Serrated lesions /PGS

Serrated lesions (sawtooth lesions, sawtooth adenomas, serrated ademomas) are a group of colon adenomas, which probably result in about a third of all colorectal cancers. Serrated lesions were first described by Longacer and Fenoglio-Preiser[1] in 1990 as a result of an analysis of a group of colorectal polyps with mixed hyperplastic polyp and adenoma properties. Serrated lesions have several subtypes that differ in the risk of developing malignancy. The serrated lesion owes its name to the fact that the prominent crypt epithelial cells resemble the saw's teeth in their arrangement of the saw blades. Such an arrangement is based on a disorder of apoptosis in the sense of higher resistance of cells to proapoptotic signals.[2]

Sesil serrated adenoma, H&E. The arrangement of the epithelium in the wall of the crypt resembles saw teeth, could incur group name lesions (eng. *serration* = perforation).

The molecular mechanism of serrated lesions and possible malignancy is different from the traditional adenoma-carcinoma pathway, which involves mutation in the APC gene, as well as from the direct mutation in mutator genes, that causes Lynch syndrome. There is talk of a **serrated pathway** leading to cancer with a hypermethylation phenotype. The initiation step of the serrated pathway is probably mutations of KRAS or BRAF, protein kinases involved in the MAPK signaling pathway, and subsequently hypermethylation of the CpG islands in the regulatory regions of the mutator genes, called the CIMP (CpG Island Methylated Phenotype). This results in a decrease in the expression of repair proteins and the cell becomes more susceptible to further somatic mutations.[3] The exact sequence of mutations and disorders during the serrated pathway is not known, it is likely that there are several partially interconnected pathways.[4]

Classification

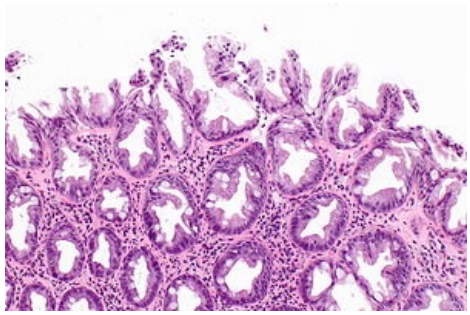
The WHO classification (2010) is as follows[2]:

- hyperplastic polyp (HP, HPP)
- sessile serrated adenoma/polyp 1 (SSA/P)
  - without cytological dysplasia
  - with cytological dysplasias (SAAD)
- traditional serrated adenoma (TSA)

[1]The terms *adenoma* and *polyp* are used, at least in English-written texts, as synonyms.

Hyperplastic polyp

Hyperplastic polyp (HP) accounts for 80-90% of all serrated lesions.[5] It occurs in more than 90% in rectosigma. It is usually smaller than 0,5 cm, but less than one quarter of the polyps are larger than 1,5cm in diameter. A characteristic feature are straight crypts, which spread symmetrically from the surface to the muscularis mucosae without significant distortion. Crypts are usually wider at the surface, at the base the width is smaller. Crypts show neither irregular nor horizontal propagation. According to the subtype, the crypt epithelium is accompanied by a number of cell types. Neuroendocrine cells can often propagate in the base of a polyp. Mitoses are rather non-abundant, in the basal half of the crypts. The serration is more markable in the upper half of the crypts and on the surface of the polyp. Cytological atypia is extremely insignificant, they may not be obvious at all. The nuclei are small, oval, or slightly elongated, without hyperchromasia, no signs of stratification. In some cases, crypt herniation through the muscularis mucosae (pseudoinvasion, inverted growth pattern) can be captured.[2][6]



Hyperplastic polyp, H&E.

