ORIGINAL ARTICLE

The Origins of Colorectal Carcinoma

Specific Nomenclature for Different Pathways and Precursor Lesions

Andrea Tannapfel, Matthias Neid, Daniela Aust, Gustavo Baretton

SUMMARY

Background: The widespread application of molecular methods in pathology has yielded steady advances in our understanding of the origins of colorectal carcinoma. Multiple pathways of carcinogenesis have been demonstrated on the molecular level and visualized on the histopathological level. The WHO has accordingly proposed a number of new designations and terms, particularly for precursor lesions, in order to establish a uniform standard for clinical diagnosis. These should be put into practice at once.

Methods: In this article, we explain the concept of intraepithelial neoplasia, which replaces the older concept of dysplasia. Moreover, we use this concept in describing a new mechanism of carcinogenesis for colorectal carcinoma, on the basis of a selective review of the literature. We estimate the frequency of precursor lesions according to the new concept using data from our own patient collective. Finally, we discuss the clinical consequences, which have been addressed in the German S3 guideline for colorectal carcinoma.

Results: The new type of precursor lesion, called “sessile serrated adenoma” (SSA), accounts for some 7% of all adenomas in our patient collective and is usually found in the right hemicolon. Traditional serrated adenomas (TSA) made up 1% to 3% of our cases and were found mainly in the left hemicolon and rectum.

Conclusion: Our observations on the frequency and location of serrated adenomas accord with the initial findings published in the international literature. In view of the risk that serrated lesions will progress more rapidly, it is recommended that they should be completely removed, with follow-up at a short interval thereafter (three years according to the German S3 guidelines).

► Cite this as

Tannapfel A, Neid M, Aust D, Baretton G: The origins of colorectal carcinoma: specific nomenclature for different pathways and precursor lesions. *Dtsch Arztebl Int* 2010; 107(43): 760–6. DOI: 10.3238/arztebl.2010.0760

The concepts of precursor lesions of adenocarcinomas of the gastrointestinal tract have significantly changed in recent years. While some innovations concern the whole digestive tract, other, new entities, for example in the colorectum, have also appeared. In this article, the term “intraepithelial neoplasia” (IEN) will generally be used to refer to the gastrointestinal tract as a whole. A new entity of precursor lesions of colorectal carcinoma is also described. This is discussed on the basis of the authors’ data and the results of a selective review of the literature.

While in the past the term “dysplasia” was used by pathologists and clinicians relatively heterogeneously, in recent years there has been a desire in Germany and abroad to use clear nomenclature. The terms “dysplasia”, “atypia” or “regenerative hyperplasia with atypia” should disappear from findings and be replaced by uniformly-defined terms.

The WHO has therefore proposed that the expression “dysplasia” be replaced by “intraepithelial neoplasia”. Intraepithelial neoplasia is to be understood as undoubted neoplastic epithelial proliferation, associated with an increased risk of carcinoma (i.e. a precancerous lesion) (1). This clearly distinguishes definite neoplasia from regenerative or metaplastic changes. When diagnosing intraepithelial neoplasia, the pathologist establishes that there are no inflammatory/regenerative or hyperplastic changes, but rather “genuine neoplasia” which is not yet invasive.

According to the WHO’s recommendations, the term “intraepithelial neoplasia” (IEN) therefore refers not only to lesions in the esophagus, Barrett’s esophagus, stomach or duodenum, but also to those in the colorectum. The rest of this article considers the particular situation of the colorectum, in which precursor lesions (adenomas) with intraepithelial neoplasias of varying severity are one of the entities most commonly examined in pathology.

Colorectal adenocarcinoma

Adenomas (IEN) of the gastrointestinal tract (stomach, small intestine, colorectum) are precursor lesions which may develop into adenocarcinomas after varying lengths of time (several months to years). The WHO divides adenomas into low-grade (LGIEN, low-grade intraepithelial neoplasia) and high-grade (HGIEN, high-grade intraepithelial neoplasia) forms.

