Medizinische Universität Graz

Colorectal Polyps

Minisympózium: Patológia Gastrointestinálneho Traktu

SD-IAP, Košice, Slovakia, 6-7 June 2019

European Network of Gastrointestinal Pathology
ENGIP

European Society of Pathology

Cord Langner MD
Diagnostic & Research Centre for Molecular BioMedicine
Institute of Pathology
Medical University of Graz, Austria

Outline

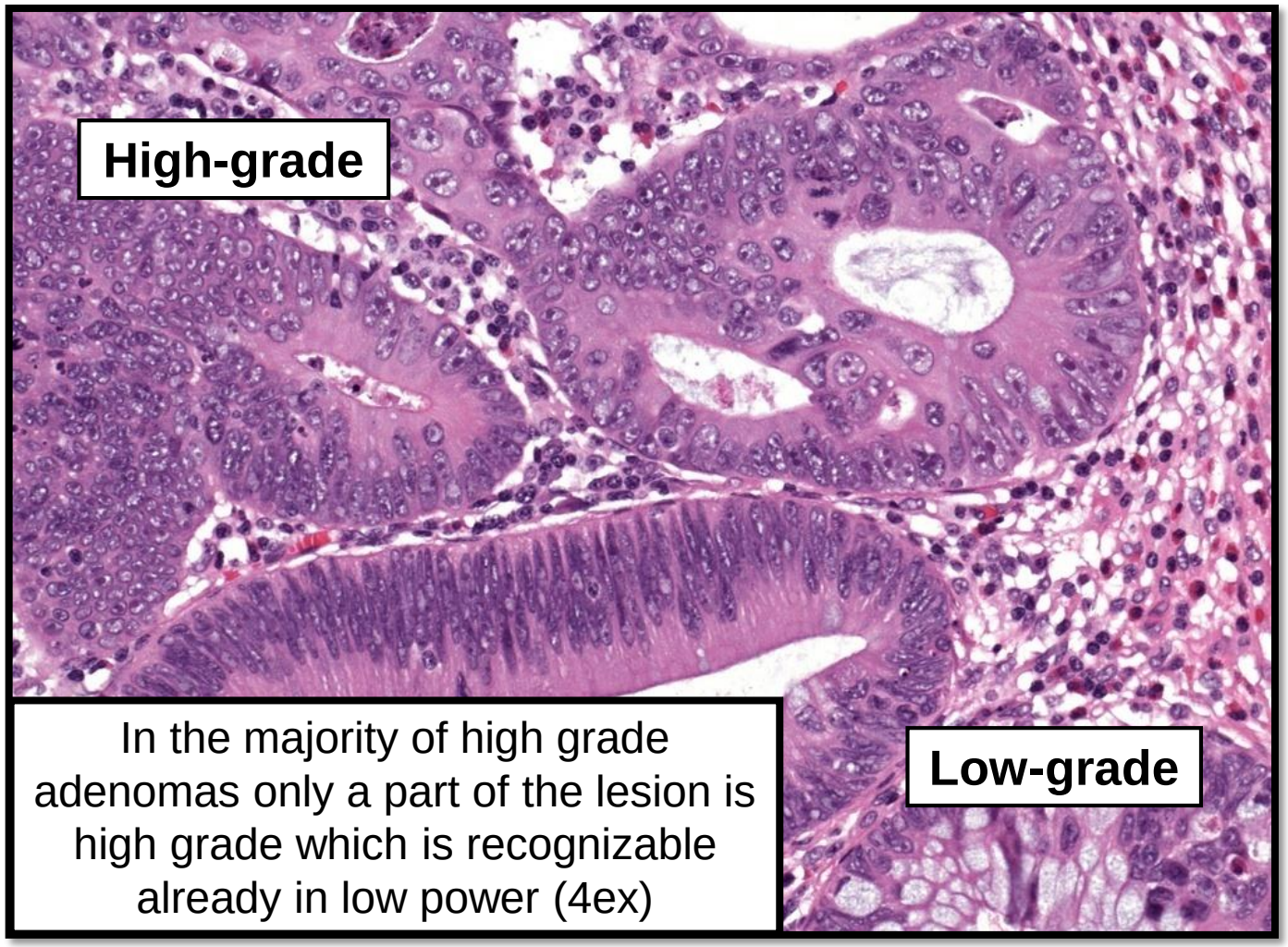
- **Classical adenomas**
  - Forms
    - Tubular adenoma (TA)
    - Tubulovillous adenoma (TVA)
    - Villous adenoma (VA)
  - Adenoma-carcinoma-sequence (sporadic and hereditary)
- **Serrated polyps**
  - Hyperplastic polyp (HP)
  - Sessile serrated adenoma / polyp (SSA/P)
  - Traditional serrated adenoma (TSA)
  - Molecular pathology: serrated route to cancer

Classical Colorectal Adenomas

- Adenomas are defined by the presence of dysplastic epithelium. This is characterized (…) by enlarged, hyperchromatic nuclei, varying degrees of nuclear spindling and stratification.

WHO Classification 2010

Classical Colorectal Adenomas



In the majority of high grade adenomas only a part of the lesion is high grade which is recognizable already in low power (4ex)

Histopathology

Histopathology 2016, 69, 187–197. DOI: 10.1111/his.12923

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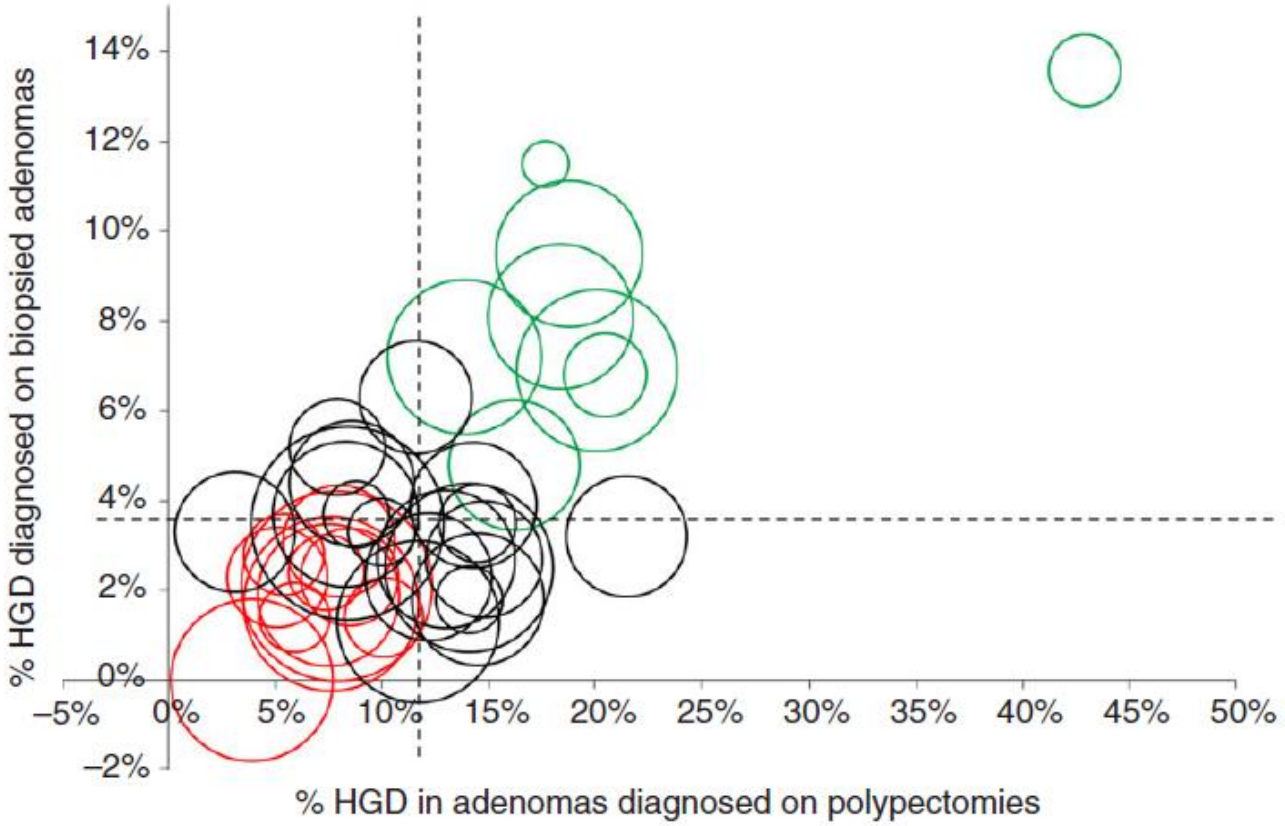
Interlaboratory variability in the grading of dysplasia in a nationwide cohort of colorectal adenomas

Chantal C H J Kuijpers,[1,2,3] Caro E Sluijter,[2,4] Jan H von der Thüsen,[5,6] Katrien Grünberg,[6,7] Martijn G H van Oijen,[2,8] Paul J van Diest,[1] Mehdi Jiwa,[1,3] Iris D Nagtegaal,[2,4] Lucy I H Overbeek[2] & Stefan M Willems[1,2]



Kuijpers et al. Histopathology 2016

Histopathology

Histopathology 2019, **74**, 925–932. DOI: 10.1111/his.13834

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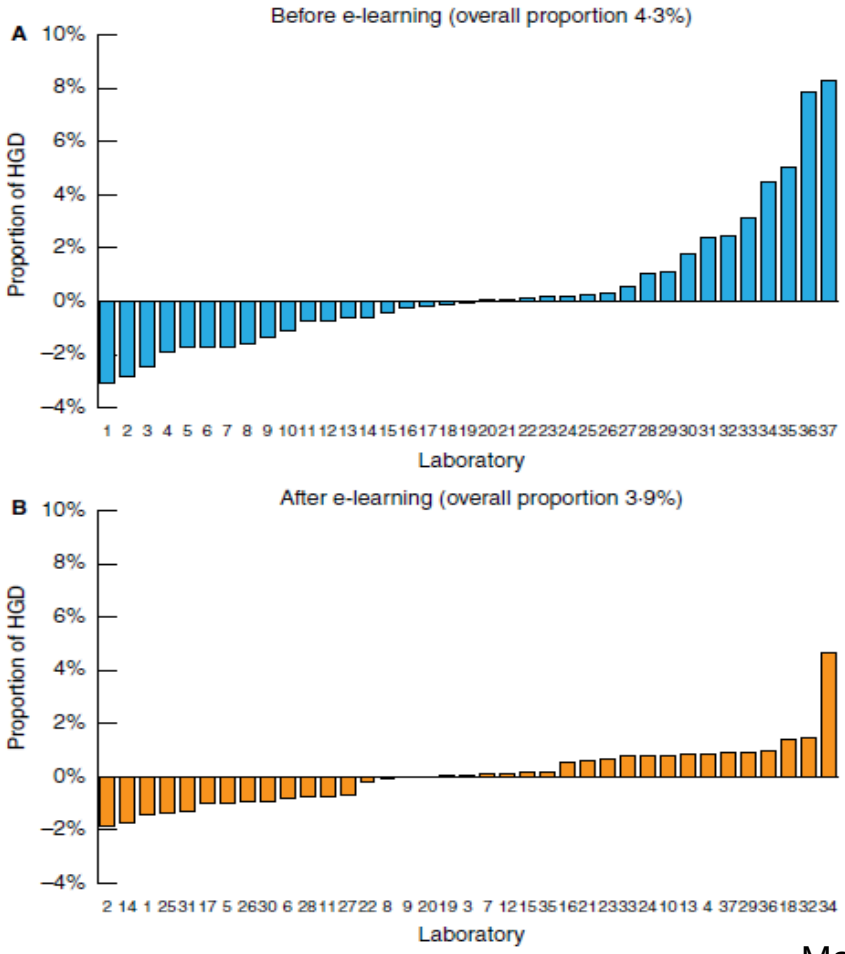
Decrease of variation in the grading of dysplasia in colorectal adenomas with a national e-learning module

Ariana Madani,[1,2,3] Chantal C H J Kuijpers,[1,4] Caro E Sluijter,[1,5] Jan H Von der Thüsen,[6] Katrien Grünberg,[5,7] Valery E P P Lemmens,[2,3] Lucy I H Overbeek[1] & Iris D Nagtegaal[1,5]