Histologically, HP can be divided into the following subtypes:

- microvesicular HP
- HP with goblet cells
- HP poor on mucin

Microvesicular hyperplastic polyp

The microvesicular hyperplastic polyp is the most common variant of a hyperplastic polyp. It is characterized by the presence of microvesicles, ie small drops of mucin, in the cytoplasm of most cells. It occurs more often in the left colon, especially in the rectum, multiple occurrences are common.[2][5]

Hyperplastic polyp of goblet cells

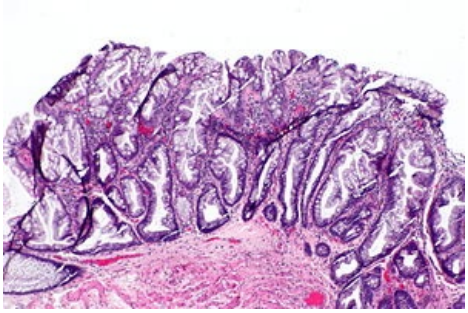
Almost exclusively goblet cells are present in the wall. Lumen serration is not very noticeable in this type, it may not be captured at all. The proliferation zone is crypt-based, usually limited to a few cells. Hyperplastic polyp with goblet cells is usually found in the left colon and is usually less than 0,5cm in diameter.[2]

Hyperplastic polyp poor in mucin

A mucin-poor hyperplastic polyp is a rare subtype of a hyperplastic polyp. It is characterized by the fact that there is at most only a small amount of mucin in the cells. The nuclei show more pronounced atypia, they are larger, oval, hyperchromatic, without demonstrable pseudostratification.[2]

Sessile serrated adenoma/polyp

Sessile serrated adenoma/polyp (SSA/P), also **sessile serrated lesions** (SSL), accounts for about 15-20% of serrated lesions.[7]


Sessile serrated adenoma, H&E.

Macroscopically, it usually presents as a flat or only slightly elevated lesion that has more than 5mm in diameter. It occurs more often in the right colon. Histologically, it is characterized primarily by a change in the growth pattern of crypts. At low magnification, these changes are clearly visible as disorganization and distortion of the crypts. The crypts may be dilated (sometimes referred to as bulbous-shaped crypts) and branched, especially in the basal parts, sometimes the crypts may grow parallel to the muscularis mucosae (sometimes known as horizontal growth). The crypts can thus take the form sometimes described as the letter "L", "boat" or "arrow". The serration in the basal half of the crypts is quite pronounced, sometimes referred to as hyperserration. Goblet cells and mucinous cells are usually visible in the basal half of the crypts.[2][7]

Proliferative activity (measured by Ki67 proliferation antigen) is evident throughout the length of the crypt, but Ki67 expression is often irregular and asymmetric. Different degrees of nuclear atypia can occur, sometimes dystrophic goblet cells can be captured. Neuroendocrine cells can sometimes be completely absent. Sometimes it is possible to capture foci of cells with an elongated to brush-like nucleus and more significant eosinophilic cytoplasm. Extracellular mucin production is common, usually marked. It is no exception that extracellular mucin is produced in such an amount that it completely fills the lumen of the dilated crypt and also covers the free surface of the polyp. In submucosa, lipoma-like adipose tissue can sometimes multiply. Herniation of the crypt through the muscularis mucosae is not an unusual finding. The diagnosis of SSA/P is mainly based on changes in tissue architecture, cytological changes are generally uncharacteristic.[2]

SSA/P with cytological dysplasias

SSA/P with foci of dysplastic changes (SSAD) similar to conventional tubular or tubovillous adenoma represent a state of progression from polyp to malignant tumor. Outside the area of dysplastic changes, the architecture may be quite typical of SSA/P.[2]

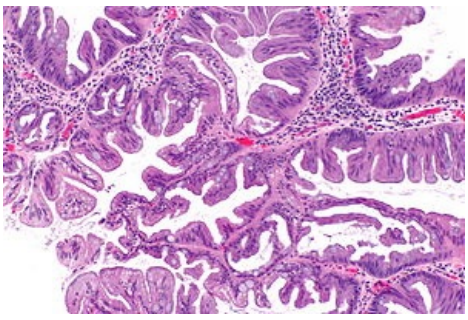
Cytological changes in displastic areas mainly include the presence of elongated cells with amphophilic cytoplasm, whose nuclei are hyperchromatic and pseudostratified. The number of mitoses is increased.[2]

The importance of evaluating dysplastic changes as low-grade and high-grade is not entirely clear, most likely low-grade dysplastic changes in SSA/P should be considered comparable to high-grade changes in conventional adenoma.[2]

Serrated dysplasia rarely occurs. We can find atypical cuboid cells with eosinophilic cytoplasm and enlarged round nuclei with distinct vesicular chromatin, evident nucleoli. Mitoses are more frequent. The significance is unclear, but rather the only assumption is that even this form of dysplasia is a sign of development towards malignancy.[2]

Traditional serrated adenoma

Traditional serrated adenoma (TSA) is a rare variant of serrated lesions, accounting for 1–6% of all serrated lesions. It has been known since 1990 when it was described as a rare variant of the adenoma.[7]


Traditional serrated adenoma, H&E.