Institut für Pathologie Ruhr-Universität Bochum: Prof. Dr. med. Tannapfel, Dr. med. Neid

Institut für Pathologie Universitätsklinikum Dresden: PD Dr. med. Aust, Prof. Dr. med. Baretton

GLOSSARY

● BRAF:

BRAF is a proto-oncogene with 94 kDa heavy protein belonging to the RAF family. It carries out serine/threonine protein kinase activity. The B-Raf protein is functionally important in signal transduction, cell division and secretion. Congenital BRAF mutations lead to cardio-facio-cutaneous syndromes. Acquired BRAF mutations are found in colorectal carcinomas, thyroid carcinomas, and also melanomas, for example. Patients with malignant melanomas who have a BRAF mutation benefit from a new drug, PLX4032, which inhibits the carcinogenic BRAF mutation.

● KRAS:

Like BRAF, KRAS is a proto-oncogene on chromosome 12, and encodes 21 kDa heavy protein which has vital functions in cell growth and cell differentiation. Congenital KRAS mutations are found in Noonan syndrome and cardio-facio-cutaneous syndromes. Acquired KRAS mutations are common in leukemias, colorectal carcinomas, and pancreatic carcinoma. KRAS is a biomarker which responds to treatment with EGFR blockades. Patients with colorectal carcinomas and wild-type KRAS respond to treatment, whereas activating KRAS mutations limit the effects of EGFR-blocking drugs.

● CpG island methylator phenotype (CIMP):

CpG islands are defined as DNA fragments 0.5 kb to 2 kb long inside a promoter. They have a guanine-cytosine base pairing proportion of more than 60%. The guanine-cytosine content of the genome as a whole is 40%. Methylation of these areas can be increased in carcinogenesis. The increased binding of methyl groups to the cytosine of a guanine-cytosine dinucleotide can suppress transcription and therefore expression of tumor-suppressor proteins in particular. This mechanism can "switch off" genes. CIMP-high tumors, in which many genes are affected, can be distinguished from CIMP-low carcinomas, in which few genes are inactivated by promoter methylation.

● Chromosomal instability:

Chromosomal instability is characterized by structural or numerical anomalies of the regular diploid (2n) genome. A distinction is made between aneuploidies, i.e. numerical increases or losses of whole chromosomes or segments of chromosomes, and structural changes in chromosomes. These structural changes include insertions, deletions, translocations, inversions and amplifications of the DNA fragments. Like numerical changes, these changes can also lead to uncontrolled growth and differentiation, and therefore to tumor development.

● Microsatellite instability:

Microsatellites are repeated preserved mono- to tetra-nucleotide sequences which are distributed throughout the genome and may be repeated between 10 and 60 times. At these locations, natural replication errors can occur frequently during DNA amplification. These are recognized and corrected by the intact mismatch repair system. This system consists of various proteins which recognize incorrect base pairs within DNA and can "repair" them. If one of these proteins, usually MLH1, is altered (e.g. by a germline mutation in HNPCC syndrome) or is no longer expressed due to increased methylation, these incorrect pairs can accumulate in the form of mutations in genes that play a role in tumor genesis. This is genetic instability, as distinct from chromosomal instability. This phenomenon can be detected using molecular biology techniques, due to the change of microsatellites in the tumor cell genome as compared to the genome of healthy cells. In terms of severity, a distinction is made between microsatellite stability (MSS), low microsatellite instability (MSI-L), and microsatellite instability (MSI).

FIGURE

	Group 1	Group 2	Group 3	Group 4	Group 5
Location Sex Precursor lesion	<p>Right > left F > M Serrated adenoma</p>	<p>Right > left F > M Serrated adenoma</p>	<p>Left > right M > F Serrated adenoma/adenoma</p>	<p>Left > right M > F Adenoma</p>	<p>Right > left F > M Adenoma</p>
Difficult differentiation (G3)	+++	+++	+	+	++
MSI status	H	S/L	S/L	S	H
Methylation	+++	+++	++	+/-	+/-
Ploidy	2n > aneuploidy	2n > aneuploidy	Aneuploidy > 2n	Aneuploidy > 2n	2n > aneuploidy
Mutations					
APC	+/-	+/-	+	+++	++
KRAS	-	+	+++	++	++
BRAF	+++	++	-	-	-
TP53	-	+	++	+++	+

Location, precursor lesions, histopathology, and genetic alterations of the (at least five) carcinogenesis pathways for colorectal carcinoma identified to date (modified according to [5, 7, 8])

If an adenoma is not removed, adenoma cells continue to proliferate. On average, adenomas increase their volume by 52% in 2 years (2). Most adenomas are located in the rectum or the sigmoid colon (66% to 77%).

