophilic cells. When seen together, the diagnosis of TSA must always be considered, regardless of the presence or absence of ECFs. That being said, the vast majority of TSAs greater than 10mm in diameter will have all three features [6]. Although protuberant growth and distal location have been emphasized in the past, it is now becoming clear that sessile and proximal TSAs are relatively common. These TSAs are mostly BRAF mutated and have frequent origin in a precursor polyp, in particular microvesicular hyperplastic polyps (MVHP) and SSAs [6,8].

This concept of TSAs arising in MVHPs/SSAs is not new but remains, surprisingly controversial [4,23,24]. In our opinion this finding has now been so well documented by numerous groups that it should no longer be an issue of debate. In fact 30-50% of TSAs appear to arise in one of these precursors [6,8,9,22]. The relative proportions arising in MVHPs versus SSAs are somewhat variable and likely reflects differences in diagnostic criteria. Groups that use the single crypt criteria for the diagnosis of a SSA are likely to have higher proportions of SSA than other groups [13,25]. More important in this context is recognition of the TSA component (as this will dictate the surveillance interval) and separating this process from dysplasia arising in an SSA. This issue will be discussed further in a subsequent section.

The final morphological point of discussion relates to the controversial concept of dysplasia in the TSA. Many (probably most) pathologists consider the TSA to be inherently dysplastic and routinely report low-grade dysplasia in TSAs mainly on the basis of elongated, penicillate nuclei. We propose an alternate view, utilizing the same schema as is accepted for the SSA and SSAD. In our view, while the ordinary TSA is undoubtedly neoplastic, it does not have inherent cytological dysplasia. The eosinophilic cells of an ordinary TSA are not overtly atypical, do not show mitoses, have minimal proliferative activity by Ki-67 staining and do not show other immunohistochemical changes to suggest dysplasia (i.e. no abnormal

staining with β-catenin, p53 and p16) [6,7,12]. However, subsets of TSAs do develop areas of definite adenomatous or conventional cytological dysplasia reminiscent of adenomatous polyps [6-9,12]. The proportions with overt dysplasia vary in different series, but after considering selection bias in the published literature, a figure of 10-20% is probably reflective of the incidence of adenomatous dysplasia in TSA. Similar to SSAs this is typically recognized as an abrupt transition from the adjacent ordinary TSA. In our experience, the pattern is usually serrated, being characterized by cells with abundant eosinophilic cytoplasm, basally located vesicular nuclei and frequent, often atypical, mitoses. This true "serrated" dysplasia is much different to the bland eosinophilic cells typical of the TSA.

Although less common, conventional adenomatous dysplasia can also occur in these polyps. Tsai et al, reported serrated dysplasia predominantly in *BRAF* mutated TSAs and conventional dysplasia occurring in *KRAS* mutated TSAs [12]. However, this dichotomy was not seen in recent series [6]. Regardless, the major issue for the practicing pathologist is to recognize areas of overt (serrated or adenomatous) dysplasia arising in a TSA and to bring this to the attention of the endoscopist. We do not feel, at this juncture, that there is any merit in separating or reporting serrated dysplasia from adenomatous dysplasia. This will sow confusion and not enough is known about the biology and natural history of these two forms of dysplasia. For the moment, it is perhaps prudent to merely "lump" the two into just

dysplasia accompanying a TSA. Although specific surveillance guidelines for this scenario have not been developed, it may be prudent to follow these patients closely. There is a slight difference of opinion whether the grade of dysplasia accompanying a TSA is mentioned or not. Practice is dictated by personal preference and regional guidelines. In some countries only high-grade dysplasia, if present, is reported. If high-grade dysplasia is mentioned in the pathology report, it may serve as a flag for more vigilant clinical

surveillance. The reporting of low-grade dysplasia is probably not necessary. The molecular changes that occur in these areas of overt cytological dysplasia will be discussed in detail in a following section, but provide further support to the concept of a non-dysplastic – dysplastic – carcinoma sequence in the TSA. "Ordinary" or usual TSAs (i.e. those without a discrete area of dysplasia) are designated as such with no mention of dysplasia. When discrete dysplasia is present it is regarded as TSA with dysplasia (TSAD) and a comment that these are polyps of an advanced nature and close surveillance may be prudent.

Differential Diagnosis

See Figure 1 and Table 1. The polyps that create the most confusion with TSAs are the SSA and a subset of TVAs with ECFs. In our opinion the latter polyps create the most problems [21]. This is very likely because these TVAs share many of the features of TSAs, namely they tend to be large, protuberant polyps with ECFs. Furthermore, they may also show filiform change, a feature typically associated with TSAs but that can be seen in large polyps of any type, even outside of the large bowel [20,26,27]. In contrast to TSAs, these TVAs do not show extensive eosinophilic cells and essentially never have the slit-like pattern of epithelial serration [21]. In the event of two distinct components (TVA and TSA) coexisting in the same polyp, these "mixed" polyps may justifiably be labelled as a TVA with TSA areas or vice versa.