TSA is a prominent or pendulous polyp, and a villous appearance is also described. It is usually not larger than 1,5cm in diameter. About 80% of TSA is located in the left colon, most often in the rectosigma. Histologically, it is characterized by a complex tubovillous or villous to filiform configuration. A characteristic growth pattern is the sprouting of new crypts perpendicular to the long axis of the filiform and villous structures, the so-called ectopic crypt formation. The crypts thus lose contact with the muscularis mucosae. TSA cells have an abundant eosinophilic cytoplasm with a basally or centrally located slightly elongated nucleus with a distinct chromatin structure. The epithelium

usually shows signs of pseudostratification, the proliferative activity is low to insignificant. Foci of dysplasia similar to conventional adenoma as well as foci of serrated dysplasia can be found. These changes can be assessed as low-grade and high-grade, about 90% of lesions show signs of low-grade dysplasia.[2][6][7]

A rare variant of traditional serrated adenoma is the **filiform serrated adenoma**, which represents about 4% of traditional serrated adenomas, ie at most about 2 ‰ of all serrated lesions. It occurs rather distally and is characterized by very long to filiform villi, marked edema of lamina propria and relatively numerous epithelial erosions. The epithelium itself is usually made up of a mixture of eosinophilic and goblet cells.[4]

Unclassifiable serrated lesions

Due to overlapping histological properties or technical reasons, it may be impossible to classify a serrated lesion. In these cases, the term "unclassified serrated polyp" may be used.[2]

Conventional adenomas can sometimes contain districts in which the architecture of the tissue is rather serrated. The term "conventional (tubular, villous, tubovillous) adenoma with a serrated variety pattern" can be used for such a finding. The biological significance of such polyps is unclear.[2] Sometimes mixed polyps containing several serrated patterns may occur.[5]. The following combinations have been described:[5]

- SSA and TSA
- SSA and conventional adenoma (all types)
- TSA and conventional adenoma (all types)
- HP and conventional adenoma (all types) – a very rare combination

The following descriptions should not be used:[5]

- circular saw polyp (*der Sägeblattpolyp*)
- serrated polyp with abnormal proliferation
- mixed polyp from HP and SSA

Serrated polyposis syndrome (SPS)

Serrated polyposis syndrome, also known as **hyperplastic polyposis syndrome**[5], is characterized by multiple serrated polyps, especially hyperplastic polyps and sessile serrated adenomas.[2]The WHO criteria for the diagnosis of SPS are met if **at least one** of the following conditions is met:[5][2]

- at least 5 serrated polyps proximal to the sigmoid, of which at least 2 are greater than 1cm
- any number of serrated polyps proximal to the sigmoid in a patient who has a first-degree relative with hyperplastic polyposis
- more than 20[2] resp. 30[5] serrated polyps of any size anywhere in the colon

As this is a genetic disorder, the diagnosis should be confirmed by genetic testing, and the endoscopic and histopathological findings should not be sufficient to confirm the diagnosis.[2]

Differential diagnosis

Diagnostically significant characteristics

Differentially diagnostically significant characteristics of individual serrated lesions are summarized in the following tables.[5][7]

hyperplastic polyp

Macroscopic appearance
rather left-hand location incl. rectum
flat, slightly forgiving above the mucosa
usually less than 5 mm
80-90% of serrated lesions
Histology
elongated crypts
"perforation" in the upper half or. third of the crypt
small, uniform, basally placed nuclei
slight cytological or architectural dysplasia

traditional serrated adenoma

Macroscopic appearance
rather left-hand localization
polyp-raised
1-6% of serrated lesions
Histology
dysplastic changes - intraepithelial neoplasia
diffuse cytoplasmic eosinophilia
intraepithelial microacins
ectopic crypt formation
significant "perforation"