In terms of their histological growth patterns, the most common form is tubular. Tubular adenomas account for more than 80% of adenomas. These (70% to 80% of all adenomas and approximately 90% of adenomas measuring <1 cm) can be distinguished from villous (>80% villous structures) and tubulovillous (20% to 80% villous location) adenomas (approximately 20% of all adenomas combined).

The incidence of HGIEN or invasive carcinoma in an adenoma is correlated with increasing adenoma size, increasing villous architecture (approximately 20% of villous/tubulovillous adenomas show HGIEN), occurrence of multiple adenomas and patient age (3, 4). For example, the incidence of invasive carcinomas in tubular adenomas measuring <1 cm is around 1% to 2%, whereas this increases to >50% in villous adenomas measuring >2 cm (4).

New pathways for colorectal carcinomas: serrated carcinogenesis

The adenoma-carcinoma sequence formally described pathologically by Morson (6) and highlighted by Fearon et al. (7) with characteristic molecular changes had been used since the late 1980s as the main pathway for sporadic carcinogenesis in the colorectum. The primary key mutation for the adenoma-carcinoma sequence affects the APC gene. Secondary genetic alterations are mutations of TP53 and KRAS, as well as development of chromosomal instability (CIN). Microsatellite status (MSS), however, is stable (5). It is currently thought that approximately 60% of sporadic carcinomas develop according to the adenoma-carcinoma sequence. The precursor lesions of this multistage concept are tubular, tubulovillous, and villous adenomas with varying degrees of intraepithelial neoplasia. In recent years, molecular genetic findings have demonstrated that there are other pathways besides the adenoma-carcinoma sequence:

- Serrated carcinogenesis, in which the relatively new entity “sessile serrated adenoma” (SSA) is considered to be the precursor lesion.

TABLE 1

Frequencies of diagnosis and location of adenomas in the patient collectives of two institutes of pathology

	Adenomas (N)	"Classical" adenomas % of all adenomas	Sessile serrated adenomas (SSAs) % of all adenomas	Traditional serrated adenomas (TSAs) % of all adenomas	Mixed polyps % of all adenomas
Ruhr University Bochum	8211	88% (n = 7226)	8% (n = 657)	3% (n = 246)	1% (n = 82)
Dresden University Hospital	2814	94.5% (n = 2654)	3% (n = 79)	1% (n = 26)	0.5% (n = 10)

Number of colorectal adenomas diagnosed in 2008 at the Institute of Pathology of the Ruhr University Bochum and the Carl-Gustav-Carus University Hospital at Dresden University of Technology, differentiated according to type of adenoma and, in the case of "classical" adenomas, according to the degree of intraepithelial neoplasia (IEN)

- A mixed type, which combines molecular features of both of the other carcinogenesis pathways and of which "traditional serrated adenoma" (TSA) or villous adenomas may be the precursor lesions (8, 9).

The primary key mutations for the alternative, serrated pathway are in the BRAF gene, with disruption to apoptosis of the crypt epithelia, followed by senescence with epigenetic methylation of promoters (CpG) and consecutive gene deletions (e.g. deletion of hMLH1, MGMT, p16), and usually high microsatellite instability (MSI-H). In the mixed type, the primary genetic aberration is KRAS mutation with secondary epigenetic methylation of promoters (CpG) and gene deletions, and there are also mutations of the APC and TP53; microsatellite status is either slightly unstable (MSI-L) or stable (MSS). This difference is therefore clinically relevant, as carcinomas which develop according to the alternative, serrated pathway are mostly located on the right or proximally and have a good prognosis, with a five-year survival rate of >70%, whereas the second subtype develops mainly on the left or distally and has an unfavorable prognosis, with a five-year survival rate <30% (8) (*Figure*).

