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Histological and molecular classification of gastrointestinal polyps

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ABSTRACT

Endoscopic diagnosis and treatment for gastrointestinal polyps became widely available within the last decades. Exact terminology is important for further therapeutic steps, follow up or treatment. Gastroenterologists, Oncologists, Surgeons and Pathologists need to be aware of the most recent terminology to ensure proper risk assessment and subsequent treatment if necessary. This manuscript aims to list the variety of gastrointestinal polyps and the molecular background where appropriate.

Contents

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1. Introduction

Despite the recent confusion over terminology the adenoma-carcinoma-sequence in the luminal gastro-intestinal tract from the stomach to the supraanal rectum is still valid. There is no doubt that the majority of adenocarcinomas still develops along this classical pathway [1–5]. A few follow a more recently described serrated pathway [6]. Adenomas are benign tumors of gastrointestinal mucosa. Since being unequivocal precursors complete endoscopic removal is recommended. The colon and rectum are more affected than the stomach or small bowel. Classical adenomas (Fig. 1) and serrated lesions (Fig. 2) are subclassified according to their histological type (Table 1) [7,8].

All of the above are defined as low grade dysplastic lesions or can develop low grade dysplasia within time and may progress to high grade dysplasia and carcinoma. In the stomach villous adenomas are often referred to as papillary adenoma.

Noteworthy is that only a complete polypectomy allows proper histological typing and staging. Thus polyps should always be removed completely, as national and international guidelines call for. Partial polypectomies should be avoided. Especially in the colon besides hyperplastic polyps the vast majority of polyps are unequivocally neoplastic and thus should always be removed completely (Table 2). In the stomach around 80% of all polyps are non-neoplastic and thus a biopsy (biopsies) seems to be the diagnostic method of choice to allow a histological diagnosis and plan further therapeutic or diagnostic steps. Generally, also gastric polyps should always be removed to allow proper histological work-up (Fig. 3).

2. Stomach

2.1. Non-neoplastic gastric polyps

As already stated the vast majority of gastric polyps consist of non-neoplastic lesions. Extremely helpful in the stomach are 2 biopsies from antrum and corpus each to determine the status of the surrounding gastric mucosa since this may ensure the correct

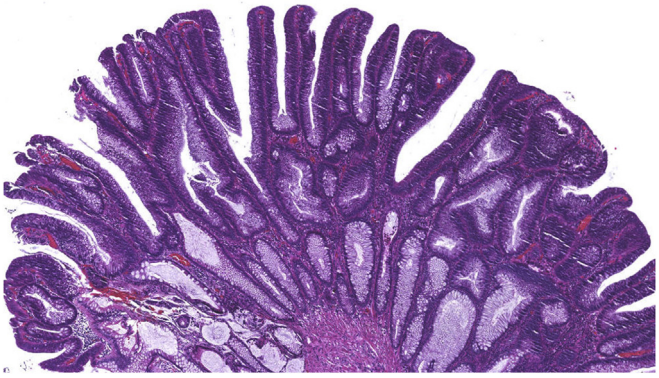

Fig. 1. Classical colon adenoma with elongated hyperchromatic palisading nuclei.

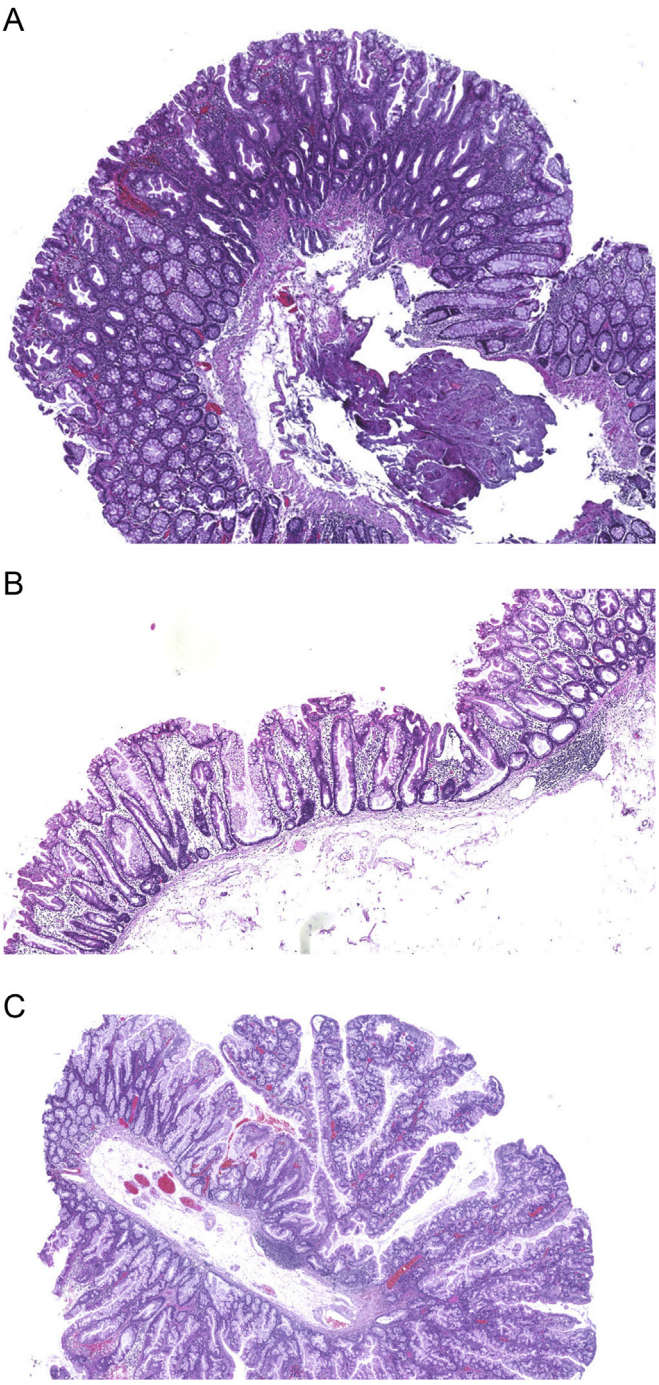

Fig. 2. A: Overview of a hyperplastic polyp with saw tooth serrated morphology confined to the upper half of the mucosa. **B:** Sessile serrated adenoma with T- and L-shaped glands at the base of the mucosa and complex hyperserration in the upper half of the mucosa. **C:** Traditional serrated adenoma with low grade dyplasia, hyperchromatic, elongated palisading nuclei and so called microacini (ectopic crypts).