sessile serrated adenoma

Macroscopic appearance
rather right-hand localization
flat-sessile look
usually larger than 5 mm
15-20% of serrated lesions
Histology (diagnostically crucial features)
marked serration (hyperseration), serration in the lower third of the crypts, may be branching of the crypts
so-called L resp. T formation crypt over muscularis mucosae
inverted crypts under the muscularis mucosae (microherniation)
columnar dilatation of the lower third of the crypt, there may be an accumulation of mucus
Histology (auxiliary features)
extension of the proliferation zone to the middle third of the crypts
vesicular nuclei with visible nucleoli
mature goblet cells at the base of the crypts

Diagnostic notes

- Differences in the biological behavior of individual subtypes of hyperplastic behavior are debatable. Because they are sometimes difficult to distinguish, it is not useful in routine diagnostics to distinguish between types.[7]
- Immunochemical detection of MUC6, which has been studied as a marker to distinguish between hyperplastic polyp (MUC6 negative) and sessile serrated adenoma (MUC6 positive), is a relatively specific but insensitive marker, so its use is not recommended. [7][2]
- In the case of sessile serrated adenoma, herniation (pseudoinvasions) through the muscular mucosae should also be assessed. If the muscularis mucosae has not been captured, it is appropriate to mention this in the description. Aust et al. recommend using the term sessile serrated polyp only in these cases[7], but the broader consensus is that the terms sessile serrated polyp and sessile serrated adenoma are synonymous[2].
- The term sessile serrated lesion is used by some authors to describe a sessile serrated adenoma without dysplastic changes.[7] This designation is outside the WHO classification[2] and therefore cannot be considered a suitable synonym.
- The distinction between the microvesicular variant of the hyperplastic polyp and the sessile serrated adenoma is absolutely essential.[4] There are several differential diagnostic recommendations:
  - **WHO 2010**[4]: At least three contiguous or at least two isolated crypts of the appearance characteristic of sessile serrated adenoma should be captured for the diagnosis of sessile serrated adenoma.
  - **Austl et al.**[7]: Capture of basal perforation, horizontal crypt growth, crypt inversion (herniation) and basal crypt dilatation in at least two crypts.
  - The presence of only one characteristic crypt is probably sufficient for the diagnosis of sessile serrated adenoma, and the polyp is likely to behave clinically as a sessile serrated adenoma. [8]
- The differences in immunochemical staining patterns between different types of adenomas for proliferating antigen [[Ki67]] and cytokeratin CK20 are statistically significant, but these are both less sensitive and less specific features, so their importance for routine diagnostics is considerably limited. The usual patterns are as follows:[9]
  - Crypts on normal mucosa show Ki67 positivity in the basal quarter, CK20 is expressed on the surface, it does not interfere with the crypts at all or only minimally.
  - The crypts of hyperplastic polyps are positive for Ki67 up to a third to a half-length, the positivity is regular and symmetric, the variability between crypts of one polyp is minimal. The positivity of CK20 penetrates deeper into the crypts, but with its decrease, the positivity decreases significantly.
  - Crypts of sessile serrated adenomas (without dysplasia) are characterized by irregularities in the distribution of Ki67 positivity between individual crypts. Positivity can reach various heights, it is usually asymmetric. CK20 also shows irregularities incl. deposits of weakly positive to negative cells on the surface. A relatively characteristic feature is the positivity of CK20 at the base of dilated crypts. Regions that express both Ki67 and CK20 may also appear.
  - In the case of traditional serrated adenomas, Ki67 is significantly positive, especially in ectopic crypts, the pattern of positivity is characterized by considerable irregularity. In contrast, CK 20, although the expression pattern may also be irregular, is limited to surface cells.
  - Conventional adenomas are characterized by very irregular expression of Ki67 and CK20.