Madani et al. Histopathology 2019

Classical Colorectal Adenomas

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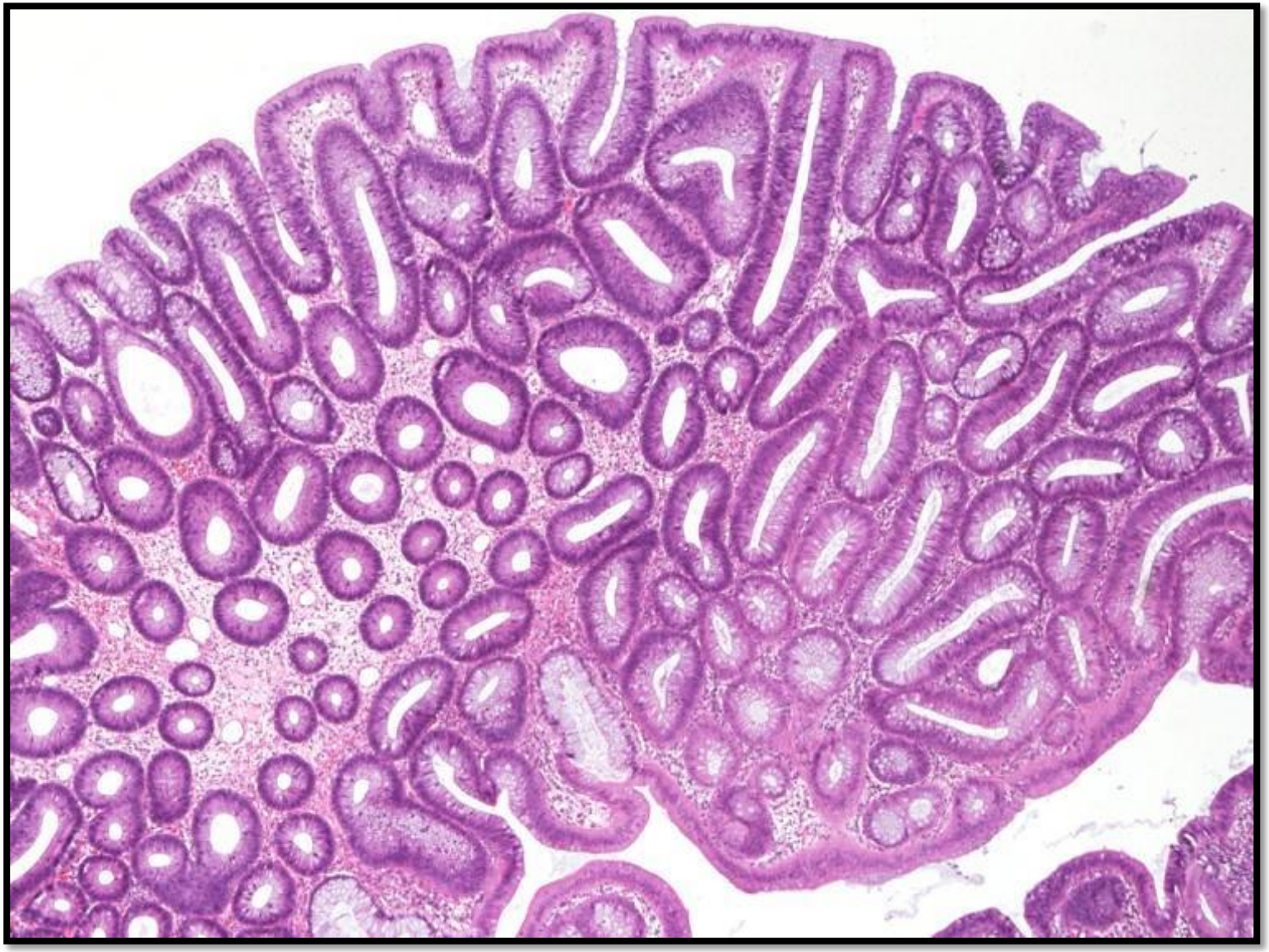
- Adenomas are defined by the presence of dysplastic epithelium. This is characterized (…) by enlarged, hyperchromatic nuclei, varying degrees of nuclear spindling and stratification.
- Most adenomas are <1cm in size and have tubular architecture.
- Villous architecture is defined as leaf- or finger-like projections of epithelium overlying a small amount of lamina propria.
- Tubulovillous adenomas are defined by a mixture of tubular and villous structures with arbitrary percentages in different studies, typically between 25% and 75% villous component.

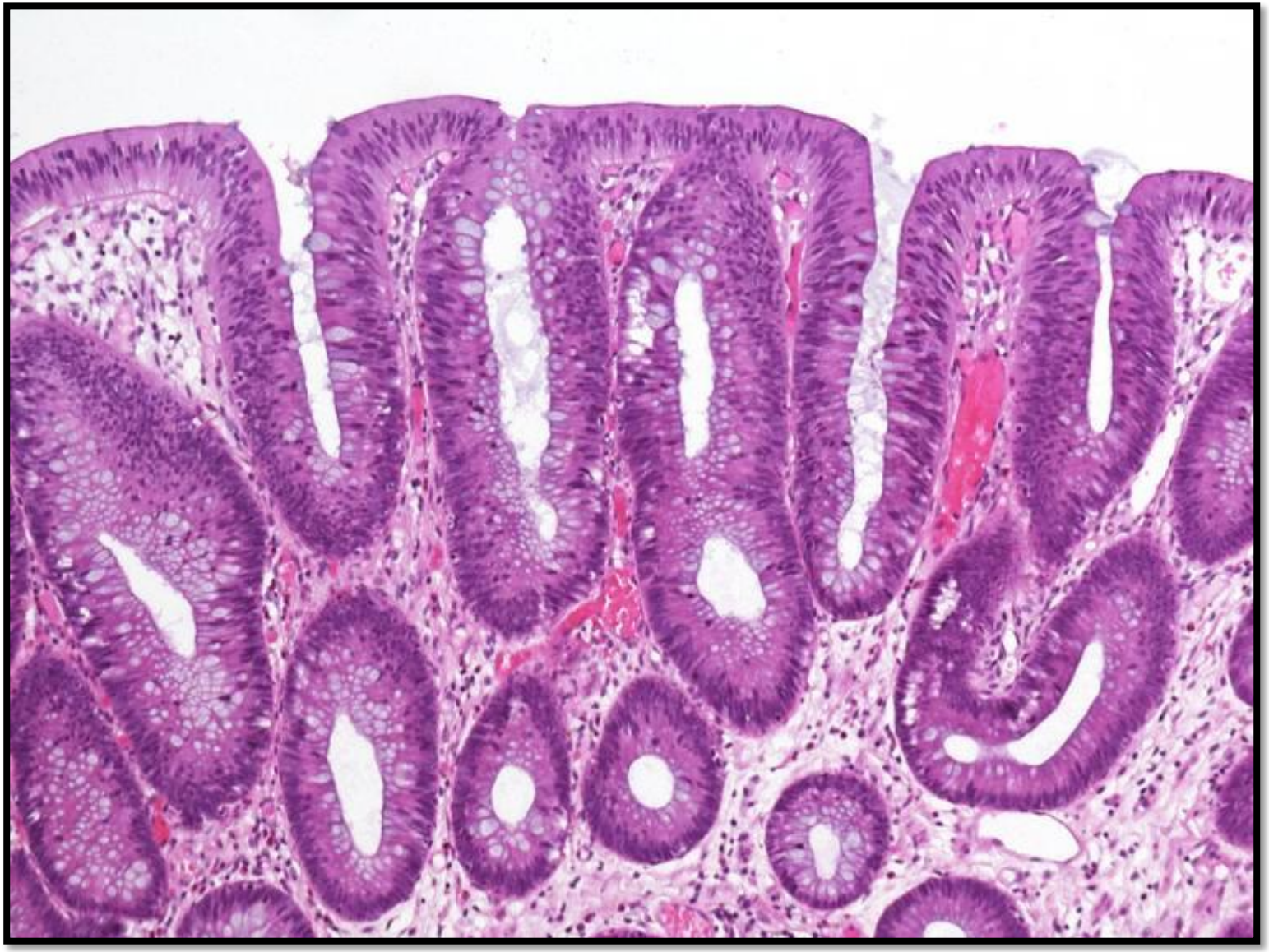
<25% villous components = tubular adenoma
25-75% villous components = tubulovillous adenoma
>75% villous components = villous adenoma