Table 1
Risk of malignant transformation in colon polyps.

	Frequency	Carcinoma
1) Classical adenoma		
a) Tubular adenoma (<25% villous pattern of growth)	28%	10%
b) Villous adenoma (>75% villous pattern of growth)	4%	56%
c) Tubulovillous adenoma (25–75% villous pattern of growth)	22%	29%
2) Serrated lesions		
a) Hyperplastic (metaplastic) polyp (on normal with no dysplasia)	35%	0%
b) Sessile serrated adenoma/polyp (on normal with no dysplasia)	8%	<5%
c) Traditional serrated adenoma	2%	<5%

histological diagnosis of polypoid lesions in the stomach. The most frequent polyp in the stomach counting for almost half of all cases is the fundic gland polyp (Elster's polyp) that has been first described by Kurt Elster in 1976 long before PPI therapy (Table 3). It is known that there is a statistical coincidence with colorectal adenomas [9] that has been recently questioned again with a questionable design of a study [10]. Genta et al. claimed that the coincidence is valid at all for elderly females only. These polyps appear a little more frequently but not statistically significant under PPI treatment [11], however this is controversially discussed in the literature [12]. They definitively grow in size under PPI [12]. Especially under PPI therapy, fundic gland polyps can become very large and can appear as tumor-like lesions. Fundic gland polyps serve as a marker for a healthy stomach since fundic gland polyps are generally found in stomachs negative for helicobacter. In 80% of patients with familiar adenomatous polyposis (FAP) fundic gland cysts are found and this is a risk factor since 50% of these develop foveolar adenomas (see below) at the luminal side of the fundic gland polyp (that may give rise to gastric adenocarcinoma in FAP patients) [13].

The second most frequent polyp is the hyperplastic or hyperplasiogenic polyp of the stomach. These polyps tend to bleed. The risk for malignant transformation is around 0.3% with discrepant higher results found in the literature as well. It has to be noted that the risk in the literature [14–24] decreases with larger size of the study. Hyperplasiogenic polyps tend to recur even if completely removed and with time a growth in size can be noted. Due to the bleeding risk there is an indication for endoscopic removal. These polyps can become rather large with risk of bleeding and anemia. Misdiagnoses can happen when no endoscopic report is send along with the biopsies and granulation tissue is biopsied, with only little adjacent epithelium and the etiology of the lesion is overseen histologically.

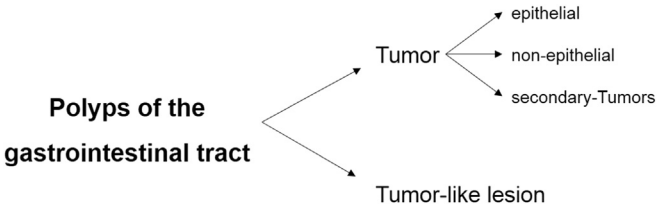

Fig. 3. Systematics of intestinal polyps.

The third frequent, very rare epithelial polyps are Peutz-Jeghers polyps, Juvenile polyps and the rare Cronhkite–Canada polyps. It needs to be noted that the histological signs of these polyps are rather subtle within the upper GI-tract and cannot be diagnosed without endoscopic diagnosis or clinical history of the patient especially when dealing with the possibility of a Cronhkite-Canada syndrome.

Another rare example are remnant oxyntic islands in autoimmune gastritis. Without the knowledge that there is an autoimmune gastritis, due to missing biopsies from non-polypoid areas in the stomach one would just assume that there are some hypertrophic parietal cells but would miss the diagnosis of a remnant island of oxyntic mucosa in autoimmune gastritis. A hitherto underdiagnosed polyp of the proximal stomach is the so called reflux polyp or sentinel polyp close to the gastro-esophageal junction [25]. The histological criteria are ill defined for the diagnosis of a reflux polyp and many pathologists are not aware of the existence of such a polyp since often the endoscopic description is not sent along with the biopsies. Normally it would take the combination of an endoscopically visible polyp with marked epithelial hyperplasia as criteria for a diagnosis but this requires an endoscopic diagnosis given to the pathologist. Smaller lesions without known cut-off levels are just diagnosed as foveolar hyperplasia that can be seen in the stomach quite often after a prior lesion or a recurrent epithelial damage such as gastroesophageal reflux.

2.2. Neoplastic gastric polyps

The adenoma-carcinoma sequence is also valid in the stomach

Table 2
Frequency of gastrointestinal polyps at the Institute of Pathology in Bayreuth in 2016.

(Frequencies in the colon are biased by the fact that small hyperplastic polyps are often not removed and thus not histologically evaluated!)