SSAs can sometimes be confused with TSA. This is unsurprising given that TSA arising within a pre-existing MVHP/SSA displays a morphological spectrum. It is not unusual to see small patches of eosinophilic cells in SSAs, but to us, this feature alone is insufficient to justify a diagnosis of TSA. Importantly, we also do not consider this change to represent serrated dysplasia and hence justifying a diagnosis of SSAD. Instead, in routine practice we simply ignore this finding and leave the diagnosis as ordinary SSA. We make a diagnosis of

TSA when two of the three features of eosinophilic cells, slit-like serrations and ECFs are seen. This is most reliable in well-oriented sections, as the crypts of SSAs, when viewed in cross-section can appear similar to slit-like serrations. In addition, some SSAs harbor cells with abundant but palely eosinophilic cytoplasm, more in keeping with a gastric phenotype than the bright eosinophilia of a TSA.

Molecular and Immunohistochemical Features

See Figure 2. The vast majority of TSAs are probably initiated by activating mutation of either *BRAF* or *KRAS* [6,8,9,12]. A small percentage of TSAs are wild-type for both of these genes, but they seem to segregate closely with the *KRAS* mutated group. Recently it has been demonstrated that *BRAF* and *KRAS* mutations are independently capable of inducing CpG island methylation [10,11]. *BRAF* mutation status is strongly correlated with the CIMP-high phenotype, whereas *KRAS* mutation tends to induce less extensive methylation. This is reflected in studies of TSAs showing that *BRAF* mutated TSAs are mostly CIMP-high, whereas *KRAS* mutated TSAs are more often CIMP-low [6]. It should be noted that different laboratories use different panels to define CIMP and this can make comparison between studies problematic [12,27-29]. Regardless, MAP kinase pathway activation and CIMP status appear to be determined relatively early in the development of the TSA, before the development of overt dysplasia.

Immunohistochemically, ordinary TSAs have a reproducible pattern of staining. In particular, CK20 staining is present in the eosinophilic cells and absent in the ECFs [4]. Ki67 shows the opposite pattern. MUC2 and MUC5AC are usually
widely expressed, whereas MUC6 is infrequently present.

The development of overt cytological dysplasia is accompanied by additional molecular events. TP53 mutation, as demonstrated by strong p53 immunohistochemical staining, is the

most frequent event and is seen in over half of TSAs with dysplasia [6,7,12]. Wnt pathway activation, evidenced by a shift to nuclear β-catenin staining, is also frequently present [6,7,12]. In the context of colorectal carcinogenesis, most Wnt pathway activation is induced by loss of function mutations of the *APC* gene; however *APC* mutation is uncommon in serrated polyps. As such it is likely that methylation induced silencing of upstream Wnt suppressors activates the Wnt signaling pathway in these polyps. Loss of staining for the critical tumor suppressor p16 protein, presumably reflecting methylation induced silencing of *CDKN2A*, occurs almost exclusively in *BRAF* mutated TSAs and appears to be a late event in malignant progression [6]. In contrast, *KRAS* mutated TSAs tend to show strong p16 staining in areas of dysplasia, presumably reflecting up-regulation of CDKN2A, in an attempt to block uncontrolled cell proliferation.

Finally and perhaps most importantly, mismatch repair enzyme function is retained in essentially all TSAs regardless of *BRAF* or *KRAS* mutation status [5,6,12]. *BRAF* mutated, microsatellite stable colorectal carcinomas are known to be aggressive tumors with a poor prognosis [30,31]. As such the TSA may be an important precursor of these aggressive cancers. Furthermore, it has recently been demonstrated that *KRAS* mutated carcinomas are also associated with a poor prognosis, meaning that essentially all cancers arising from TSAs are aggressive [32,33].

Although TSAs are thought to be rare, they are encountered, not infrequently, in centers with high gastrointestinal case volumes and an active gastroenterology/endoscopic service. As such pathologists are likely to encounter more examples of TSA. Awareness of the constellation of histologic features and variants will enable a correct diagnosis to be made. Surgical pathologists should also be aware that overlap of histologic features occurs and not to label a polyp based on one

feature only. In addition, transitions between TSA and other serrated polyps as well as conventional adenomas occur. TSAs are important to recognize as they may flag a molecularly aggressive type of colorectal cancer.

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LEGENDS TO FIGURE

Figure 1 A-G:

1A&B: Hyperplastic polyp showing a semi-sessile lesion composed of serrated tubules with most prominent serration seen in the superficial or upper third of the crypt and surface (luminal tufting). In 1B the base of the hyperplastic polyp can be appreciated as narrow, pointed with fewer goblet cells and lacking luminal serration.

1C: Sessile serrated adenoma or polyp by contrast, has more goblet cells throughout the lesion, has basal dilation with bases often distended by mucin producing a club-shaped appearance. In addition, other characteristic architectural features are evident: serrations present at the base of some crypts, boot-shaped crypts showing horizontal spread along the muscularis mucosae.