WHO Classification 2010

Tubular Adenoma



Tubular Adenoma



Tubular Adenoma

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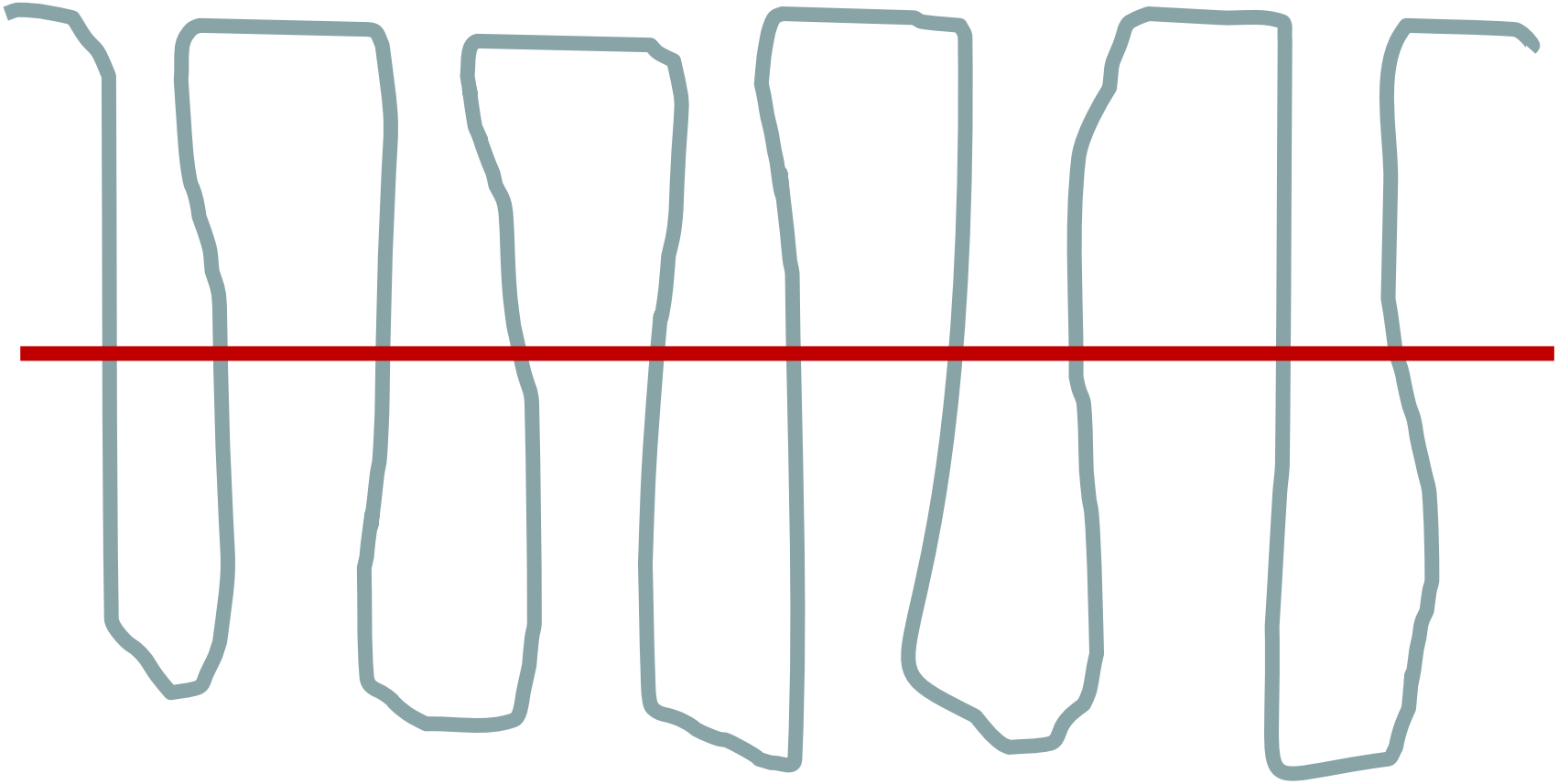
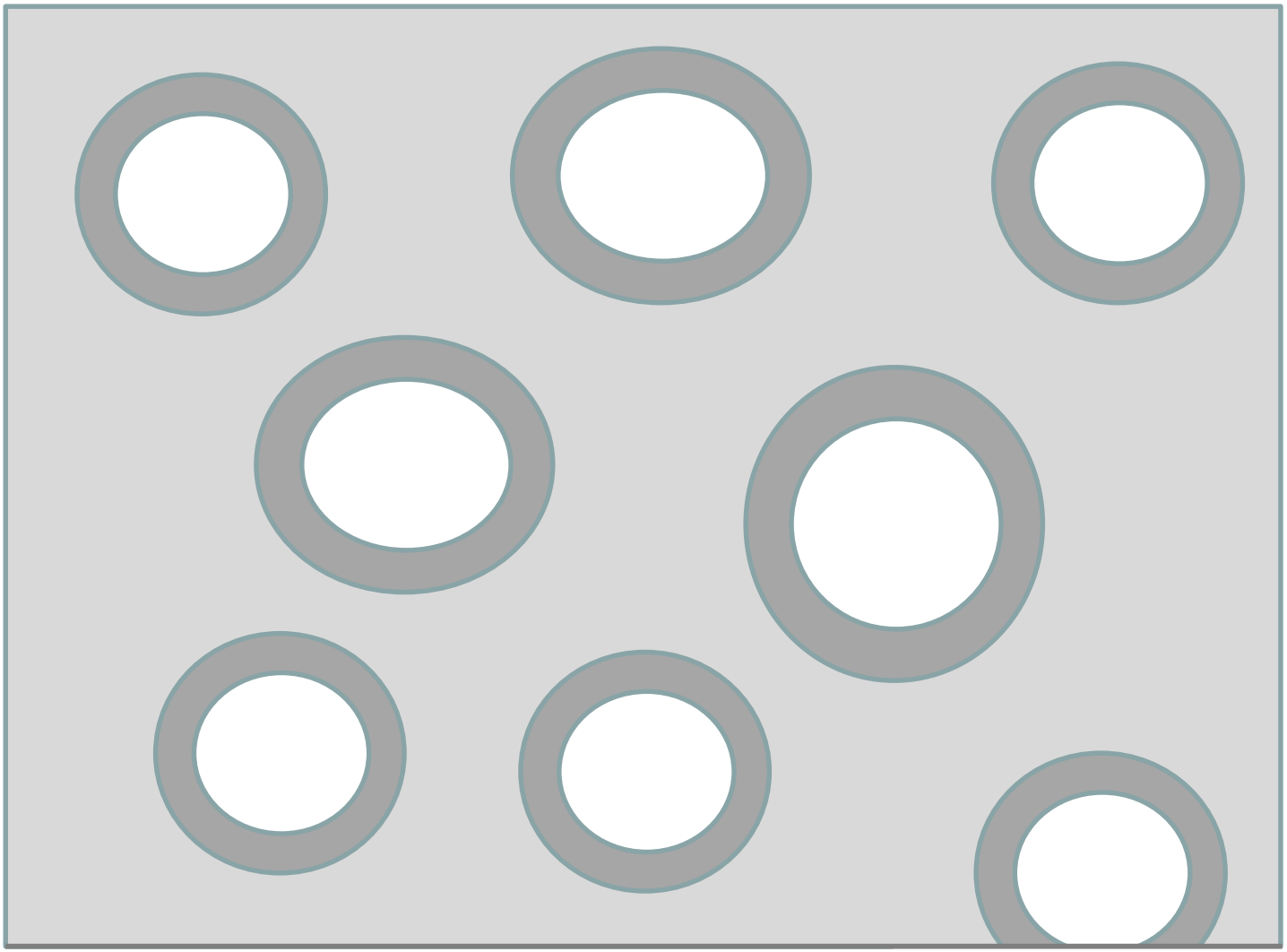
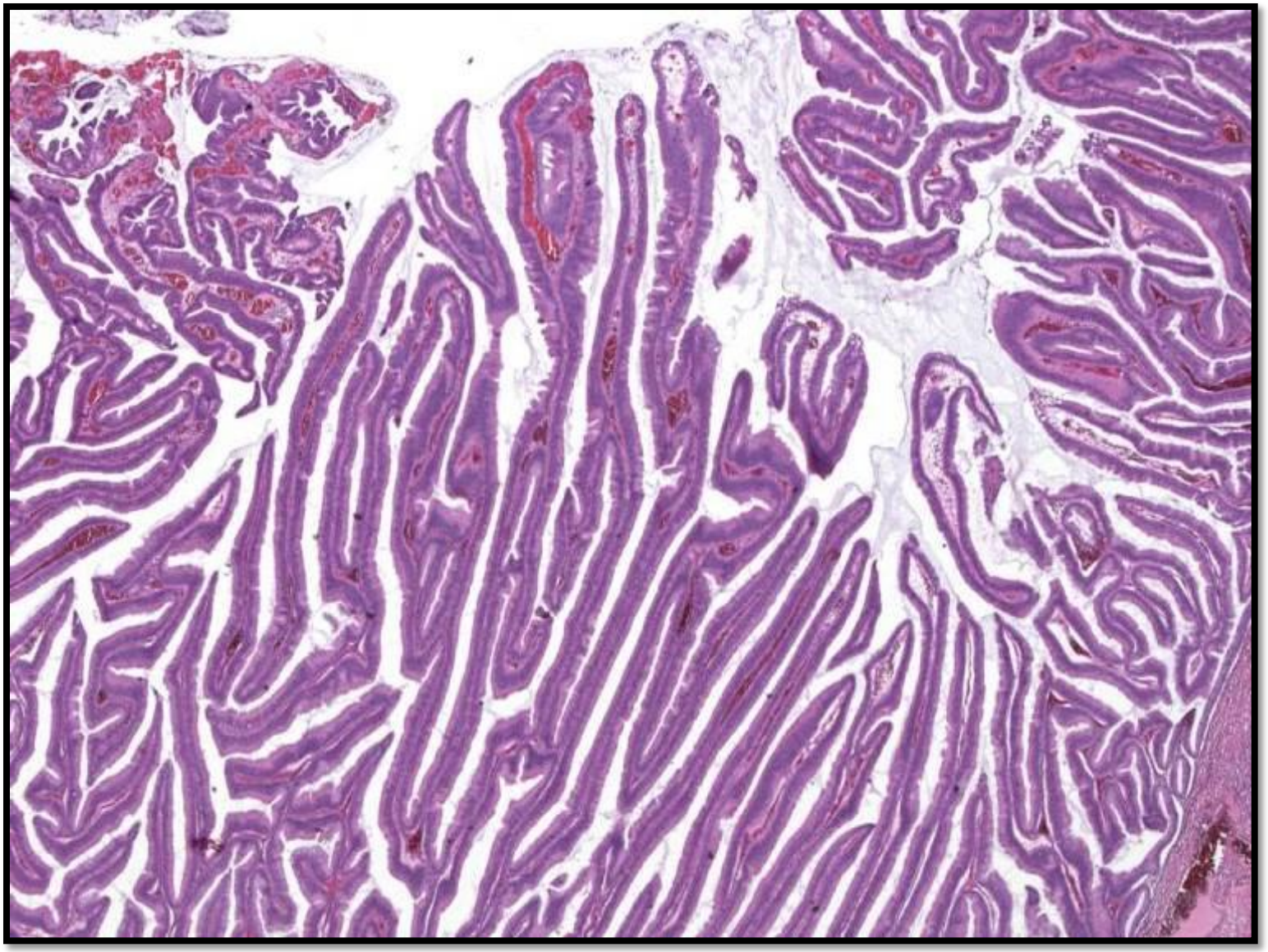