As the serrated pathway for colorectal carcinoma development may progress more rapidly, knowledge and diagnosis of precursor lesions are vitally important.

Histologically identified precursor lesions

The new entities (sessile serrated adenoma [SSA] and traditional serrated adenoma [TSA]) have only recently been defined. They are precursor lesions of carcinomas which develop according to the serrated carcinogenesis pathway. Hyperplastic polyps (HPs) are non-neoplastic lesions. However, data which have come to light only now and the relatively similar, but not identical, morphology of hyperplastic polyps and sessile serrated adenomas (SSAs) make it likely that SSAs were previously wrongly classified as hyperplastic polyps.

Sessile serrated adenomas

Typically, sessile serrated adenomas (SSAs) measure >5 mm, are located in the right colon, and are flat. They do not protrude into the gut lumen like polyps (10–13). SSAs are relatively difficult to identify via endoscopy.

They can be distinguished from the surrounding area by a supporting mucous membrane. Because of their morphology and location, they could be a major cause of so-called interval carcinomas.

It is no longer disputed that SSA is a precursor lesion of the serrated carcinogenesis pathway. Differential diagnosis of HP and SSA rests on a typical overall picture with characteristic SSA criteria such as the following:

- L- and T-shaped branching at the crypt base
- Serration as far as the crypt base
- Dilated crypts, basally often angular
- Occasional "inverted crypts" extending under the lamina muscularis mucosae.

Traditional serrated adenomas

Unlike SSAs, traditional serrated adenomas (TSAs) are polypoid lesions which develop in the gut lumen. They combine the serrated architecture of hyperplastic polyps with the IEN of classical adenomas. They account for approximately 1% of all colorectal adenomas and are mainly located in the left colon or in the rectum.

Molecularly, TSAs are characterized by a high frequency of KRAS mutations (12).

Mixed polyps

The term "mixed polyp" covers a varied group of lesions which may include features of serrated adenomas, hyperplastic polyps and classical tubular, tubulovillous, or villous adenomas.

In general, the term "polyp" is ill-advised, as it does not reflect the preneoplastic nature of these lesions. However, international literature does use this term. The Gastrointestinal Pathology working group of the German Society of Pathology therefore recommends that the morphological components of the lesion should be stated first and the term "mixed polyp" given in brackets afterwards, e.g. "sessile serrated adenoma and tubular adenoma with low-grade intraepithelial neoplasia (mixed polyp)" (personal communication citation).

Hyperplastic polyps

Hyperplastic polyps (HPs) are the most common type of colorectal polyp. They are located mainly in the

TABLE 2

Location of sessile serrated adenomas (SSAs) in the colorectum (cf. Table 1)

SSA location			
	Colon to left flexure	Left flexure to rectum	Unclear
Ruhr University Bochum	73% (n = 482)	20% (n = 131)	7% (n = 44)
Dresden University Hospital	70% (n = 55)	18% (n = 14)	9% (n = 7)

rectum and the left colon and generally have a diameter <5 mm.

Hyperplastic polyps (HPs) are part of the hyperplastic subtype of the aberrant crypt focus. Some HPs, particularly lesions larger than 1 cm, are considered to be precursor lesions of TSA or SSA. A high proportion of these polyps have KRAS or BRAF mutations (11). It is thought that approximately 20% of all (larger) HPs located on the right-hand side progress to colorectal carcinomas. Endoscopic ablation should therefore be the target for these cases.

Do the location and morphology of entities affect diagnosis?

As differential diagnosis of precursor lesions as sessile serrated adenomas (SSAs) or traditional serrated adenomas (TSAs) is new, and criteria for diagnosis were not developed until recently, the question arises as to whether and to what extent lesions identified as hyperplastic polyps in the past would now be diagnosed as serrated lesions. As yet, the literature contains no unambiguous data on this. It is speculated that a high proportion of, in particular, hyperplastic polyps measuring more than 1 cm in the right hemicolon belong to the new category of serrated lesions now identified.