Stomach (among 72439 cases with gastric biopsies in 2016)
- 3647 tubular Adenomas
  - 7 pyloric gland adenomas
  - 9 foveolar Adenomas
- 3408 hyperplasiogenic (hyperplastic) polyps
- 5196 fundic gland polyps (Elster's cysts)

Duodenum (among 34373 cases with duodenal or peripapillar biopsies in 2016)
- 1752 tubular adenomas
  - 1 pyloric gland adenoma

Colon (50559 cases with colon biopsies or polypectomies in 2016)
- 17490 tubular Adenomas
- Serrated lesions
  - 15329 hyperplastic (metaplastic) polyps
  - 1532 sessile serrated adenomas
  - 41 traditional serrated adenomas

Table 3
Frequency of non-neoplastic and neoplastic gastric polyps (modified after [14,85]).

Non neoplastic (tumor-like) polyps: (N=7135)	
Fundic gland polyp (Elster's polyp)	47%
Hyperplasiogenic Polyp	28.3%
Inflamm. fibroid. Polyp	3.1%
Heterotopia	2.0%
Peutz-Jeghers Polyp	0.3%
Juvenile Polyp	0.1%
Cronkhite-Canada Polyp	0.1%
Neoplastic polyps	
Tubular Adenoma	18.3%
Pyloric gland Adenoma	2.1%
Tub. Pap Adenoma	1.6%
Papillary Adenoma	0.1%
Adenocarcinoma	10.1%
Neuroendocrine Tumor (NET)	2.7%

as it is in the small and large bowel. Endoscopically the variants and subtypes of gastric adenomas cannot be subclassified and require histology. In the stomach there are intestinal adenomas (approx. 95% of all adenomas within the stomach (Table 2)) found that share the morphology and genetics with tubular adenomas in the colon. It needs to be pointed out that tubular adenomas of the gastric cardia exist but are rare and Barrett's neoplasia growing into the proximal stomach should always be excluded [26]. Most adenomas are found in the antrum compared to other gastric sites. Interestingly this is not the site were most gastric carcinomas are found [27–30]. The most challenging task for a pathologist is to identify so called gastric differentiated adenomas that can derive from deep gastric mucous gland called pyloric gland adenoma (approx. 4.5% of all adenomas in the stomach), foveolar adenoma (approx. 0.5% of all adenomas) deriving from the surface epithelium and more rarely variants like chief cell adenoma (<0.1% of all gastric adenomas). These adenomas do not fulfill the classical criteria of neoplasia within the GI-tract since these lesions represent a different pathway of malignant transformation. The gastritis status may aid the diagnosis: pyloric gland adenomas are found more frequent in autoimmune gastritis of the elderly whereas foveolar adenomas are found mostly in normal stomachs of polyposis patients at the luminal side of fundic gland polyps (Elster's cysts) in the corpus mucosa [14].

2.3. Polyps due to secondary lesions in the stomach

Secondary lesions are not necessarily malignant, such as pancreatic heterotopia that can be seen in the form of acinar pancreatic heterotopia. They vary from mucosal lesions close to the gastro-esophageal junction that are so small that they cannot be readily identified endoscopically, to larger lesions in the antrum. They also include pure duct heterotopias that can be rather bothersome in cases of frozen sections performed during an operation and can be mistaken as neoplastic tubules.

On the other hand the stomach is a frequent site of metastasis of lobular carcinoma of the breast. In females with an otherwise normal stomach, immunohistochemistry helps to differentiate a metastasis from a primary gastric signet ring cell carcinoma. Kaposi sarcoma can also be seen in the stomach as dark polypoid lesions but due to more sufficient anti-viral therapies these lesions became far less frequent within the last decade.

Primary and extranodal lymphoma can involve the stomach as well. Always when dealing with a lymphoma especially when not a MALT Lymphoma, the primary site should be identified thoroughly.

2.4. Mesenchymal polyps in the stomach

Mesenchymal lesions found in the stomach are the same as in the small and large bowel, only their frequencies are different. The most frequent is probably the inflammatory fibroid polyp, followed by gastrointestinal stromal tumors. Neuroendocrine tumors (NET) are rare with no autoimmune gastritis. NET with no autoimmune gastritis tend to be more aggressive and TNM grading doesn't necessarily depict the clinical risk properly, since there can be very small NET in a normal stomach that are rather aggressive. On the other hand there could be those in autoimmune gastritis with high MIB-1 labelling but without a very aggressive behavior clinically (own data, unpublished).

3. Duodenal

The small bowel can contain all lesions that are found in the stomach and the colon as well. Also, pyloric gland adenoma can be found on the basis of a corpus heterotopia or gastric metaplasia in the small bowel [31]. The most frequent polyp in the small bowel especially in the bulb is hyperplasia of Brunner's gland. The term Brunnerom should be avoided since this could be confused with pyloric gland-like adenomas of the Brunner's glands. The second most frequent polyp is probably found close to the Papilla of Vateri in form of adenomyosis or more rare adenomyomatosis. Small accessory papillae should not be mistaken as a tumor. After biopsy there is a considerable risk for acute pancreatitis. Neuroendocrine tumors are rare and at least in the duodenum they often show a less aggressive clinical behavior. In the terminal ileum, NET have already metastasized in around 50% at first diagnosis. The TNM grading is not helpful at all since high mitotic count and high proliferation is almost always missing in these lesions. Even serrated polyps (see below) can be seen within the small bowel [32]. The clinical relevance is still not known. Multiple small polyps in the duodenum should let one think of a follicular lymphoma. Chott A. et al. described this entity in the small bowel in 2011 [33] and showed that these lymphomas are an own entity and are rather inert and stable and the best strategy for most cases is “watch and wait”.

A rather new finding is the spectrum of serrated lesions in the small bowel that seem to be rather rare and can be mistaken as reactive lesions. The same criteria as in the large bowel (see below) are applied. A very comprehensive series with histological criteria of these lesions is found at Rubio C. with animal experiments that can easily be transferred to the human small and large bowel [32].