Molecular Pathology

There are at least three general genetic and epigenetic mechanisms that can lead to colorectal cancer:[2]

1. chromosomal instability
2. defective DNA repair leading to microsatellite instability

3. epigenetic hypermethylation of CpG promoter sequences leading to CpG Island Methylator Phenotype

In the case of serrated lesions, the last two mechanisms apply. Physiologically methylation of CpG promoter sequences leads to attenuation of gene expression; if the promoter sequences of tumor suppressor genes are hypermethylated, the cell is more susceptible to tumor reversal due to the accumulation of uncorrected errors. Tumors with the CIMP phenotype are often associated with the BRAF mutation, whereas tumors with chromosome instability have usually KRAS mutation. The basic molecular characteristics of individual lesions are summarized in the following table:[2]

Basic molecular characteristics of benign and malignant lesions, Rex et al. (2012)

lesion	CpG methylation	methylation of MHL1	instability of microsatellites	mut. BRAF	mut. KRAS
conventional adenoma	+	-	-	-	++
hyperplastic polyp	+	-	-	+	+
sessile serrated adenoma without dysplasia	+++	-	-	+++	-
sessile serrated adenoma with dysplasia	+++	++	++	+++	-
traditional serrated adenoma	++	-	-	+ (i -)	+ (i -)
chromosome instability cancer	+/-	+	-	+/-	++
Lynch syndrome associated with cancer	-	-	+++	-	++
carcinoma with a CIMP-high phenotype	+++	+++	+++	+++	-

Molecular characteristics of individual lesions

Hyperplastic polyp

Usually, a BRAF or KRAS mutation is present, probably the initial mutation of most hyperplastic polyps.

The microvesicular hyperplastic polyp, which is the most common of the hyperplastic polyps, is most often characterized by a V600E mutation in the BRAF gene. This mutation leads to constitutive stimulation of the MAPK signaling cascade and thus to increased proliferative activity and inhibition of apoptosis. It is the apoptosis disorder that is responsible for the characteristic appearance of the "saw teeth".[4]

Sessile serrated adenoma

As with microvesicular hyperplastic polyps, sessile adenomas appear to have an initial disorder of the BRAF mutation. This mutation can be detected in 70-80% of cases. As progression towards dysplastic changes and cancer occurs, hypermethylation results in a decrease in p16 protein expression and thus an escape from the process of activation-induced aging. Similarly, one of the typical changes in SSA, attenuation of MLH1 mutator (repair) gene expression, is common in dysplastic polyps, and even more in high-grade dysplasias. During the progression of the sessile serrated adenoma, activation of the Wnt, signaling cascade has also been observed, which is usually associated with tumorigenesis through chromosomal instability. Decreased Beta catenin, expression was observed in some sessile serrated adenomas with dysplasia, but without a demonstrable mutation. Methylation of the regulatory sequences of several Wnt signaling cascade antagonists has been demonstrated in some sessile adenomas. Methylation of the promoter sequences of the MGMT mutator gene has been demonstrated in some sessile serrated adenomas.[4]

Because the initial mutation is usually identical, the question of the relationship between the microvesicular variant of the hyperplastic polyp and the sessile serrated adenoma is still unclear. Diametrically different biological behavior, as well as different localization, speak for the kinship, just the same initial mutation for the kinship and to some extent a similar histological structure. It is possible that a sessile serrated adenoma develops from a hyperplastic polyp only under a few circumstances, so a reversal is unlikely.[4]

Traditional serrated adenoma

Because traditional serrated adenoma is a relatively uncommon lesion, the molecular properties are relatively poorly described and some results contradict each other. Compared to other serrated lesions, traditional serrated adenoma may be characterized by higher methylation of MLH1. BRAF (55%) and KRAS (29%) mutations, and attenuation of MGMT expression (63%) are also relatively common. In particular, KRAS mutations and MGMT attenuation appear to be more common in advanced lesions. The hypermethylation phenotype is demonstrable in most traditional serrated adenomas (79%).[4]

Serrated path of colorectal cancer

Three relatively broad molecular profiles of carcinomas arising from the serrated pathway have been described:[4][10]

1. BRAF mutation and significant CpC methylation (CIMP-H)
    1. associated with marked microsatellite instability (MSI-H)
    2. associated with microsatellite stability (MSS)
2. KRAS mutation and low CpC methylation (CIMP-L), microsatellite stability (MSS)