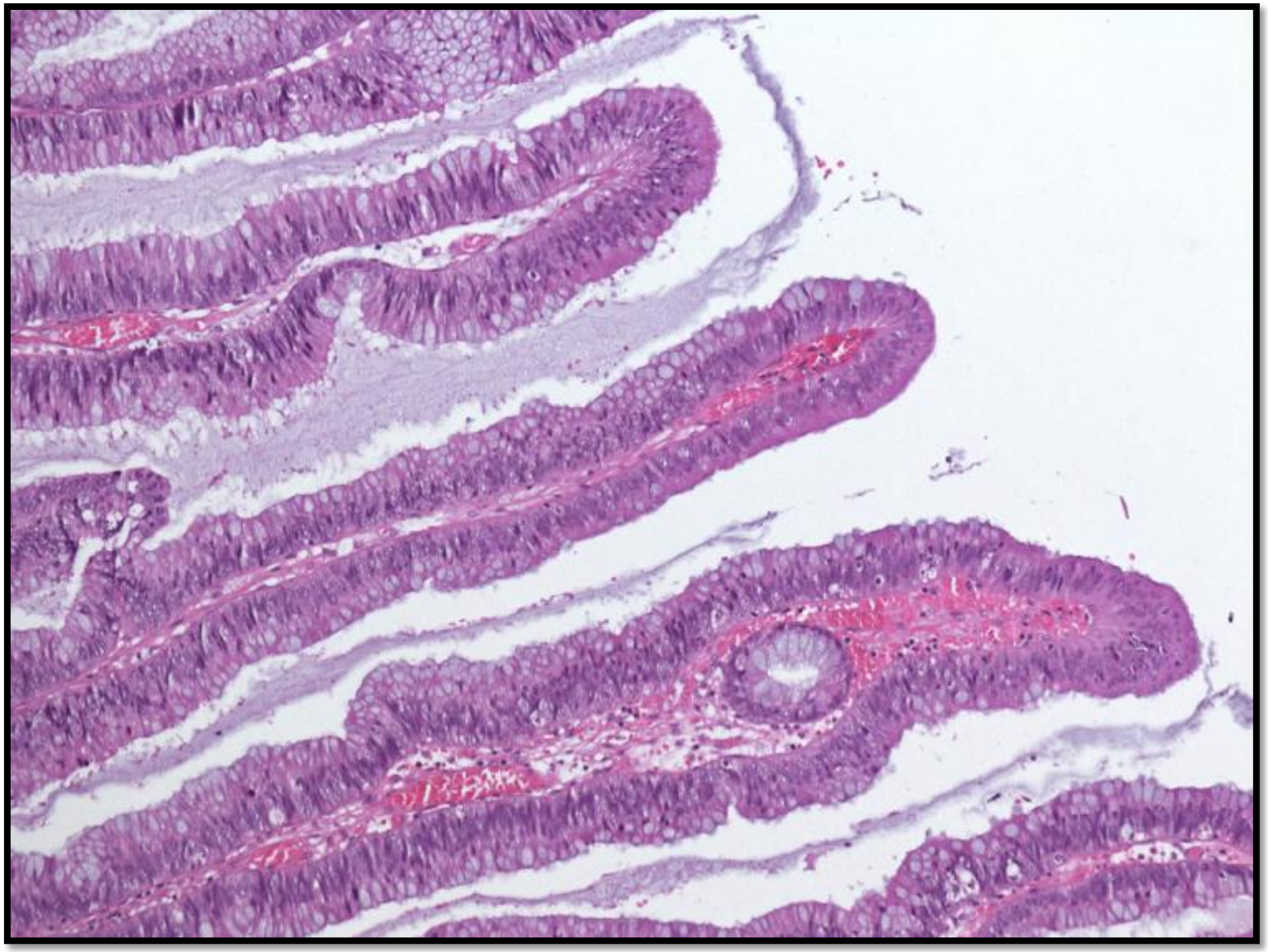
Tubular Adenoma



Villous Adenoma



Villous Adenoma



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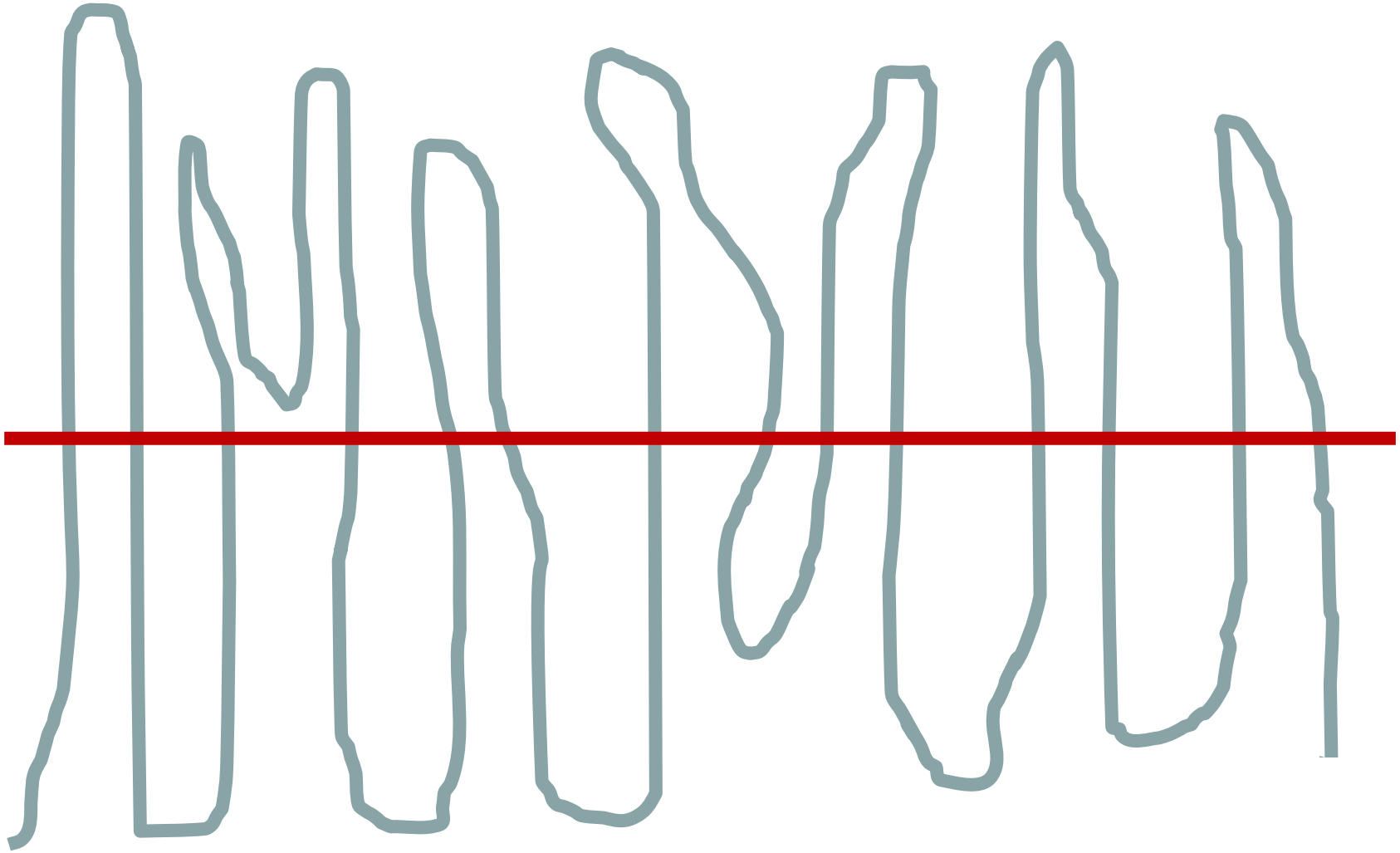
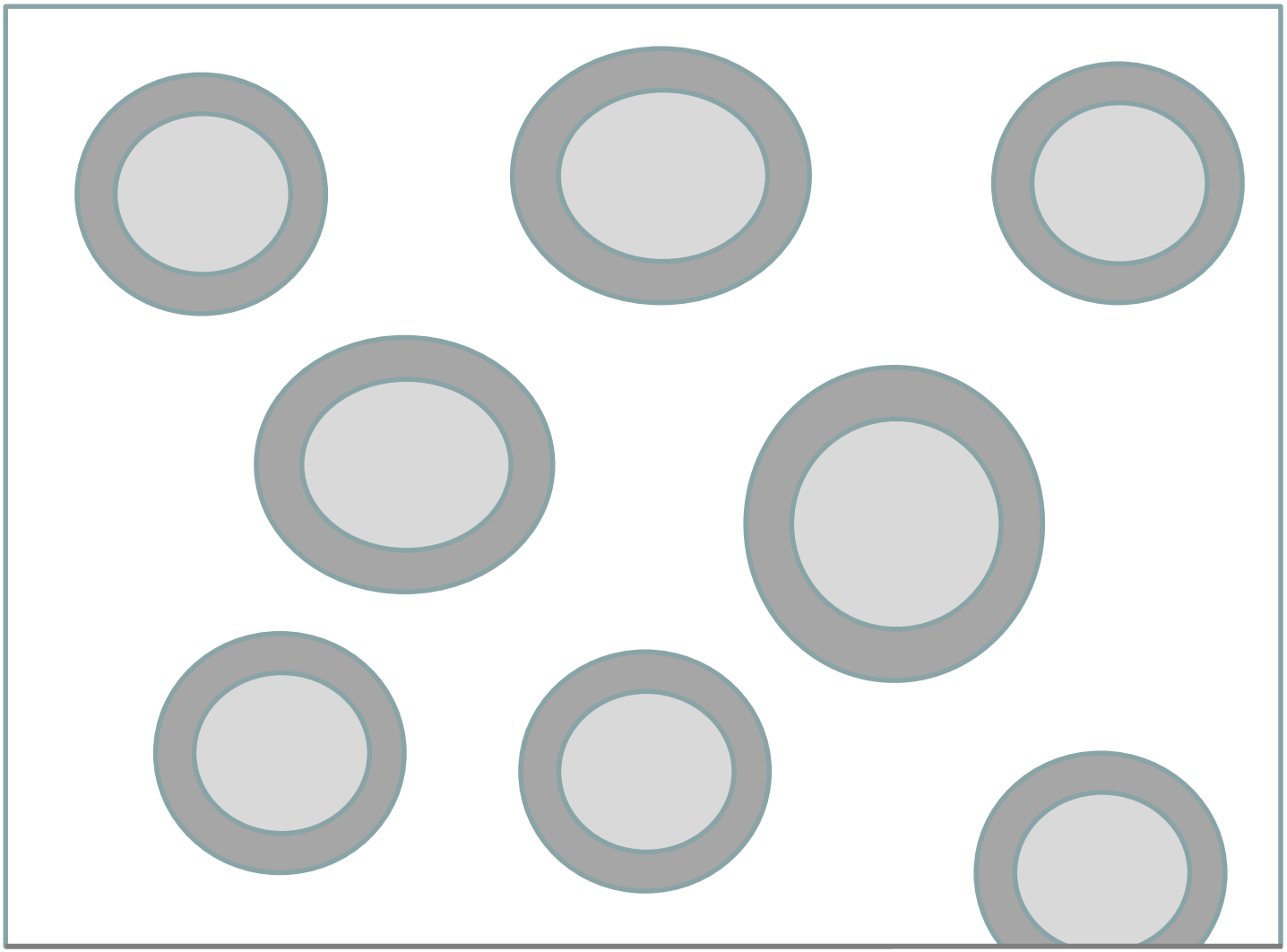
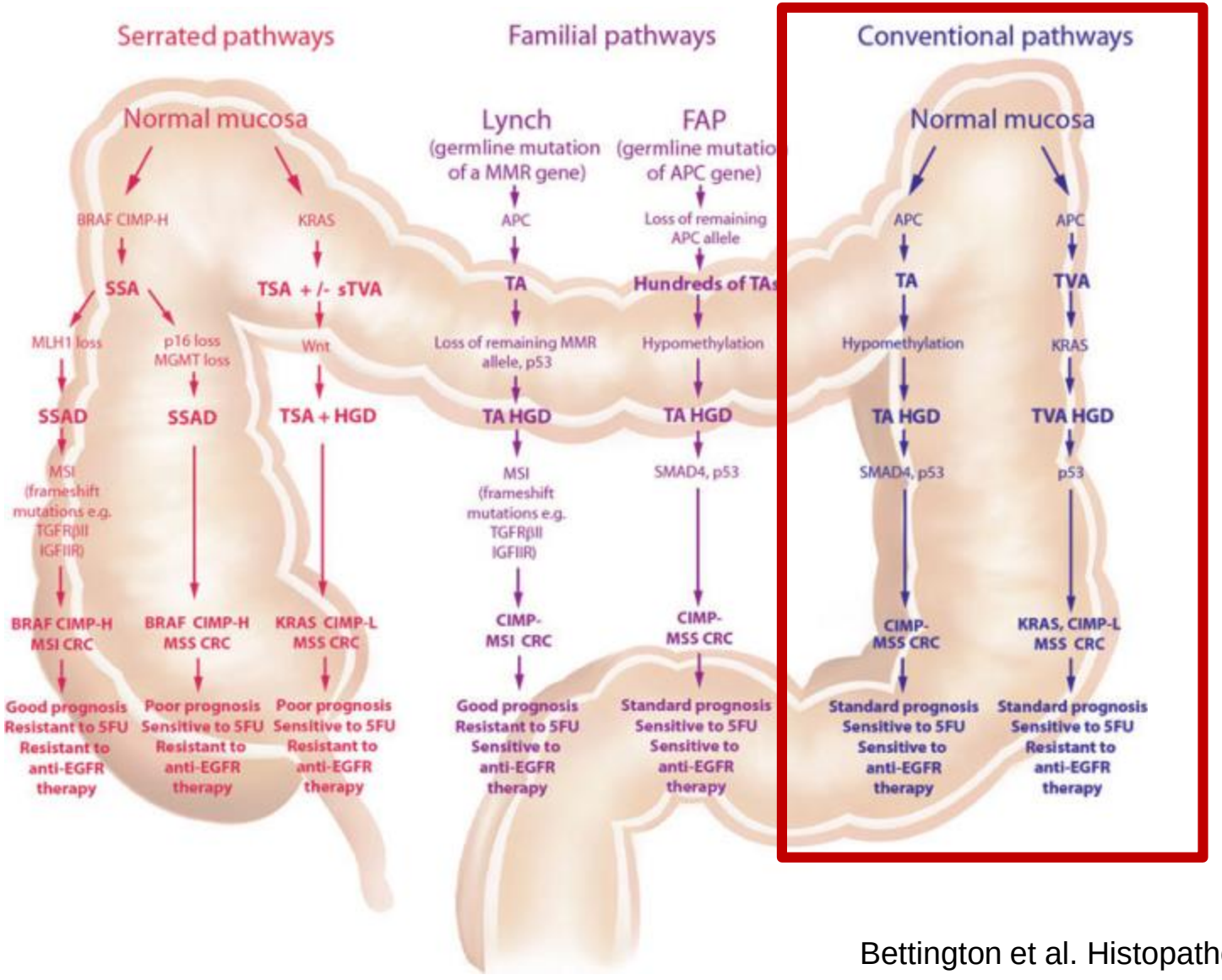