Only limited statements can be made on epidemiology and etiology, as several entities (e.g. sessile serrated adenoma) have only recently been defined. Our own data from 2008 may therefore not be representative. However, they can be used as comparative evidence.

Our data

In 2008, a total of 8211 patients in whom colon polyps had been detected endoscopically and for whom the diagnosis “adenoma” had been given or encoded were examined at the Institute of Pathology of the Ruhr University Bochum. There were 6819 diagnosed cases of “hyperplastic polyp” in Bochum in 2008, and naturally these were not classified as “neoplasia” or “adenoma.” As hyperplastic polyps do not present with intraepithelial neoplasia, they are benign and do not require any further clinical intervention.

At the Institute of Pathology of Dresden University Hospital, a total of 8452 colorectum biopsies were examined histologically in 2008. The diagnosis “adenoma” was given or encoded for 2814 of these biopsies.

Evaluation of the Bochum histological diagnoses showed that “classical” adenoma was diagnosed in 7226 cases, compared to a total of 2654 cases in Dresden. This gave a “classical adenoma” rate of 88% in Bochum and 94.5% in Dresden (Table 1).

Sessile serrated adenomas (SSAs) were found in 8% of the Bochum adenoma cases (n = 657) and 3% of the Dresden cases (n = 79), while traditional serrated adenomas (TSAs) were found in 3% of the Bochum cases (n = 246) and 1% of the Dresden cases (n = 26). Mixed polyps were identified in 82 patients from the Bochum collective (1%) and 10 cases from the Dresden collective (0.5%).

TABLE 3

Location of traditional serrated adenomas (TSAs) in the colorectum (cf. Table 1)

TSA location				
	Colon to left flexure	Left flexure to sigmoid colon	Rectum	Unclear + NS
Ruhr University Bochum	17% (n = 42)	23% (n = 56)	36% (n = 89)	24% (n = 59)
Dresden University Hospital	15.5% (n = 4)	19% (n = 5)	46% (n = 12)	19% (n = 5)

NS: Not stated

In the Bochum collective, 482 of the 657 sessile serrated adenomas (73%) were located in the cecum, ascending colon, and transverse colon. 131 of the lesions (20%) were removed from the descending colon, sigmoid colon, and rectum. In 44 cases (7%), the location could not be stated retrospectively.

55 (70%) of the 79 sessile serrated adenomas (SSAs) from the Dresden collective were located in the cecum, ascending colon, and transverse colon. 14% of the remaining SSAs (n = 11) were in other parts of the colon, and 4% (n = 3) were located in the rectum. In 7 cases (9%), the location could not be stated retrospectively. This means that 73% of the Bochum SSAs and 70% of the Dresden SSAs were in the cecum, ascending colon, and transverse colon (Table 2).

Of the TSAs from the Dresden collective, only 15.5% (n = 4) were located in the cecum, ascending colon, and transverse colon. 19% (n = 5) were in other parts of the colon. 46% of TSAs (n = 12) were located in the rectum. In 5 cases (19%), the location could not be stated retrospectively (Table 3).

6.5% of the SSAs and 34.5% of the TSAs in Dresden presented with high-grade intraepithelial neoplasia/epithelial dysplasia.

Comparison of the frequencies of the entities from each collective shows that the diagnosis "sessile serrated adenoma" (SSA) seems to increase in the right hemicolon in particular. This increase in incidence is doubtlessly also caused by altered biopsy behavior of those performing endoscopies, who recognize the significance of lesions previously described as "hyperplastic polyps."

Clinical consequences for treatment and precautions

According to the current S3 guideline of the German Society for Digestive and Metabolic Diseases (*Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten*, DGVS), polyps (diameter <5 mm; no coagulation artifacts affecting histological evaluation) must be completely removed using forceps or a loop or by mucosal resection (diameter >5 mm) and sent separately for histological examination, stating the location of the polyps.