The BRAF mutation with microsatellite instability is a variant that occurs in 9–12% of colorectal cancers and is considered a classic tumor pathway derived from serrated lesions. Histologically, tumors are usually poorly differentiated or mucinous, inflammatory infiltration around the tumor is common, and tumor-infiltrating lymphocytes are numerous. The precursor lesion is a sessile serrated adenoma, the remnants of which can sometimes be detected. The key event is probably excessive DNA methylation. The attenuation of MLH1 expression is then probably responsible for the development of high-grade cytological dysplasias and for the instability of microsatellites. The changes lead to a very rapid progression to malignancy. This type of tumor is relatively resistant to non-surgical therapy, but its prognosis is relatively good.[4]

BRAF mutations with stable microsatellites represent a variant of approximately 9–8% of colorectal cancers. Histologically, these are usually poorly differentiated or mucinous carcinomas. Carcinomas have a relatively large potential to spread in lymphatic system and blood, and perineural spread is not uncommon. Hypermethylation is also responsible for the accumulation of mutations, but this is most likely due to p16/Wnt attenuation. The prognosis is probably poor.[4]

The KRAS mutation probably includes a group of 15–20% colorectal cancers. To some extent, this group is still a subject of controversy. It is thought that the precursor lesion could be a traditional serrated adenoma. Because the relatively high proportion of this group contrasts with the relatively rare occurrence of traditional serrated adenomas, the existence of other precursors is assumed. In addition to the KRAS mutation and (difficult to detect) lower methylation (CIMP-L), the methylation attenuation of MGMT expression is a hallmark.[4]

Clinical Behavior and Management

The biological behavior of individual lesions

Hyperplastic polyp, especially if small, has a very low risk of progression to colorectal cancer regardless of location. Hyperplastic polyps located to the right and with a diameter greater than 10mm may have a greater potential for malignant reversal, although only case reports and small numbers of cases are described.[5][7]

Traditional serrated adenoma has roughly the same risk of progression to colorectal cancer as conventional adenoma.[5]

Sessile serrated adenoma has the potential for malignant reversal. If cytological dysplasias are also present, the malignant potential is very high.[11]

Serrated polyposis syndrome poses a significant risk of colorectal cancer.[5]

Management of serrated lesions

The prevailing consensus is that all serrated lesions should be removed colonoscopically. The only exceptions are small hyperplastic rectosigma polyps, where several random samples are sufficient for histological examination.[11][2] Lesions smaller than 10mm are better tolerated by sharp technique, larger lesions can be tolerated by an electrocautery.[11] The margins of the serrated lesion may not be clearly visible, so it is sometimes appropriate to use contrast enhancement techniques such as mucosal staining, submucosal injection of contrast media, or special lighting.[2] Removal of serrated lesions can be very difficult or even impossible if they are located in the mouth of the appendicula or on the ileocecal valve.[2]

Surgical resection of a part of the intestine is rarely necessary. It may be suitable if the serrated lesion cannot be tolerated endoscopically. Surgical resection is considered even in the presence of multiple serrated lesions in the proximal colon.[2]

The ability of both sessile serrated adenoma and traditional serrated adenoma to turn into a tumor is relatively well demonstrated at the molecular level. At the clinical level, only case reports and studies monitoring only a small number of patients are available, so current knowledge is relatively limited. Therefore, it is necessary to approach recommendations and information on factors that predict further biological development with relative caution.[12]

The main factors identified so far that influence the prognosis of further development, ie the risk of reversal of colorectal cancer, is the following:[11]

- **Histological subtype**: SSA and TSA have a significantly higher risk than HP. The significance of dysplastic changes in SSA and TSA is not entirely clear, but they are likely to pose a higher risk than SSA or TSA. TSA without dysplastic changes.
- **Number of polyps**: A higher number of polyps is a risk factor for both the development of new polyps and malignant reversal.
- **Concurrent occurrence of conventional adenomas**: This is thought to be a higher risk condition, but direct evidence is lacking.
- **Localization**: The occurrence of SSA in distal colonies is unusual, but the prognostic significance is unknown.
- **Polyp size**: Serrated lesion size is a likely prognostic marker. E.g. the value of 10mm for SSA is to some extent arbitrary and it is possible that this limit will be changed.