Villous Adenoma

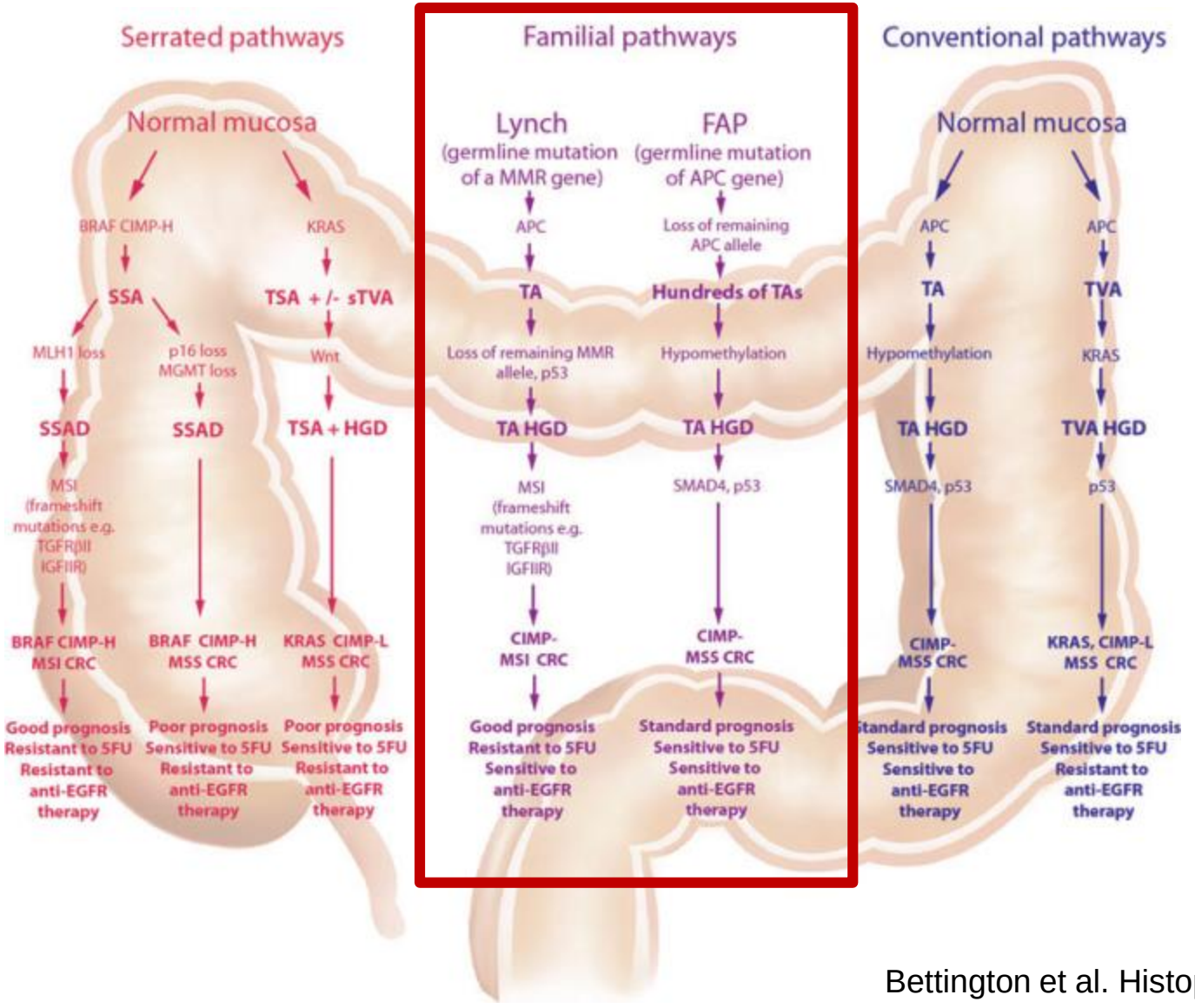


Molecular Carcinogenesis



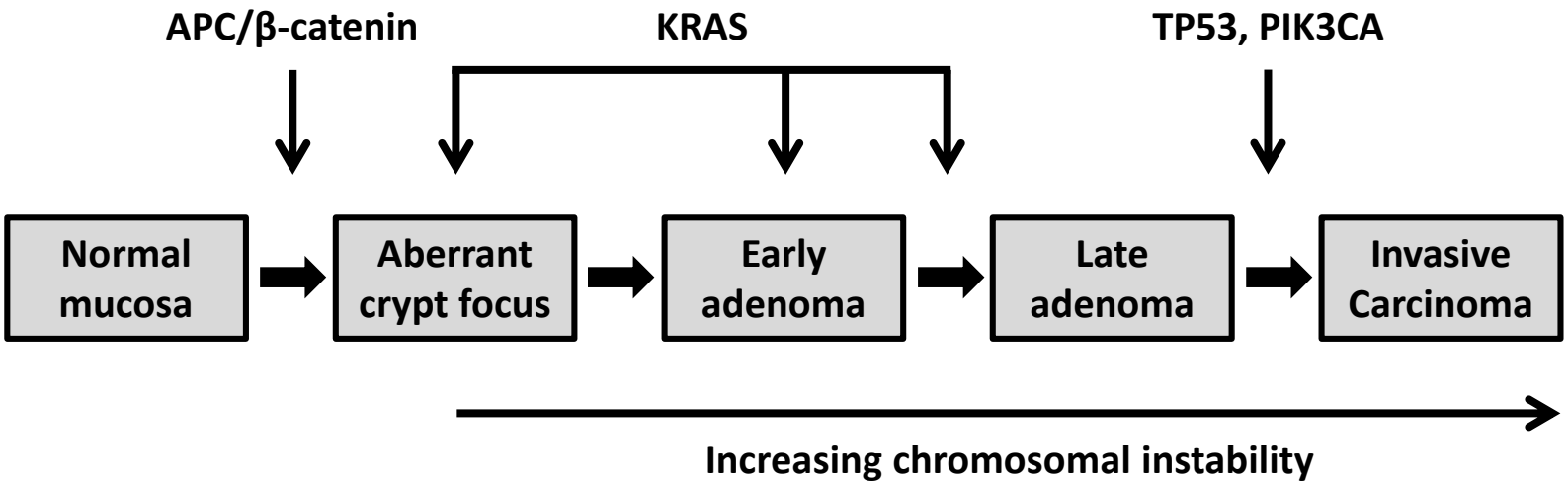
Bettington et al. Histopathology 2013

Molecular Carcinogenesis



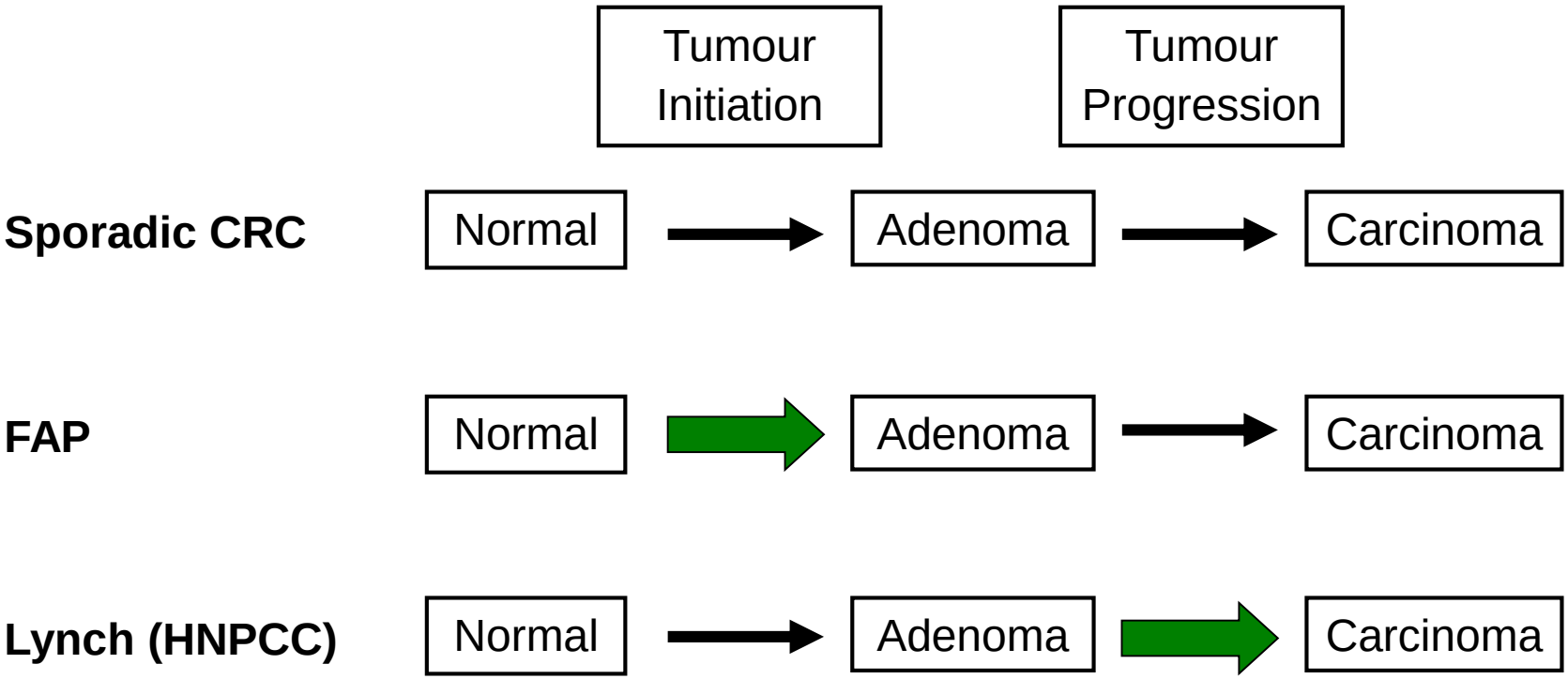
Bettington et al. Histopathology 2013

Adenoma-Carcinoma-Sequence („Suppressor Phenotype“)



Fearon und Vogelstein. Cell 1990
Langner. Dig Dis 2015

„Suppressor Phenotype“ and „Mutator Phenotype“: Time-Related Differences in Cancer Development



Fearon. Annu Rev Pathol 2011
Langner. Pathologe 2011

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Molecular Pathology of Colorectal Cancer

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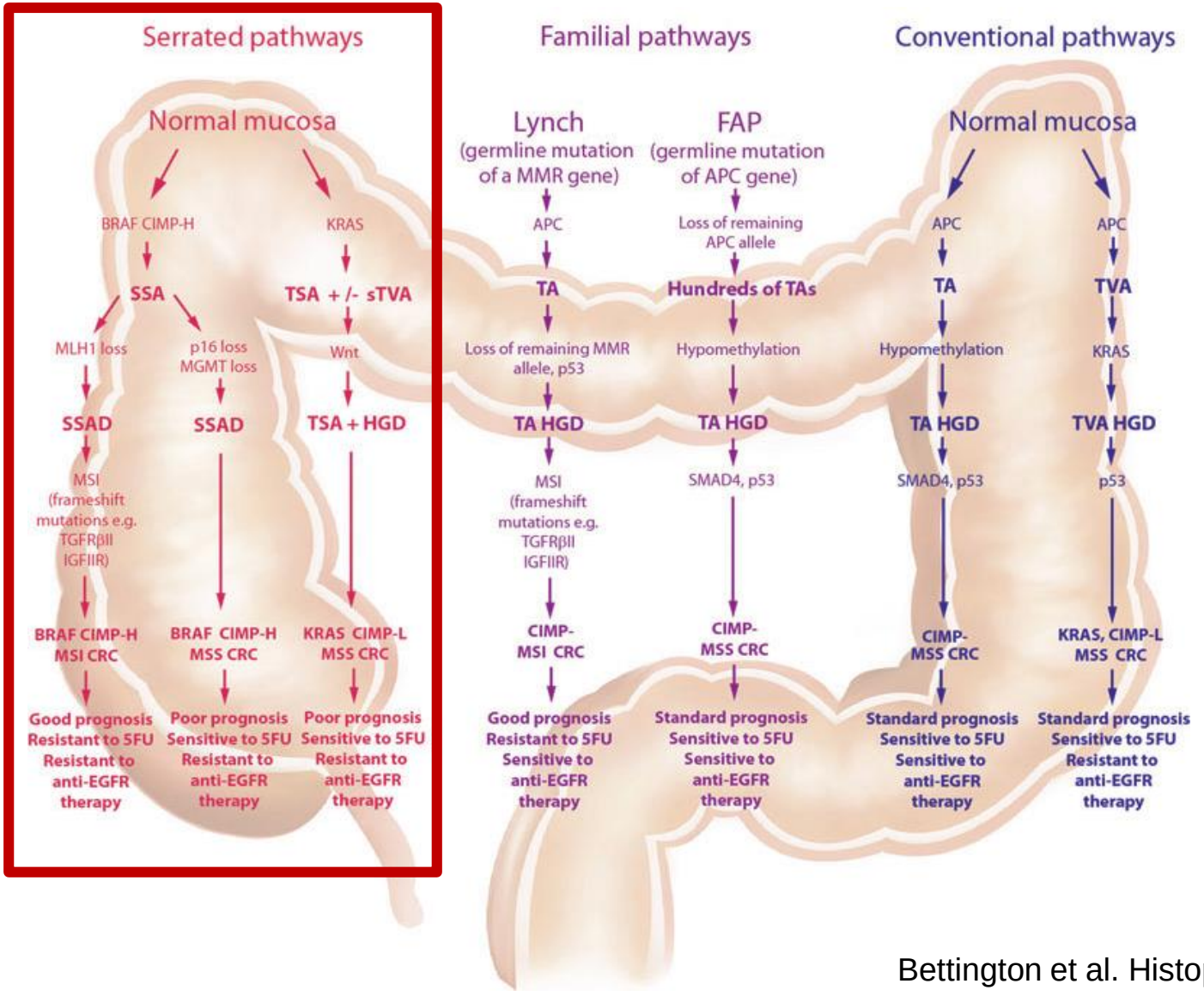
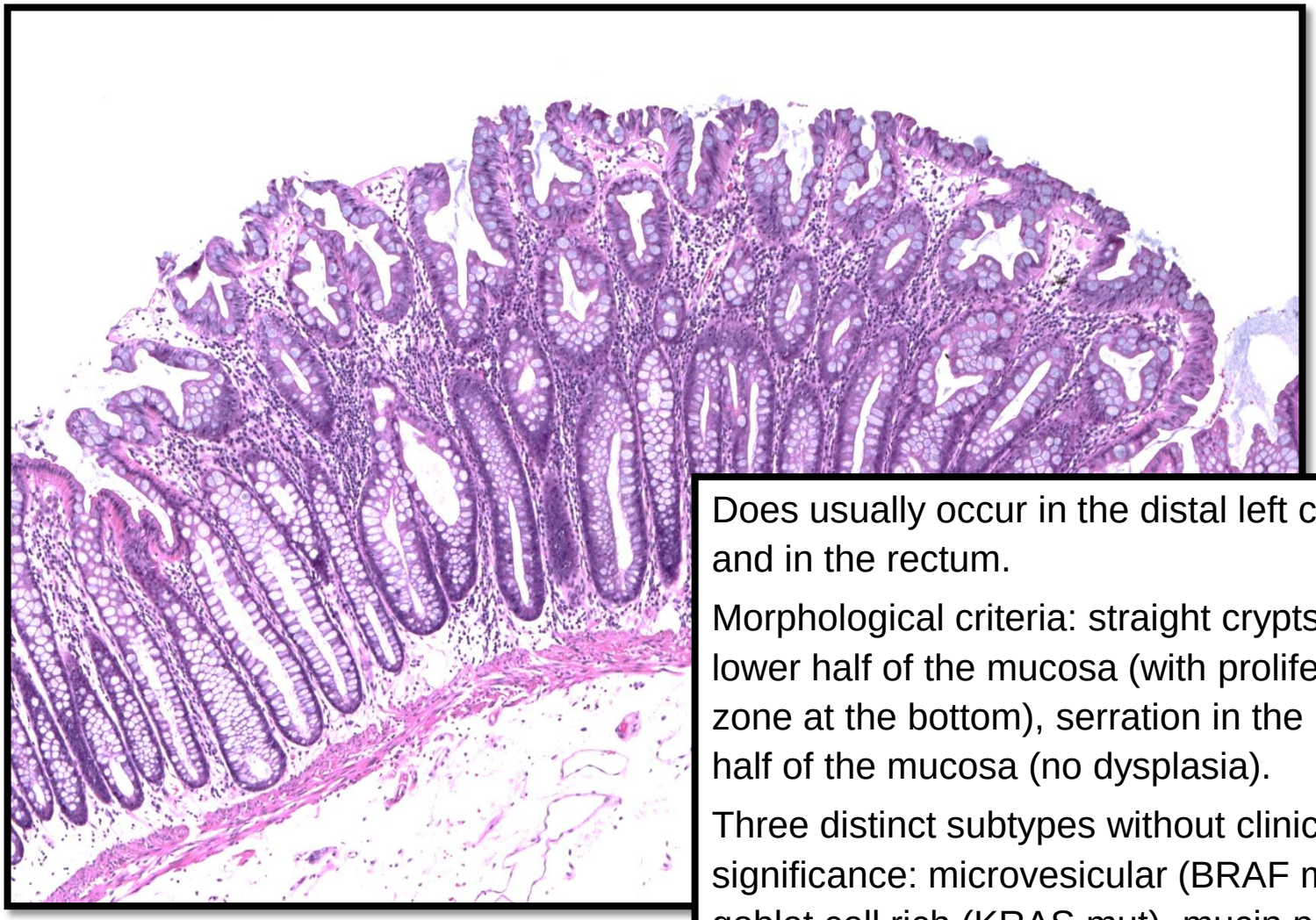