4. Colorectal

4.1. Background classical colonic adenomas

The vast majority of colorectal adenomas consist of tubular adenomas (Table 2). Tubular adenomas are defined as unequivocal low grade intraepithelial neoplasia or low grade dysplasia. They can be stalked, wide or narrow based but also non-polypoid (less than 3 mm in height or less than twice the mucosal height) [34,38]. A notion aside is that non-polypoid adenomas are more frequently found in the stomach than within the colon. The discussion of neoplasia found in polyposis syndromes and neoplasia in chronic inflammatory bowel disease is not the topic of this article.

4.2. Etiology

Most of the molecular events concerning the etiology of the origin of adenomas are known. Normal proliferation is limited to the bottom of the crypts. The epithelial cells move towards the apical crypt openings and lose their ability to proliferate with their position within the crypt and will be desquamated into the lumen after their life time. *apc* mutations keep the ability of proliferative capacity within the cells especially in those cells migrating upwards. The results are little proliferative buds or aberrant crypt foci that can give rise to adenomas.

The size of the adenoma correlates with the frequency of malignant transformation (Table 4).

Thus the size represents a prognostic marker for the risk of

Table 4
Size of colon-adenoma and their frequency of malignant transformation [84].

Size	Frequency of transformation (adenocarcinoma)
≤ 5 mm	virtually 0%
6-15 mm	ca. 2 5%
16-25 mm	ca. 19%
26-35 mm	ca. 43%
>35 mm	ca. 76%

malignant transformation. That is why the size of a polyp should be given in endoscopic and histological reports [34].

Almost 50% of all adenomas are found in the rectum and sigmoid especially in individuals less than 60 years old. After the 6th decade right sided adenomas do increase with time.

4.3. Malignant polyp vs TNM stage

On general the term "malignant polyp" should be avoided and instead the correct TNM-stage used. The pathology report needs to include a size, the type of the polyp and proper staging according to TNM including depth of infiltration in micrometers from the lowest fiber of the muscularis mucosae [35]. The status of resection needs to be mentioned in the report as well. Further risk factors such as lymphatic vessel permeation, blood vessel permeation and tumor budding [36] and the distance to the basal margin should be given in micrometers as well [34]. In case of a stalked polyp with invasion into the submucosal layer, Haggitt levels [37] need to be given [34].

4.4. Non-polypoid adenomas

The term "flat" should be omitted since ill defined. Instead, the term "non-polypoid" is recommended and defined as less than twice the mucosal height and/or less than 3 mm in height [38]. It seems that these more aggressive adenomas especially when depressed are identified less frequently in western populations compared to Asian populations. With the help of chromoendoscopy the incidence rates of non-polypoid adenomas increased in the western world whereas it was always high in Japan even with no chromoendoscopy. This questions the accuracy of endoscopy in the West versus Japan [39].

The incidence of high grade dysplasia or high grade intraepithelial neoplasia in non-polypoid adenomas varies between 10 and 41% depending on size and study population. It is up to 10 times higher than the rate of malignant transformation of classical adenomas: 4% [40].

4.5. Pseudoinvasion

Pseudoinvasion is defined as misplaced glands within the submucosal layer. Etiologically this could be due to a prior biopsy or resection or is a sequel of glands proliferating through vascular gaps of the muscularis mucosae. Normally these pseudoinvasive glands are non-neoplastic or show low grade dysplasia only. They are surrounded by lamina propria that has been pulled into the submucosa as well. Characteristically hemosiderin loaded macrophages are found regularly. Men are more affected then females. The frequency is believed to be around 3% of all adenomas [41]. It is important not to overdiagnose pseudoinvasion as submucosal carcinomatous invasion. Some cases can be really challenging. If in doubt, a second opinion is recommended especially in cases with high grade dysplastic changes. But even pseudoinvasion can be an indication for surgery if not completely removed.

4.6. Background of serrated lesions

The emerging role of non-polypoid precursors of colorectal cancer especially within the proximal colon challenged the classical adenoma-carcinoma-sequence (Table 3, Table 5). So called interval carcinomas fueled the discussion. In the meantime it has turned out that also serrated lesions may lead to neoplasms [42]. The most frequent serrated lesion is the so called hyperplastic or metaplastic polyp (due to the fact that the mucin composition counts for a gastric metaplasia within the colon [43]), often found in the left hemicolon, often small and multiple and mostly considered as harmless.

Table 5
Risk of malignant transformation of colorectal polyps [61].

Polyp	Frequency	Risk of malignant transformation
Hyperplastic polyp	>85%	practically 0%
Hyperplastic polyposis	rare	50%
Adenoma	55%	Up to 35%, if > 1 cm
- tubular	→ 63%	
- villous	→ 11%	
- tubulovillous	→ 26%	
Fam. adenom. Polyposis	1%	100%
Traditional serrated adenoma	1%	estimated <5%
Sessile serrated adenoma	~11%	estimated <5%
Juvenile Polyposis	<1%	20-60%
HNPCC	5%	80%

Another member of the family of serrated lesions is represented by the traditional serrated adenoma described in 1990 by Longacre et al. [44]. The term adenoma was chosen since there is an unequivocal intraepithelial neoplasia present like in classical adenoma within an additional sawtooth −like glandular morphology with so called microacini. These microacini count for a special pathway in neoplastic transformation since they harbor neoplastic stem cells that lead to the unique morphology of such lesions. In classical adenomas the neoplastic stem cells are found within the middle to lower third of the crypt where they proliferate up- and downwards to colonize the whole crypt. Often traditional serrated adenomas are stalked and found in the sigmoid or rectum of elderly patients.