There are several recommendations for monitoring and re-checking:

Recommended patient follow-up according to Rex et al. (2012)[2]

subtype	size	number	localization	control interval
HP	<10 mm	Any	rectosigma	population screening/10 years
HP	≤5 mm	≤3 mm	proximal to the sigmoid	population screening/10 years
HP	any	≥4 mm	proximal to the sigmoid	5 years
HP	> 5 mm	Any	proximal to the sigmoid	5 years
SSA/TSA	<10 mm	<3 mm	anywhere	5 years
SSA/TSA	≥10 mm	Any	anywhere	3 years
SSA/TSA	<10 mm	≥3 mm	anywhere	3 years
SSA/TSA	≥10 mm	≥2 mm	anywhere	1-3 years
SSA with dysplasia	any	Any	anywhere	1-3 years

Follow-up recommendations according to the German S3 guideline from 2008[7][5]

subtype	risk of cancer	control interval
HP	is not	no further checks are indicated
SSA	is, the severity is unknown!! 3 years	
TSA	is, the same or possibly higher than for conventional adenomas	3 years
mixed polyp	Yippee	3 years

If complete removal has not taken place, follow-up endoscopy should follow 2 to 6 months after the procedure.[7]

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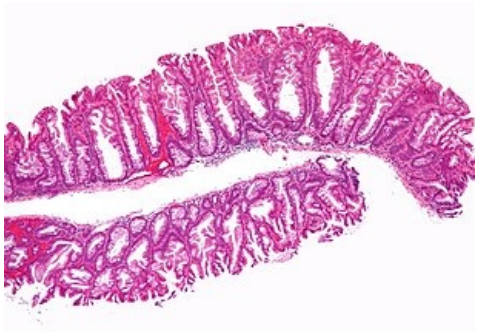
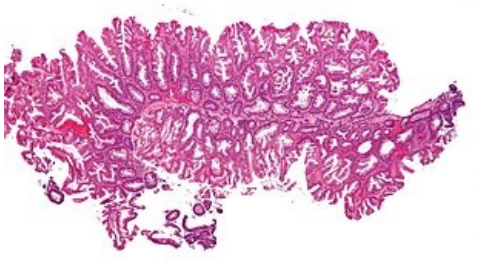
Virtual preparations



sessile serrated adenoma, H&E



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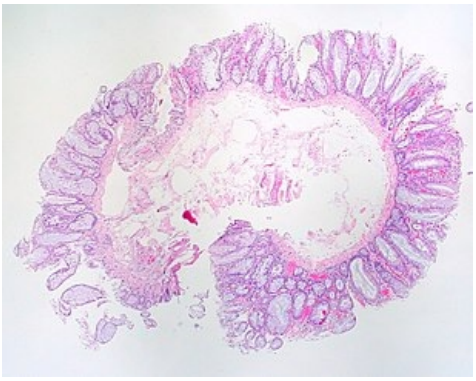
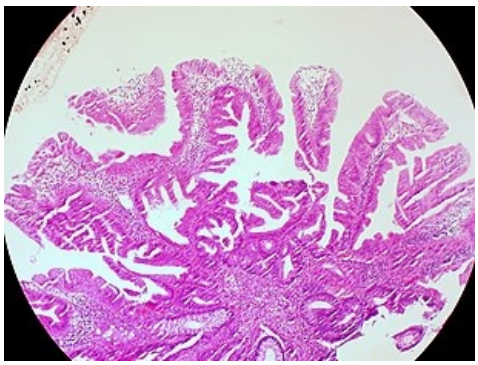
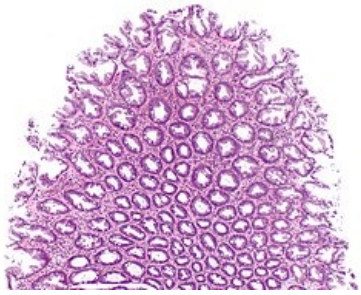


sessile serrated adenoma, pseudoinvasion, H&E



traditional serrated adenoma, H&E



hyperplastic polyp, H&E

Related Articles

- Vienna Classification of Gastrointestinal Neoplasias (2002)

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External links

- PathologyOutlines.com. *Colon tumor > Polyps > Serrated adenoma/polyp* [online]. ©2011. [cit. 2021-12-16]. <http://www.pathologyoutlines.com/topic/colontumorserrated.html>.