Bettington et al. Histopathology 2013

Hyperplastic Polyp

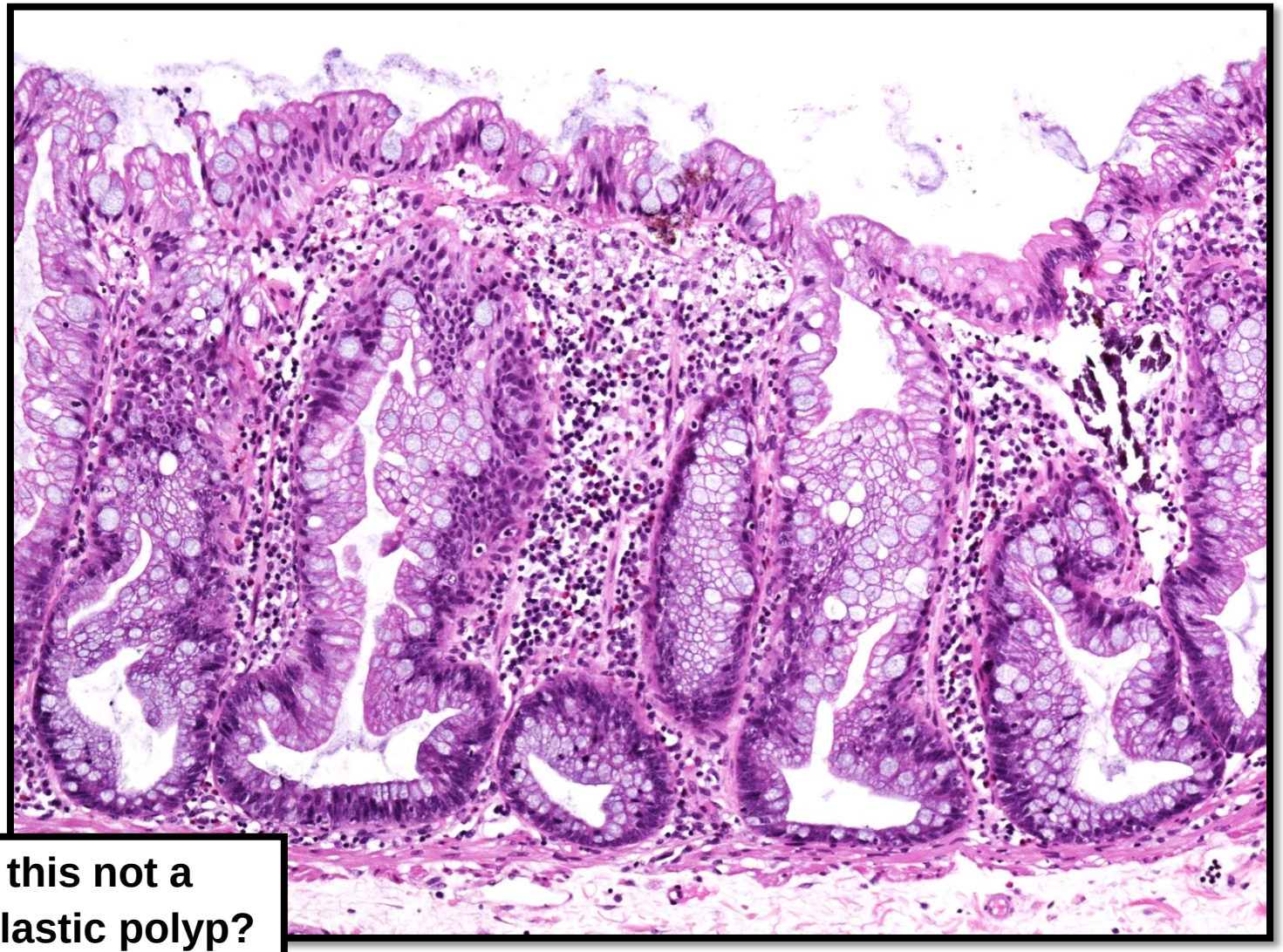


Does usually occur in the distal left colon and in the rectum.

Morphological criteria: straight crypts in the lower half of the mucosa (with proliferation zone at the bottom), serration in the upper half of the mucosa (no dysplasia).

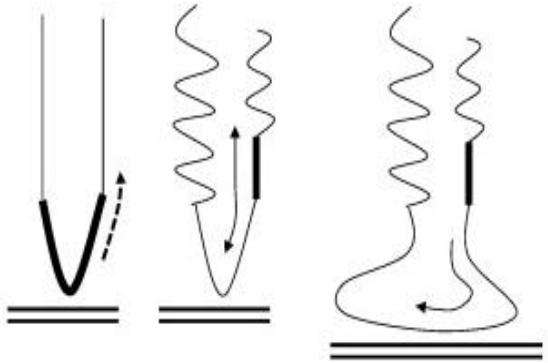
Three distinct subtypes without clinical significance: microvesicular (BRAF mut), goblet cell rich (KRAS mut), mucin poor.

Sessile Serrated Adenoma/Polyp (SSA/P)



Why is this not a hyperplastic polyp?

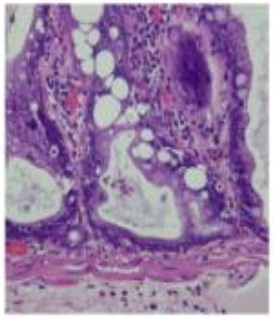
Sessile Serrated Adenoma/Polyp (SSA/P)



Early stage of SSA/P with movement of proliferative zone to side of crypt (dotted arrow) and bidirectional maturation (solid arrow)

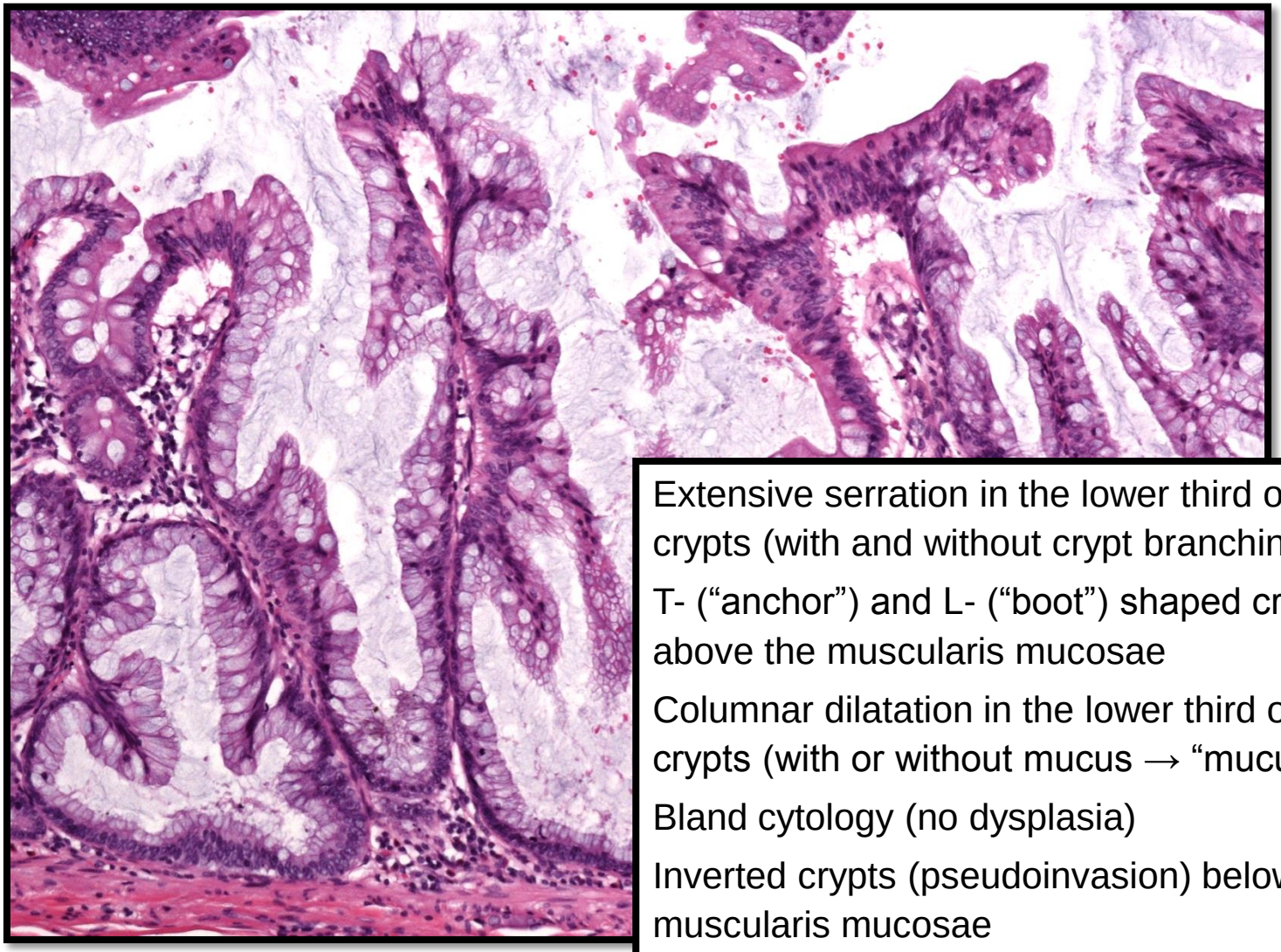
Progression of SSA/P with downward growth of mature epithelium leading to distorted crypt

Sessile serrated adenoma/polyp (SSA/P)



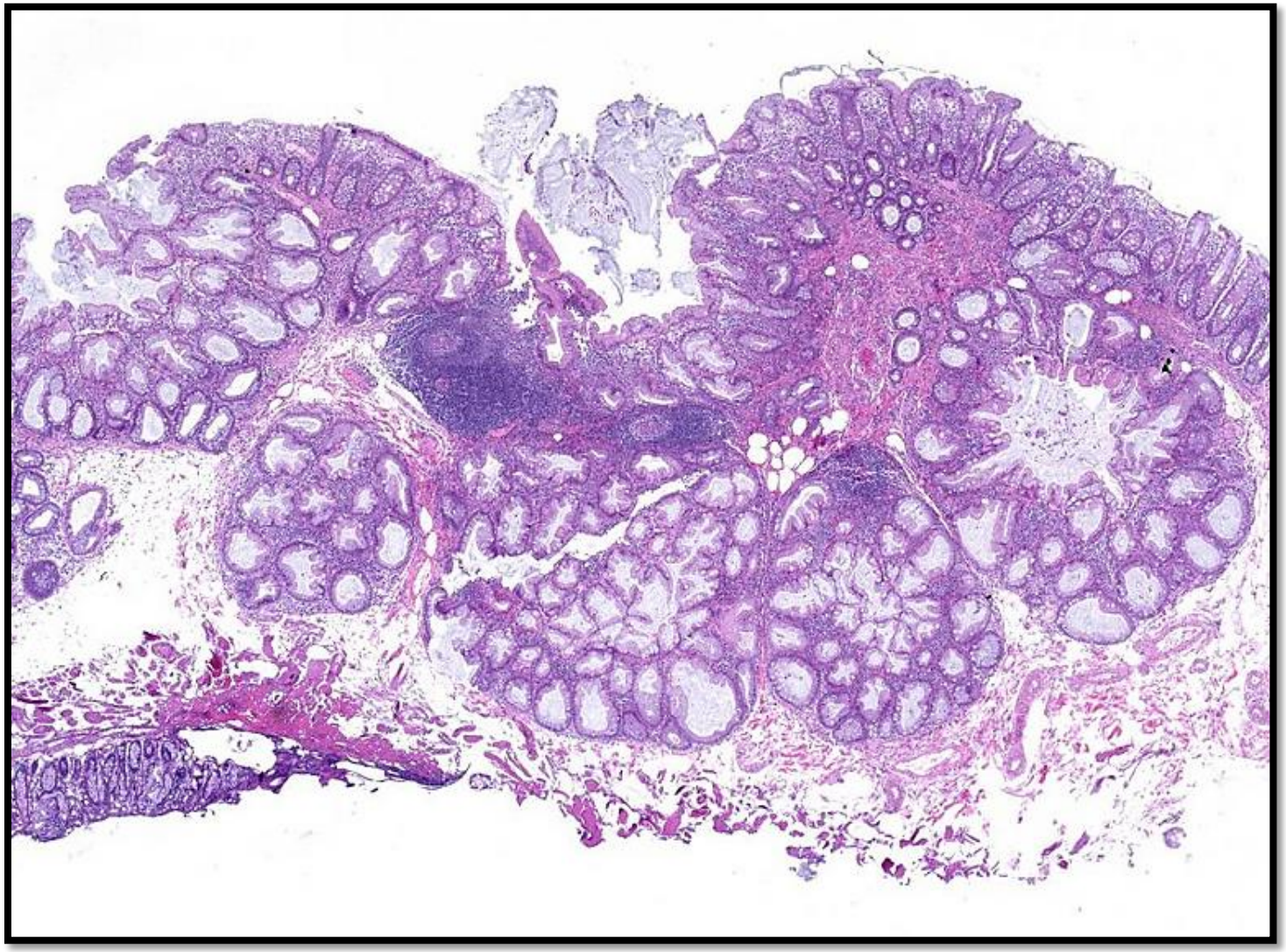
Snover Hum Pathol 2011

Sessile Serrated Adenoma/Polyp (SSA/P)