In 1996 Torlakovic et al. [45] were able to show the increased risk for colorectal carcinomas in patients with hyperplastic polyposis especially in the proximal colon. It could be shown that the precursor lesions were non-polypoid, broad based, hyperplastic polyps measuring more than 1 cm in diameter. Morphologically they can be seen as standing in between a hyperplastic (metaplastic) polyp and a traditional serrated adenoma. The confusion of terminology began when Jass et al. [46] identified such lesions in patients with no syndromatic background. First, nobody took note when Jass et al. described the malignant potential of these lesions and showed that this potential differs from the up till then known harmless hyperplastic (metaplastic) polyps. Only when Jass started to call those lesions "sessile serrated adenoma" to point out the difference to harmless hyperplastic polyps and draw more attention to such lesions [47], the scientific community woke up, especially when being able to show the genetic changes leading to malignant transformation in these lesions. This was the start of the

Table 6
Main and side criteria of sessile serrated adenomas by the German society of Pathology [50].

There are controversies about how many crypts need to be affected. Nevertheless this is a comprehensive list of criteria described in the literature	
Endoscopical	- often right sided - non polypoid (flat-sessile) - often > 5 mm
Histological	
• Major criteria	- Hyperserration, serration within the lower third of the crypt with or with no crypt branching - T- bzw. L-like crypts above muscularis mucosae - Inverted crypts (micro herniation) below muscularis mucosa - "column like" dilatation of the lower third of the crypt (with or with no mucus depletion)
• Minor criteria	- move of proliferation zone into middle third of the crypt displacement - Vesicular nuclei with nucleolei - - Mature goblet cells at the base of the crypts

confusion in terminology and histological definitions. What makes these lesions special is that they don't show any morphological signs of cytological neoplasia such as in a classical adenomas or traditional serrated adenomas. The chosen term "adenoma" for such lesions is thus a misnomer. But to make it more complicated these lesions can develop classical unequivocal intraepithelial neoplasia.

Secondly, these lesions are rather non-polypoid than justifying the term "polyp" suggested by some authors, resulting in another misnomer. In 2008 an international consensus conference [2,48] together with the late Jeremy Jass recommended to rename these lesions as "sessile serrated lesions".

The European Guidelines of colorectal cancer screening followed this recommendation. However this was ignored for reasons not very clear by national and international committees [49,50]. To help to overcome these difficulties and harmonize international terminology East et al. recommended in 2015 to name these lesions "sessile serrated polyp" [48]. Again this seems to be widely ignored for what reasons ever. Now, the latest British guidelines on colorectal carcinomas [51] went back to the European approach of calling such lesions 'sessile serrated lesion' which makes a lot of sense in terms of terminology. The future will show whether this late approach will be more successful than the earlier ones.

All this results in a confusion that is still ongoing since it was believed that up to 35% of all colorectal carcinomas develop from sessile serrated lesions [52]. It turned out that the frequency of malignant transformation has been anticipated around 15% [53]. On the other hand, the overall detection rate of sessile serrated polyps is believed to be around 1–2% of all colorectal polyps and thus is far lower than to be expected from the above mentioned numbers [54]. These lesions have distinct molecular pathways that are different from the well-established "adenoma–carcinoma" sequence by Fearon & Vogelstein [55]. In contrast to conventional adenomas, premalignant sessile serrated lesions show a higher incidence in females in the proximal colon, and are characterized by *braf* mutations, CpG island methylation, and microsatellite instability [56].

4.7. Molecular models of colorectal carcinoma

Colorectal carcinomas develop through a multistep model of various genetic and epigenetic alterations (Table 7) [46,57,58].

4.7.1. Genetic alterations

a) Chromosomal instability (CIN) follows after *apc* mutation with blockage of the Wnt-signaling pathway and affects chromosomes partly or complete. This leads to aneuploidy (that can be detected via cytomorphometric methods before histological changes can be seen) and activation of oncogenes (*kras*, *braf*) or inactivation of further suppressor genes (*tp53*). CIN is categorized as present or absent (CIN positive, CIN negative).
b) Microsatellite instability (MSI) follows a deactivating mutation of mismatch repair genes (*mlh1, msh2, msh6, pms2*) and leads to non-corrected mutations and/or deletions in important (for tumorigenesis) target genes. MSI is subclassified into not present (microsatellite stable: MSS), high grade (MSI-high: ≥2 loci) or low grade (MSI-low: 1 locus) (Table 8).

Table 8
Immunohistochemical results of tumors with microsatellite mutations.

MLH1	PMS2	MSH2	MSH6	Mutation
–	–	+	+	mlh1
+	–	+	+	pms2
+	+	–	–	msh2
+	+	+	–	msh6

Markers:

- DNA-mismatch-repair proteins are interacting as heterodimers (MLH1/PMS2, MSH2/MSH6) (Fig. 4).
- PMS2 and MSH6 proteins are instable in the absence of their respective dominant partner.
- With a combined staining for *mlh1* and *msh2* 92% sensitivity and 100% specificity for the identification of MSI-high tumors could be achieved [59].

Possible staining results:

- Loss of MSH2 and/or MSH6 is highly suggestive for hereditary tumors (Lynch Syndrome/HNPCC) (Fig. 5).
- Loss of MLH1 occurs more often in sporadic tumors than in hereditary, i.e. Lynch Syndrome tumors (serrated route: transcriptional silencing, i.e. promoter methylation of *mlh1* in *braf* mutated tumors, but *mlh1* methylation may also occur also in *braf* wild type tumors)

4.7.2. Epigenetic alterations

These are based on hypermethylations of promoter regions of certain genes (CIMP). This hypermethylation phenotype is directly connected to an initial mutation of the *braf* oncogene. A high degree of aberrant promotor hypermethylation leads to deactivation of various genes especially the O6-Methylguanin–DNA-Methyltransferase (*mgmt*). The CIMP phenotype is subclassified into negative (CIMP-negative), low grade (CIMP-low) and high grade (CIMP-high) [60].