1D: This is an example of a sessile serrated adenoma with high-grade dysplasia (SSAD). The dysplasia has the same cytologic features associated with adenomatous high-grade dysplasia: stratification of hyperchromatic, elongated, pleomorphic nuclei, and suprabasal mitoses. In addition, there is architectural complexity (crowded, coalesced glands) to supplement the cytologic atypia. The luminal serrated profile is retained and is an important feature separating SSAD from a conventional adenoma. Another useful feature to look for is the presence of SSA without dysplasia admixed within such polyps; there is a usually a sharp transition from non-dysplastic to dysplastic areas. Low-grade dysplasia within a SSA has less severe cytologic atypia and also retains luminal serration.

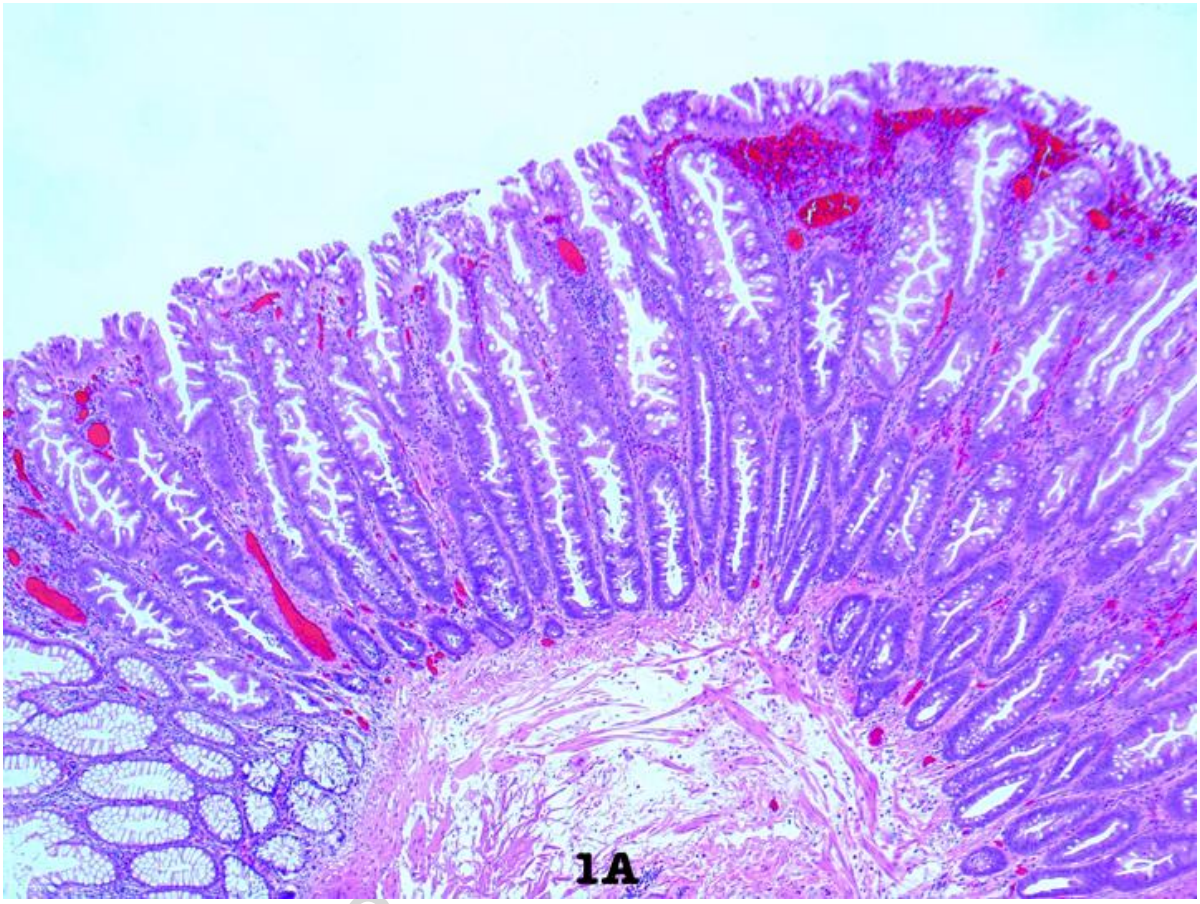
1E-G: Traditional serrated adenoma (TSA) as opposed to hyperplastic and sessile serrated polyps is a more exophytic, villiform lesion. The individual fronds or villi constituting the lesion are lined by tall columnar cells with deeply eosinophilic cytoplasm (although a goblet cell-rich variant with less eosinophilic cytoplasm has been described). The luminal aspect has a very characteristic pattern of serration:

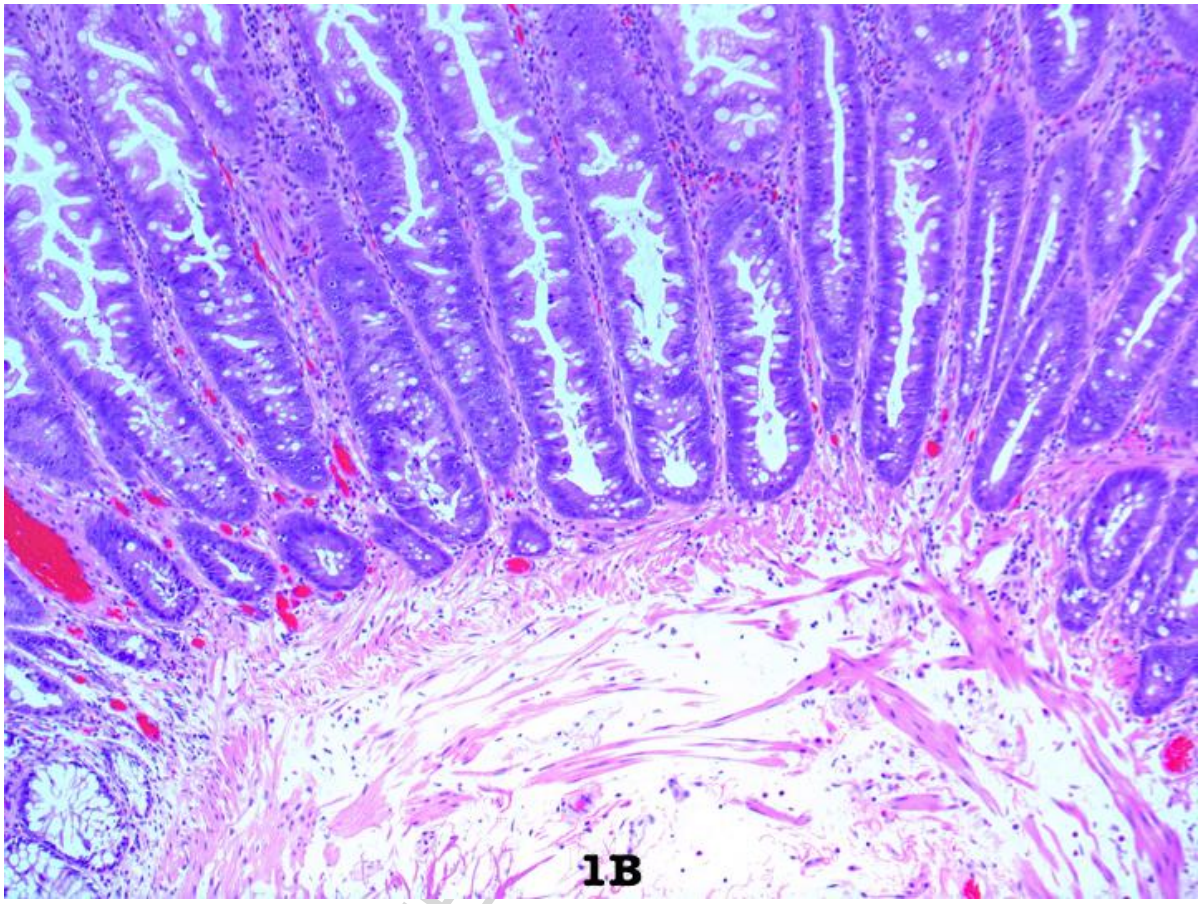
there are clefts creating flat-topped serrations rather than delicate saw-toothed tufts seen in hyperplastic and sessile serrated polyps. In addition the luminal surface has a brush border reminiscent of small bowel mucosa. The nuclei are elongated and penicillate, basal oriented and generally lacking stratification, pleomorphism and mitoses. It is for this reason we feel that traditional serrated adenomas do not show inherent adenomatous dysplasia. Like SSA with dysplasia, we believe that TSAs exist with and without adenomatous dysplasia. Ectopic crypt foci (ECFs) are a hallmark (but not exclusive) feature of TSA (arrows). They are encountered most readily and in the highest numbers in TSA.