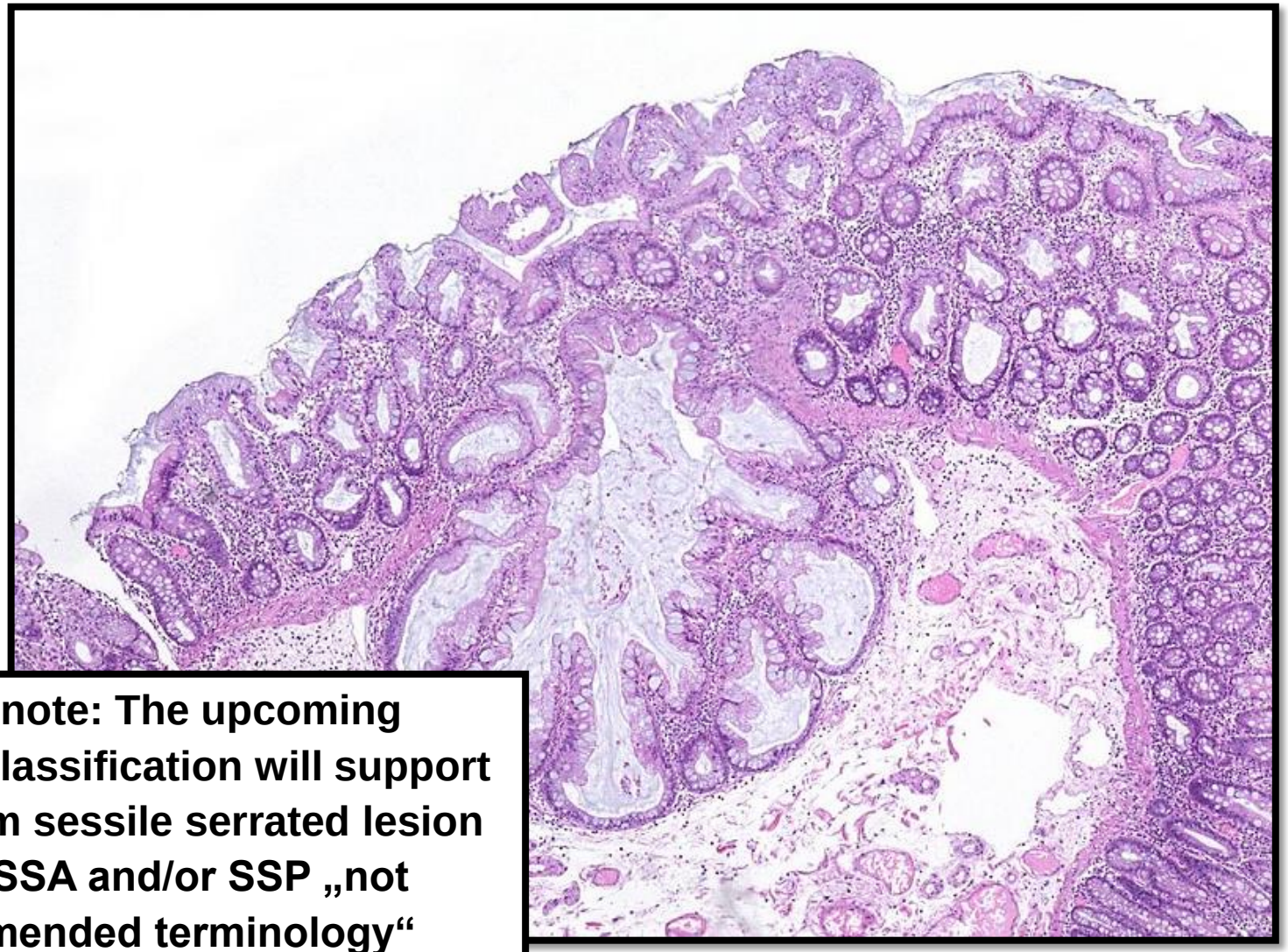
- Extensive serration in the lower third of the crypts (with and without crypt branching)
- T- (“anchor”) and L- (“boot”) shaped crypts above the muscularis mucosae
- Columnar dilatation in the lower third of the crypts (with or without mucus → “mucus cap”)
- Bland cytology (no dysplasia)
- Inverted crypts (pseudoinvasion) below the muscularis mucosae

Sessile Serrated Adenoma/Polyp (SSA/P)



ENGIP. Case of the Month 8/2014

Sessile Serrated Adenoma/Polyp (SSA/P)



Please note: The upcoming WHO Classification will support the term sessile serrated lesion (SSL); SSA and/or SSP „not recommended terminology“

ENGIP. Case of the Month 8/2014

UK guidance for the pathological reporting of serrated lesions of the colorectum

Adrian C Bateman,[1] Neil A Shepherd[2]

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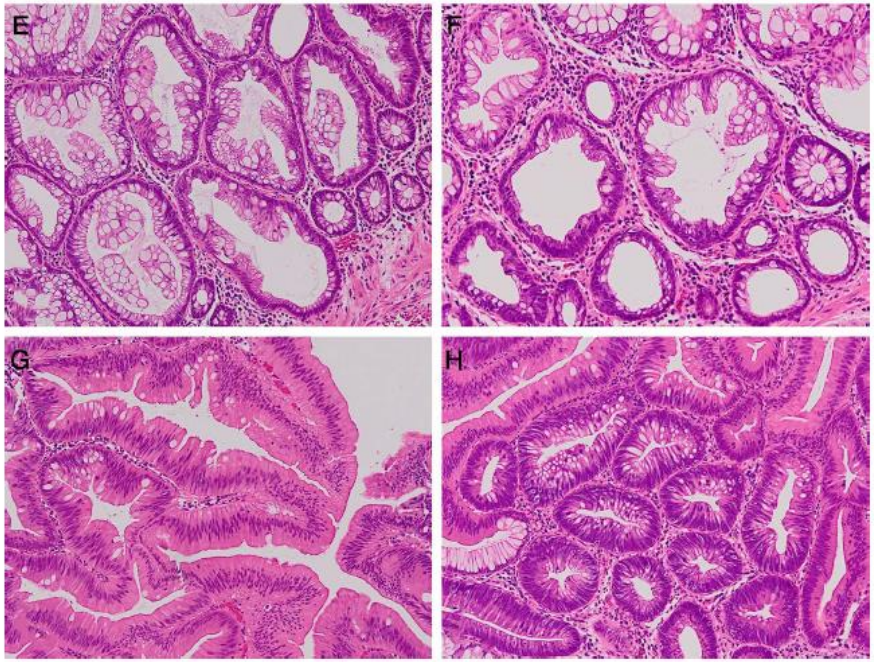
Box 1 Recommended terminology for (non-invasive) serrated lesions of the colon and rectum

- Hyperplastic polyp (HP)
- Sessile serrated lesion (SSL)
- SSL with dysplasia
- Traditional serrated adenoma (TSA)
- Mixed polyp



Mixed polyps

While it is our opinion that the majority of 'mixed' polyps, especially in the right colon, represent SSLs with and without dysplasia, we accept that polyps may rarely be encountered, particularly in the left colon, that appear more likely to have arisen due to a 'true' collision event between an HP and a 'classical' adenoma. Furthermore, TSAs are not uncommonly encountered in which a significant component shows the features of a 'classical' adenoma. The minimum proportion of a TSA that is required to show features of a 'classical' adenoma in order for the polyp as a whole to be considered 'mixed' has yet to be defined. Furthermore, occasionally, polyps showing a combination of SSL and TSA-like features are encountered, with or without areas with a 'classical' adenoma appearance (figure 3E–3H). Another variant of the mixed polyp is the combination of HP changes and serrated low-grade dysplasia with features of a TSA. These lesions are more unusual and are seen usually in the sigmoid colon and rectum. While a collision lesion is possible, we believe that the latter mixed polyps usually represent different stages in the traditional serrated neoplasia sequence with serrated dysplasia deriving from a pre-existing HP. Due to the existence of lesions such as these, we believe, it is sensible to retain the term 'mixed polyp' within the recommended terminology list, even if it manifests that they may represent different serrated entities and different serrated neoplasia pathways.

Bateman and Shepherd. J Clin Pathol 2015

British Society of Gastroenterology position statement on serrated polyps in the colon and rectum

James E East,[1] Wendy S Atkin,[2] Adrian C Bateman,[3] Susan K Clark,[4] Sunil Dolwani,[5] Shara N Ket,[1] Simon J Leedham,[6] Perminder S Phull,[7] Matt D Rutter,[8,9] Neil A Shepherd,[10] Ian Tomlinson,[11] Colin J Rees[9,12]

Statement 1

Some SSLs have molecular, genetic and pathological features consistent with being precursor lesions to CpG island methylator phenotype (CIMP)+ colorectal cancers (CRCs), which represent 15%–30% of all CRCs (*moderate quality evidence, 100% agreement*).

Statement 2

We suggest adopting the terms hyperplastic polyp (HP), SSL, SSL with dysplasia, traditional serrated adenoma (TSA) or mixed polyp to describe SLs in the colorectum, using the WHO criteria to define SSL (*weak recommendation, low quality evidence, 82% agreement*).

Box 1 Key histological features of sessile serrated lesions (SSLs)

- Irregular distribution of crypts
- Dilatation of crypt bases
- Serration present at crypt bases
- Branched crypts
- Horizontal extension of crypt bases*
- Dysmaturation of crypts†
- Herniation of crypts through muscularis mucosa
- WHO criteria—at least three crypts or at least two *adjacent* crypts must show one or more of these features to enable a diagnosis of SSLs[31]
- American Gastroenterology Association criteria—one crypt showing the characteristic features is sufficient for the diagnosis of SSLs[26]

*Involved crypts often have an 'L' or inverted 'T' shape.
†Dysmaturation is disordered cellular maturation within crypts and is evidenced by subtle nuclear enlargement, crowding, pseudostratification and mitotic activity together with the presence of a disorganised mixture of non-mucus containing epithelial cells and mature goblet cells within the deep aspects of crypts. In this context, assessment of proliferation index, for example, using MIB-1 may provide supporting evidence for a diagnosis of SSLs by highlighting epithelial cell proliferation within the superficial half of crypts. However, such immunohistochemistry, while sometimes helpful, does not reveal features that are alone diagnostic of SSLs.

East et al. Gut 2017

Epidemiology and minimum criteria for diagnosis of sessile serrated adenomas/polyps (sessile serrated lesions)

Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy

Authors

Yark Hazewinkel[1], Thomas R. de Wijkerslooth[1], Esther M. Stoop[2], Patrick M. Bossuyt[3], Katharina Biermann[4], Marc J. van de Vijver[5], Paul Fockens[1], Monique E. van Leerdam[2], Ernst J. Kuipers[2], Evelien Dekker[1]

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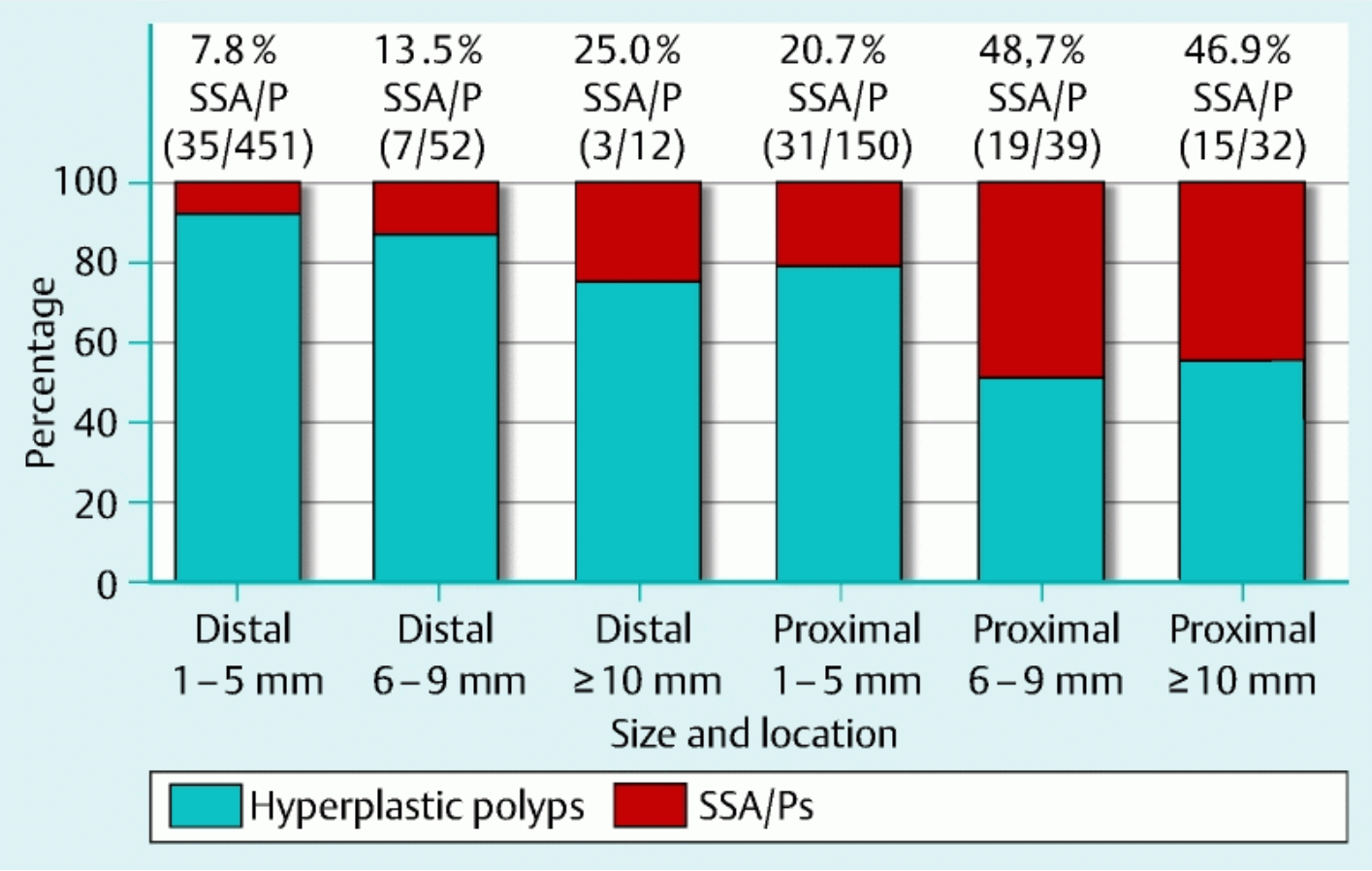