4.7.3. Genomic profiles

Colorectal carcinomas can be subclassified according to their morphology (e.g. mucinous carcinoma vs. tubular adenocarcinoma). It has to be noted that this subclassification based on morphology is unsafe concerning the serrated vs. non-serrated pathway since the initial changes often cannot be seen in advanced tumors anymore. Genomic profiles can help in such a situation [46]. In colorectal carcinomas CIN, MSI, CIMP and the initial mutations of *kras* and *braf* oncogenes are important since

Table 7
Mutational analysis of serrated subtypes of colorectal lesions (modified after [49]).

	Proliferation	BRAF mut.	KRAS mut.	CIMP	MLH1 methyl.
a) Microvesicular	basal portion	+++	–	+	–
b) Goblet cell rich	basal portion	–	+++	Not clear	–
c) Mucin-poor	basal portion	Not clear	Not clear	Not clear	Not clear
SSA	variable	+++	–	+++	–
SSA with dysplasia	variable	+++	–	+++	++
TSA	ectopic crypts	+	+	++	–
Serrated polyposis	as per polyp subtype	++	+	+++	+

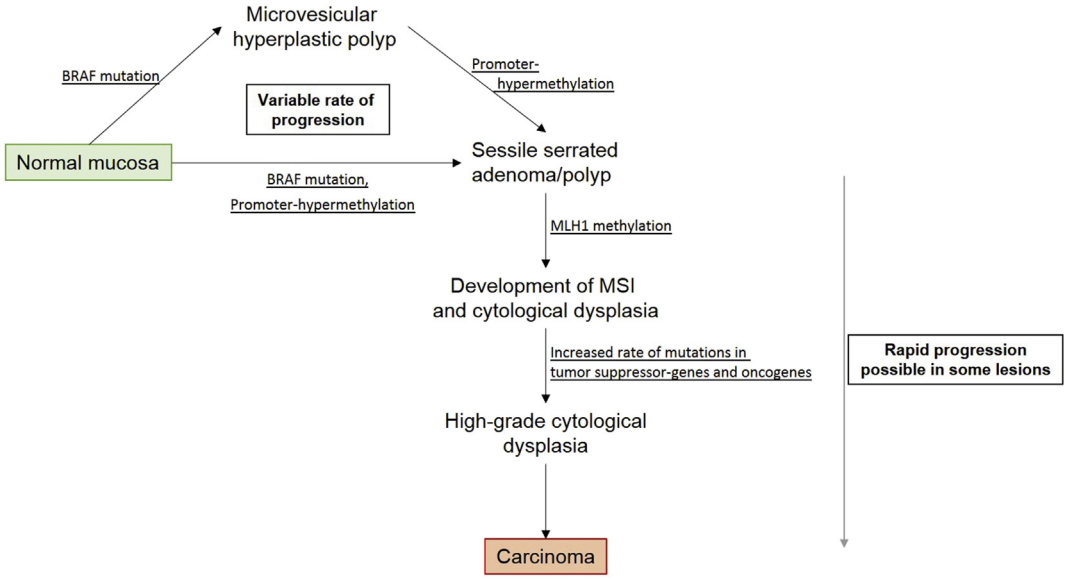

Fig. 4. Serrated pathway of colorectal lesions and malignant transformation (modified after [77]).

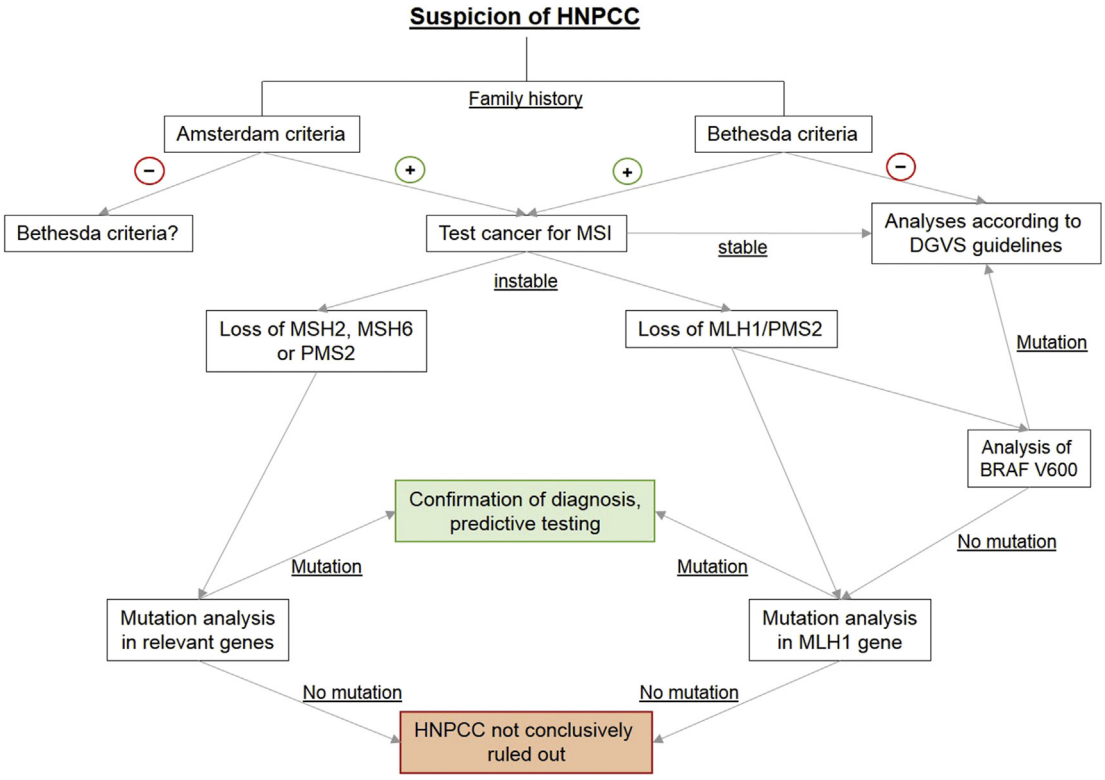

Fig. 5. Clinical pathway in MSI and mutation testing for clinical routine (modified after [86,87]).

therapeutically relevant [60–68]. The combination of CIMP negative, MSS and CIN points to a non-serrated lesion (Fig. 6).