Following piecemeal ablation of flat or sessile adenomas, the recurrence rate is significantly higher, particularly with larger adenomas (9% to 28%). The group of patients treated in this way should receive a follow-up colonoscopy at short intervals because of the increased rate of local recurrence or of metachronous lesions: first after 2 to 6 months, then after 3 years, and then after 5 years, or sooner for individual patients if needed.

For larger (≥ 1 cm) sessile serrated adenomas, particularly those on the right-hand side (previously classified as hyperplastic polyps), there seems to be a potential risk of accelerated progression to carcinoma (following the serrated carcinogenesis pathway). Complete removal and short follow-up intervals are therefore recommended in these cases (after 3 years according to current knowledge).

The follow-up care recommended after ablation of TSAs, which mainly develop in the left colon, is similar to that for SSA, due to an increased risk of progression.

In the event of incomplete or piecemeal ablation (edges impossible to identify with certainty using histological techniques), the follow-up interval for the biopsy site must be short. In these cases too, the target follow-up interval should be 2 to a maximum of 6 months.

In studies from the English-speaking world, the significance of the recommendation of the German guideline is discussed frequently, and the biopsy/ablation of precursor lesions larger than 1 cm in the colorectum is recommended. For these cases in particular, the way should be paved for virtual colonoscopy methods, which are not well accepted, at least in Germany, because of the lack of histological confirmation. In one current study (14), which recommends that lesions measuring less than 1 cm should not be biopsied or should be left in situ, the histological findings are extremely difficult to interpret, as serrated precursor lesions account for less than 1%.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 20 November 2009, revised version accepted on 20 April 2010.

Translated from the original German by Caroline Devitt, MA.

REFERENCES

1. Hamilton SR, Aaltonen LA (eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. Lyon: IARC Press 2000.
2. Hoff G: Colorectal polyps. Clinical implications: screening and cancer prevention. *Scand J Gastroenterol* 1987; 22: 769–75.
3. Jorgensen OD, Kronborg O, Fenger C: The Funen Adenoma Follow-Up Study. Characteristics of patients and initial adenomas in relation to severe dysplasia. *Scand J Gastroenterol* 1993; 28: 239–43.
4. O'Brien MJ, Winawer SJ, Zauber AG, et al.: The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. *Gastroenterology* 1990; 98: 371–9.
5. Hamilton S, Vogelstein B, Kudo S, et al.: Carcinoma of the colon and rectum. In: Hamilton S and Aaltonen L (eds.): Pathology and Genetics Tumors of the Digestive System. Lyon: IARC Press 2000; 105–43.
6. Morson BC: Precancerous lesions of the colon and rectum. Classification and controversial issues. *JAMA* 1962; 179: 316–21.
7. Fearon ER, Vogelstein B: A genetic model for colorectal tumorigenesis. *Cell* 1990; 61: 759–67.
8. Jass JR: Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007; 50: 113–30.
9. Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP: Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. *Am J Clin Pathol*. 124: 380–91.
10. Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM: Morphologic reappraisal of serrated colorectal polyps. *Am J Surg Pathol* 2003; 27: 65–81.
11. Carr NJ, Mahajan H, Tan KL, Hawkins NJ, Ward RL: Serrated and non-serrated polyps of the colorectum: their prevalence in an un-

selected case series and correlation of BRAF mutation analysis with the diagnosis of sessile serrated adenoma. *J Clin Pathol.* 2009; 62: 516–8.

12. Kim KM, Lee EJ, Kim YH, Chang DK, Odze RD: KRAS Mutations in Traditional Serrated Adenomas From Korea Herald an Aggressive Phenotype. *Am J Surg Pathol* 2010; 34: 667–75.
13. Bartley AN, Thompson PA, Buckmeier JA, et al.: Expression of gastric pyloric mucin, MUC6, in colorectal serrated polyps. *Mod Pathol* 2010; 23:169–76.
14. Ignjatovic A, East JE, Suzuki N, Vance M, Guenther T, Saunders BP: Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. *Lancet Oncol* 2009; 10: 1171–8.

Corresponding author

Prof. Dr. med. Andrea Tannapfel
 Institut für Pathologie
 Ruhr-Universität Bochum
 Bürkle-de-la-Camp Platz 1
 44789 Bochum, Germany