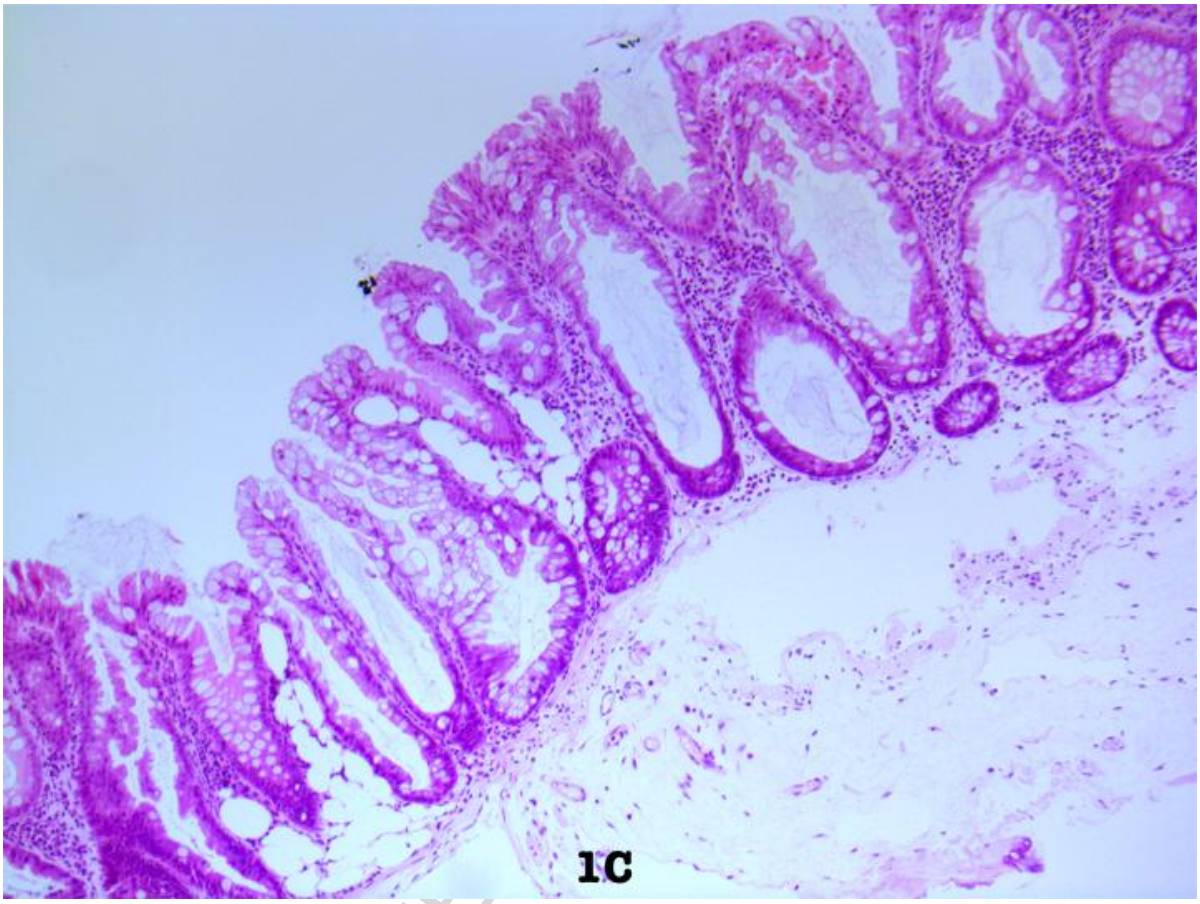
Figure 2:

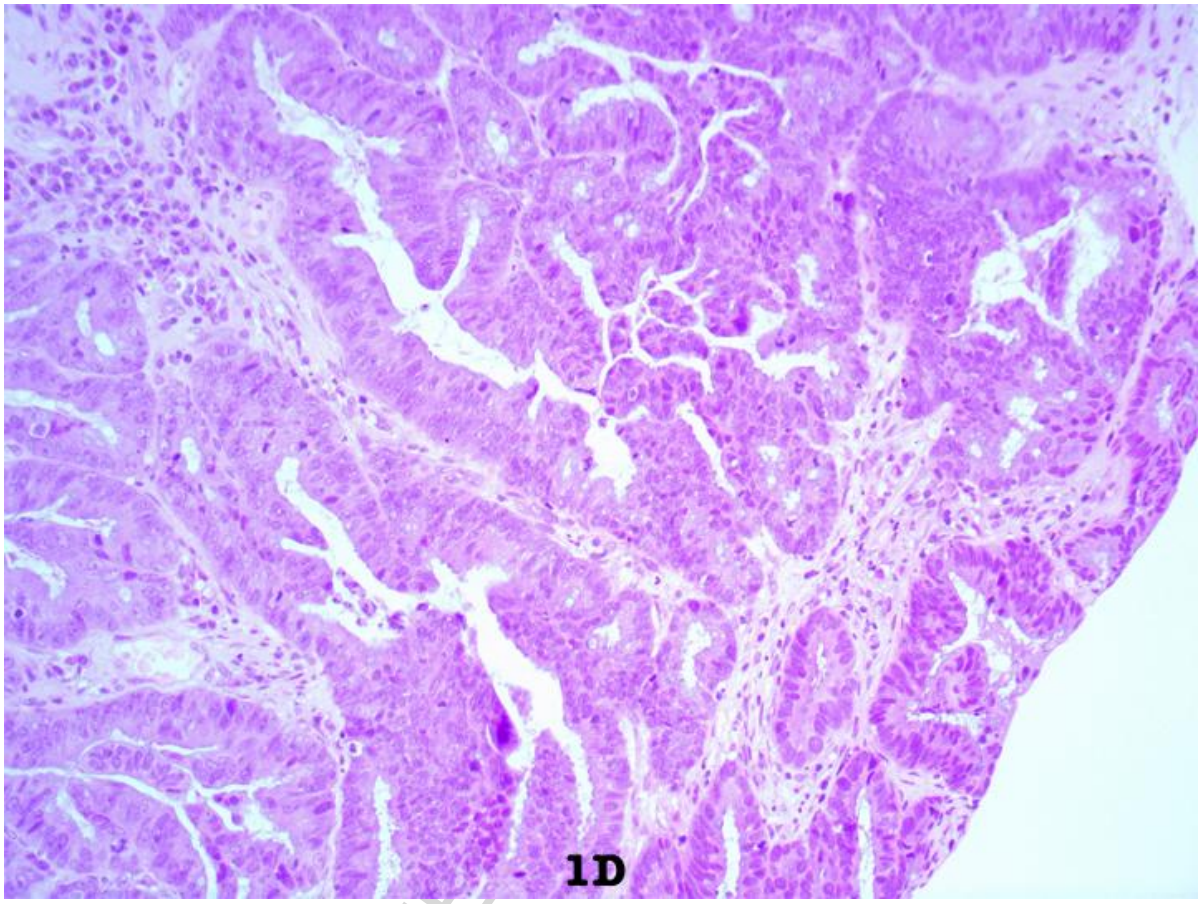
This is a schematic representation of the currently known molecular alterations in sessile serrated adenomas with dysplasia (SSAD) and traditional serrated adenomas with dysplasia (TSAD).