4.8. Non-neoplastic serrated lesions

4.8.1. Hyperplastic polyp

Hyperplastic (metaplastic) polyps are the second frequent polyps after tubular adenoma. Characteristically they show a sawtooth morphology by epithelial protrusions into the crypt lumen. They are often small (less than 10 mm in diameter), stalked or broad based and most frequently found in the left hemicolon and the microvesicular variant harbors a *braf* mutation [68–75]. In the right hemicolon they are more frequently the starting point for the so called serrated pathway of malignant transformation. The vast majority of Hyperplastic polyps do not undergo a malignant transformation [72,73]. Often the serration is limited to the upper

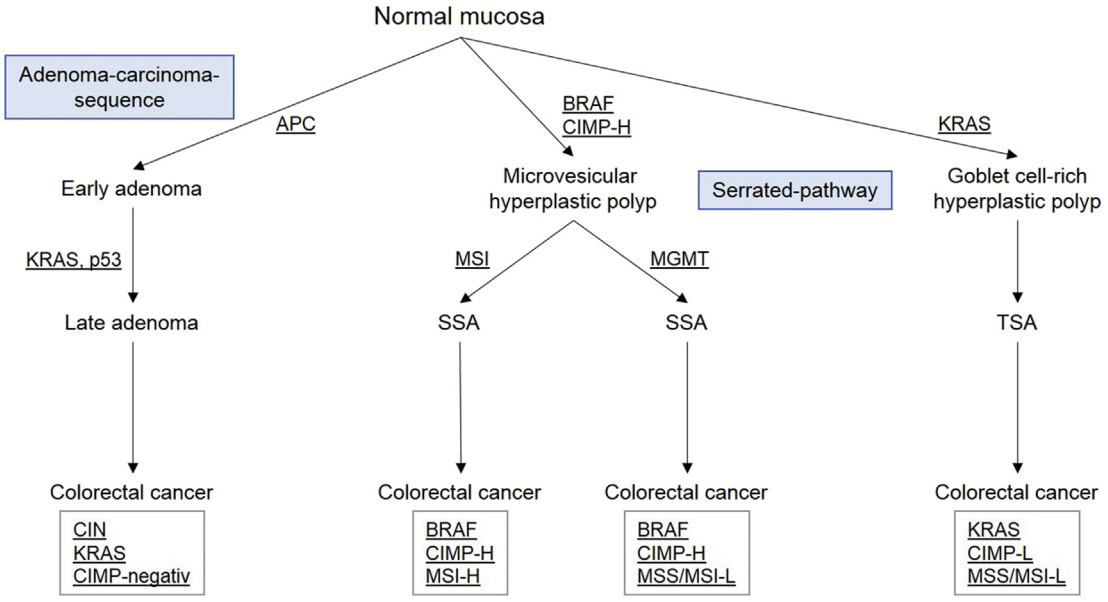

Fig. 6. Mutational analysis and classical and serrated pathways leading to four molecular different colon carcinomas (modified after [88]).

half of the crypts with no increased proliferation and no cellular atypia in the basal compartments. Several subtypes have been described but it is difficult and clinically not very important to subclassify different subtypes and thus guidelines recommend not to do so in routine cases [34]. The microvesicular variant is believed to have the capacity of progression towards sessile serrated adenoma/polyp.

4.8.2. Hyperplastic "aberrant crypt focus" (ACF)

The serrated subtype of ACF is the mono-(or oligo cryptal) precursor of a hyperplastic polyp and other serrated lesions. Serrated ACF show the characteristic serrated morphology with saw-tooth like epithelial protrusions within the upper half of the mucosa whereas the lower half shows a preserved regular proliferation. The serration is believed to be caused from a hampered maturation towards the surface including a reduction of apoptosis by inhibition of CD95 (FAS). The FAS receptor is a surface transmembranous receptor of tumor necrosis factor (TNF) that may activate apoptosis. Mutations of *kras* and *braf* are often detected at this stage but without the *apc* mutation which is a characteristic mutation in adenomas. Besides the serrated ACF there are also so called dysplastic ACF that are the basis for classical adenomas [76].

4.8.3. Sessile serrated adenoma

Sessile serrated adenomas do not contain classical signs of cytological intraepithelial neoplasia/dysplasia but structural alterations. The striking feature is an increased basal proliferation. Normal cryptal proliferations are directed to the apical portion of the mucosa but these lesions proliferate up- and downwards to a greater extent than is seen in all other gastrointestinal polyps/lesions. This leads to a unique morphological feature, namely a sideways directed growth of the crypts blocked by the muscularis mucosae resulting into L- and T-shaped or markedly dilated crypts with sawtooth like epithelial protrusions. At vascular gaps the glands grow through the muscularis mucosae leading to so called micro-herniations as another possible feature in some of the lesions. Further structural alterations are the presence of basal goblet cells as well as luminal hyperserration.

Nevertheless the criteria applied on how to diagnose are still not harmonized worldwide. The WHO classification cautiously withholds in naming clear cut diagnostic criteria but requests at least three affected crypts [49]. National guidelines are more practical in this respect but differ markedly. German guidelines give a list of major and minor criteria (Table 6) to identify such lesions with a good inter-and intraobserver variation [50]. The main difference to the more pragmatic approach of US recommendations lies in the fact that the Germans want to see at least 2 major criteria fulfilled by at least two neighboring crypts (Table 6). In the US [77] one crypt with the typical enhanced basal proliferation in combination with a complex architecture and showing T- or L-shaped crypts at the base is enough to make the diagnosis. This more simple approach shows good intra-and interobserver variation as well. It has never been tested so far whether one approach is superior to the other. Recently most experts favor the pragmatic and also reproducible approach of

Table 9
Follow-up intervals based on national and international colorectal guidelines (modified after [34,38]).

Polyp	Follow-up interval	Comment
Hyperplastic polyp	10 years	except hyperplastic polyposis
1-2 small tubular adenomas (LGD)	5-10 years	
3-10 small tubular adenomas	3 years	
1 adenoma >1 cm or villous component, serrated adenomas		
Adenoma with HGD/HGIEN	3 years	if not R0: control in 2–6 months
>10 adenomas	<3 years	familiar polyposis?
Adenoma in piece meal	2-6 months	if R0, further follow up 5 years

the US consensus. Unfortunately the three approaches lead to the situation that in Europe the number of sessile serrated adenomas is lower than in the rest of the world. The clinical implications are not clear yet.

Now doubt internationally that sessile serrated adenomas are found more often in the right colon and a *braf* mutation is found more often as compared to traditional serrated adenomas (see below) [78]. Regardless of the absence of cytological atypia sessile serrated adenomas show a risk of malignant transformation but the percentage of the risk is still under controversial debate. Around 15–20% of all colorectal carcinomas are believed to be developed from sessile serrated adenomas by mutational analysis [79, 80]. Interestingly the precursors of such carcinomas are rarely seen in routine, especially sessile serrated adenomas with low grade or high grade intraepithelial neoplasia. The finding of an invasive carcinoma within a sessile serrated adenoma is even far more rare than previously anticipated. Despite that a sessile serrated adenoma is a non-neoplastic lesion there is a risk of malignant transformation and a few of the progressive cases seem to progress very fast [81]. Thus all sessile serrated adenomas are pragmatically seen as ordinary adenomas that should be removed and receive a control endoscopy after 3 years [34].

These precursor lesions showing a sessile serrated adenomas with intraepithelial neoplasia were previously called mixed polyp but it turns out that such lesions should be seen as sessile serrated adenoma complicated by conventional neoplasia/dysplasia [82].

The guidelines recommend and a follow-up endoscopy 3 years after the initial diagnosis (Table 9).

4.9. Neoplastic serrated lesions

4.9.1. Mixed polyp

Most probably all mixed polyps represent sessile serrated adenomas complicated by conventional dysplasia [82]. Some authors recommend to name the different parts. It seems that these polyps are progressing to neoplastic serrated adenomas. The risk of malignant transformation is given by the unequivocal neoplastic adenomatous part.

4.9.2. Traditional serrated adenoma

These lesions are representing a mix of a serrated morphology and the cytology of classical adenomas. By their so called micro-acini they represent a different and unique pathway of neoplasia in the GI-tract [32]. A synonym for such micro-acini are ectopic crypts and are the characteristic morphological feature of these polyps. Most often traditional serrated adenomas are found in the distal colon of elderly patients. It is believed that the prognosis of carcinomas originating from traditional serrated adenomas is worse than compared to carcinomas based on other serrated lesions [83].

4.10. Mesenchymal polyps in the colorectum

Soft tissue tumors within the colorectum, small bowel and stomach include gastrointestinal stromal tumors, leiomyoma, lipoma and their malignant counterparts such as leiomyosarcoma, Karposi sarcoma and angiosarcoma. Non-neoplastic lesions include lymphangioma and lymphangiectasia (especially in the small bowel during digestion), hemangioma, inflammatory fibroid tumor (Vanek's polyp) that is found most frequently in the stomach and far less frequently in the small and large bowel. Granulation tissue polyps can be seen in the whole GI-tract often after a prior lesion. In the distal rectum a special variant that consists partly of granulation tissue is the so called mucosa prolapse found often in the elderly, and may appear as a polyp or an ulcer as well.

5. Summary

Precursor lesions in the GI-tract can be subdivided into classical adenomas (tubular, villous, tubulovillous) and serrated lesions (hyperplastic polyp, sessile serrated adenoma/poly, traditional serrated adenoma). The colon and the rectum are more affected than the stomach or the small bowel. In the stomach, as well as in the small and large bowel, non-neoplastic and neoplastic lesions are possible. Whereas the vast majority of gastric polyps consist of non-neoplastic lesions, the majority of colorectal adenomas are tubular adenomas (neoplastic). Classical adenomas and serrated lesions differ in their way of malignant transformation. The adenoma-carcinoma-sequence is characterized by a mutation in the *apc*-gene which leads to an uncontrolled growth of the cells. This results in little proliferative buds or aberrant crypt foci that can give rise to adenomas. Also a *kras* mutation can be seen in such carcinomas. In contrast, carcinomas arising from the serrated pathway are characterized by a CIMP-high or CIMP-low status as well as a *braf* or *kras* mutation. Polyps should always be removed completely, to enable a proper histological typing and staging.

Conflict of interest

None.

Practice points

- The adenoma-carcinoma-sequence is valid in the stomach as well as in the small and large bowel.
- A few adenocarcinomas result from a recently described serrated pathway.
- Polyps should always be removed completely, to allow proper histological typing and staging.
- The size of polyps represents a prognostic marker for the risk of malignant transformation. Thus the size should be given in endoscopic and histological reports.

Research agenda

- A consistent terminology should be defined and used for "sessile serrated adenoma/polyps/lesions.
- There should be worldwide uniform criteria applied on how to diagnose sessile serrated lesions.

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