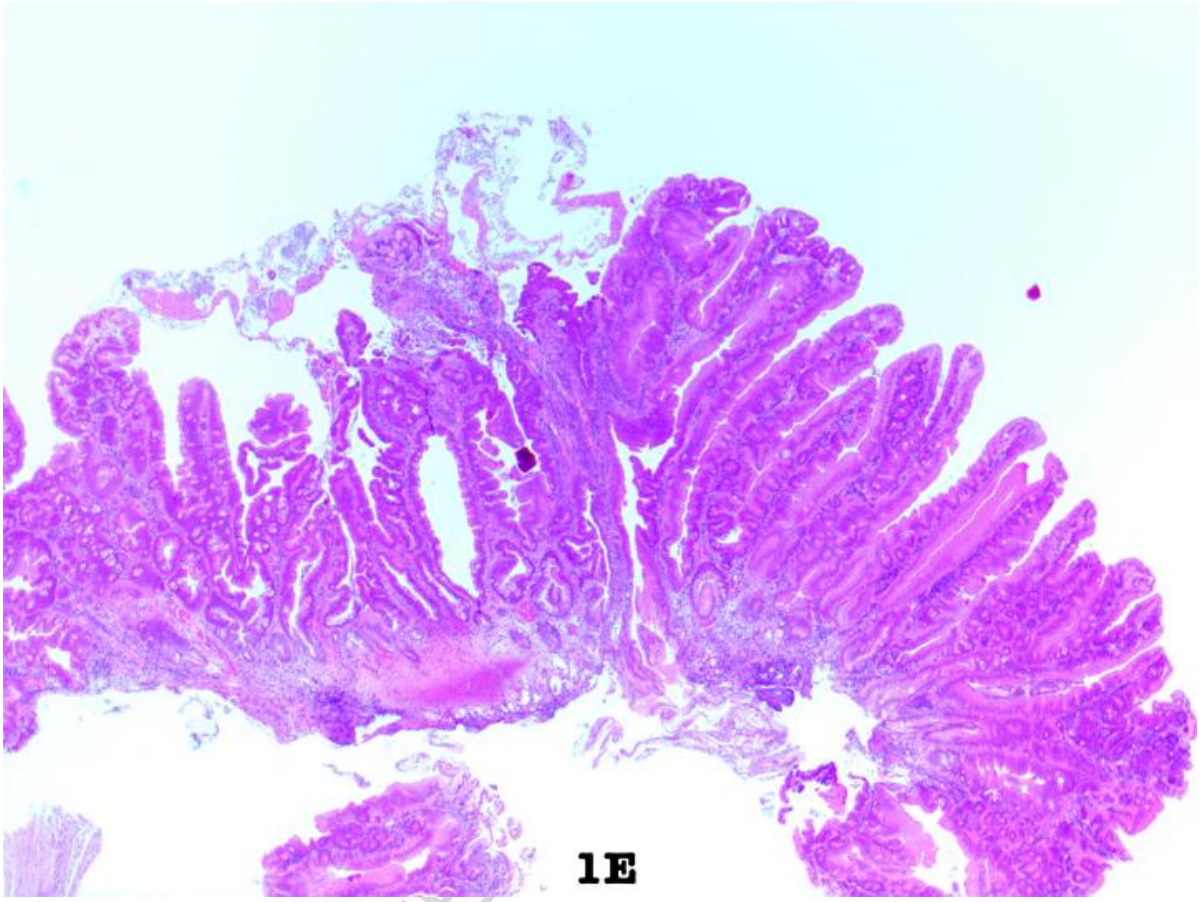
Figure

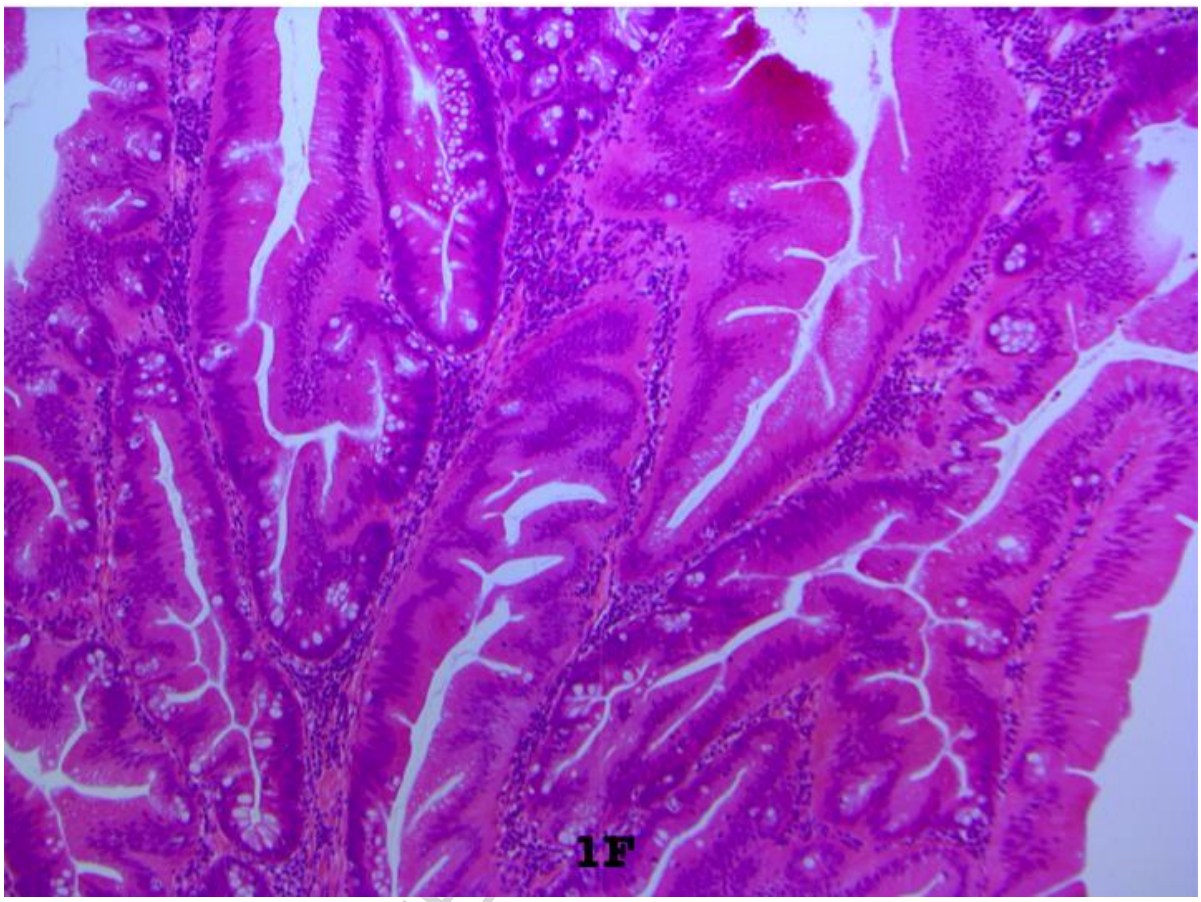


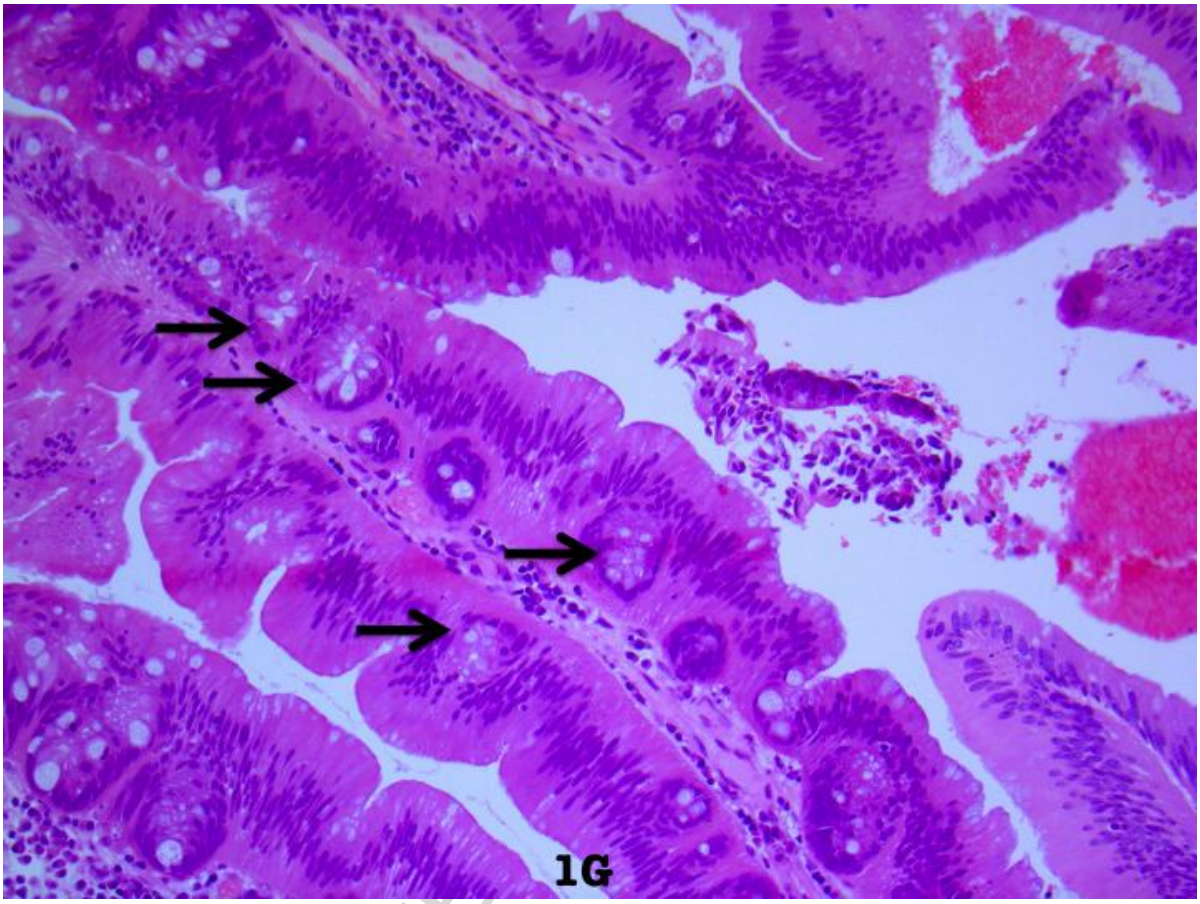












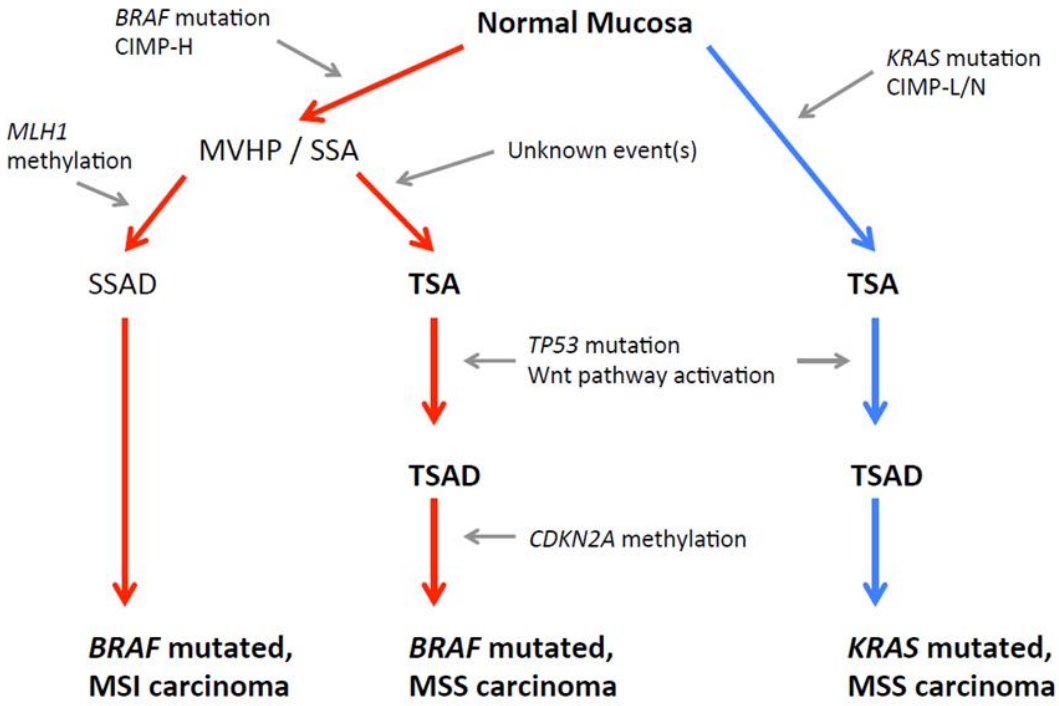


Figure 2

Table 1: Comparison of Serrated polyps

Polyp	Location	Endoscopy	Cancer risk	Molecular alteration	Surveillance
HP	Mainly right	sessile pale, star-like pit pattern	none/minimal	Microvesicular HP *BRAF*	<10mm: 5 yrs
SSA	Mainly Right	sessile, flat on crest of mucosal fold, mucus cap, cloud-like surface	1 with dysplasia: 2x, >/=10mm: 3x	*BRAF*	1;<10mm: 5yrs >1;<10mm: 3-5 yrs 1-3; >/= 10mm: 3yrs
TSA	Mainly Left	pine cone, fern like, Stellate pit pattern	Yes	*BRAF* and *K-ras*	every 3 yrs