Hazewinkel et al. Endoscopy 2014

Prevalence, distribution and risk of sessile serrated adenomas/polyps at a center with a high adenoma detection rate and experienced pathologists

Authors

Joep E. G. IJspeert[1], Koos de Wit[1], Manon van der Vlugt[1,2], Barbara A. J. Bastiaansen[1,2], Paul Fockens[1,2], Evelien Dekker[1,2]

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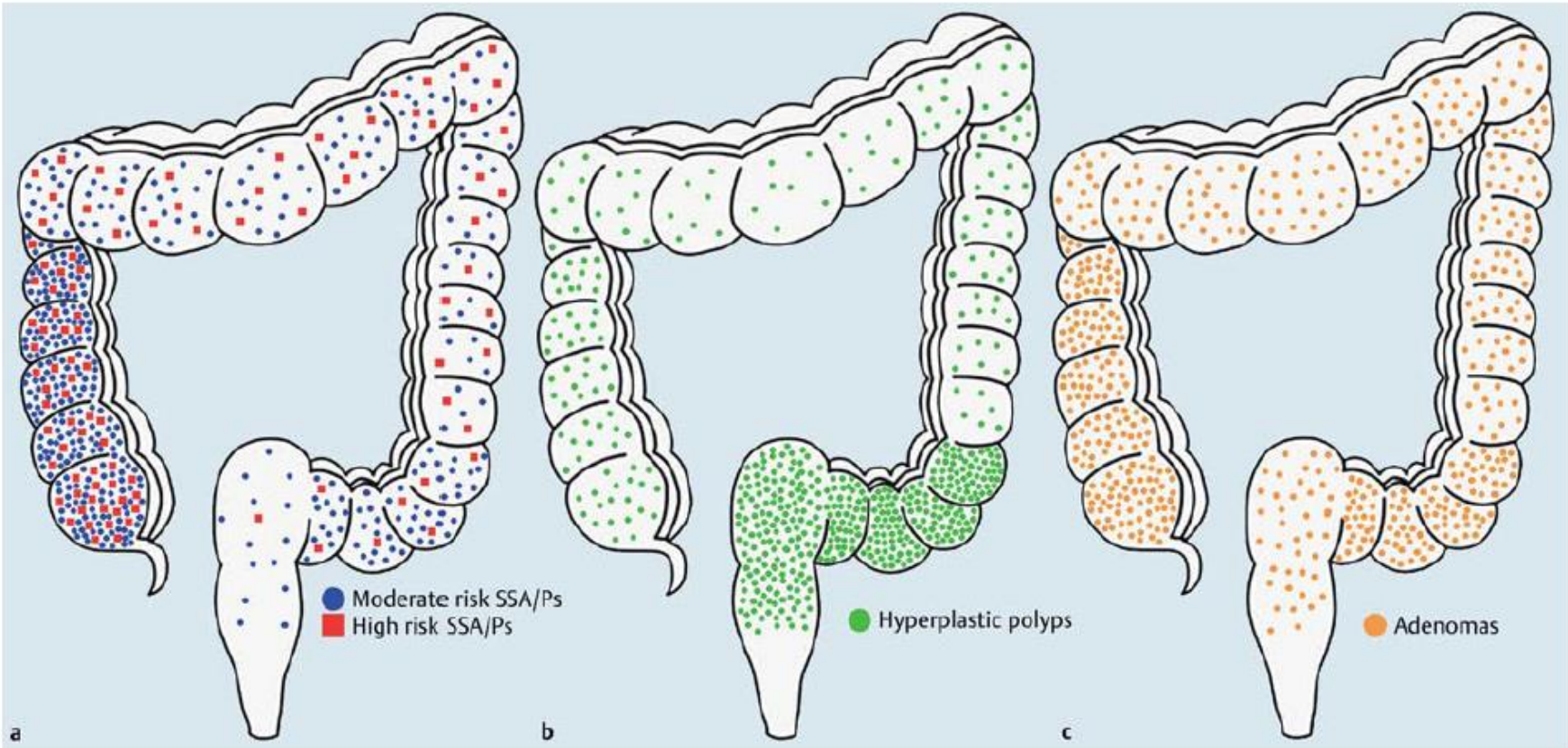

Fig. 2 Colonic distribution of polyps: **a** distribution of moderate risk and high risk sessile serrated adenomas/polyps (SSA/Ps); **b** distribution of hyperplastic polyps; **c** distribution of adenomas.

Ijspeert et al. Endoscopy 2016

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Critical Appraisal of the Diagnosis of the Sessile Serrated Adenoma

Mark Bettington, FRCPA,†‡ Neal Walker, FRCPA, MD,†‡*
Christophe Rosty, FRCPA, PhD,†‡§ Ian Brown, FRCPA,‡‖
Andrew Clouston, FRCPA, PhD,†‡‖ Leesa Wockner, PhD,¶
Vicki Whitehall, PhD,†# and Barbara Leggett, FRACP, MD*†***

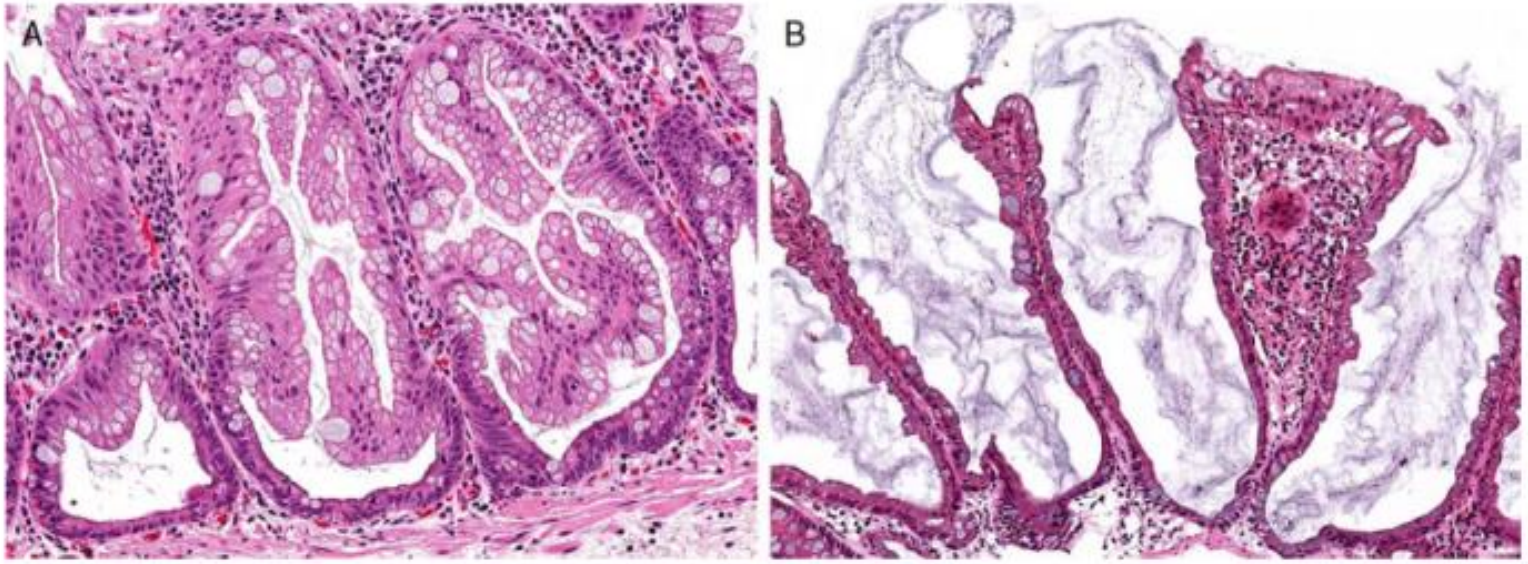

FIGURE 1. Features of an SSA-type crypt. Horizontal growth along the muscularis mucosa, deep serration and asymmetric proliferation (A), dilation of the crypt bases (B) (hematoxylin and eosin stain).

Cross-sectional study of 6340 colorectal polyps received at a high-volume community-based pathology practice over a 3-month period

Bettington et al. Am J Surg Pathol 2014

TABLE 1. Diagnostic Subcategories for MVHPs and SSAs

Subcategory	Definition
MVHP	No SSA-type crypts
pSSA (type 1)	One SSA-type crypt
pSSA (type 2)	Two nonadjacent SSA-type crypts
pSSA (type 3)	Multiple crypts with poorly developed SSA-type features
SSA (type 1)	Minimal WHO criteria to 4 SSA-type crypts
SSA (type 2)	5 to 9 SSA-type crypts
SSA (type 3)	10 or more SSA-type crypts

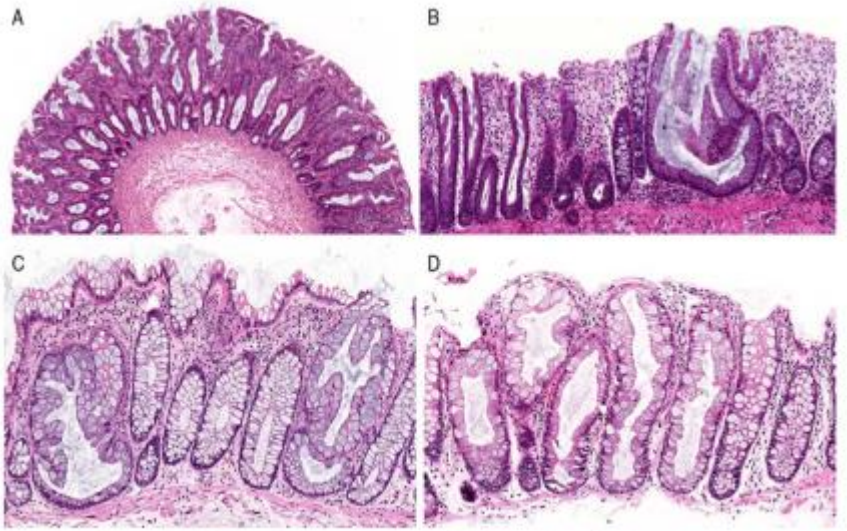

FIGURE 2. Examples of study MVHP (A) and pSSAs types 1 to 3 (B–D) (hematoxylin and eosin stain).

TABLE 2. Number, Location, and Average Size of the Polyps by Type Using WHO Diagnostic Criteria*

Polyp Type (n = 6340)	Subtype	n (%) Total Number	Proximal	Distal	Rectum	Mean Size (SD) (mm)
All adenomatous polyps						
TA (LGD)		2648 (41.8)	1559 (59)	854 (32)	196 (7)	5.8 (3.0)
TA (HGD)		20 (0.3)	10 (50)	9 (45)	1 (5)	7.3 (4.0)
TVA (LGD)		363 (5.7)	168 (46)	123 (34)	68 (19)	12.9 (9.0)
TVA (HGD)		49 (0.8)	15 (31)	22 (45)	12 (24)	17.3 (10.1)
Villous adenoma (LGD)		6 (0.1)	0 (0)	4 (67)	2 (33)	NA
Villous adenoma (HGD)		5 (0.1)	1 (20)	2 (40)	2 (40)	20.0 (NA)
All serrated polyps						
Hyperplastic polyp	GCHP	825 (13)	129 (16)	418 (51)	266 (32)	4.5 (2.4)
	MVHP	1343 (21.2)	202 (15)	593 (44)	533 (40)	4.6 (2.4)
SSA		741 (11.7)	594 (80)	128 (17)	11 (1)	8.5 (4.1)
SSAD		27 (0.4)	21 (78)	3 (11)	0 (0)	7.8 (3.6)
Traditional serrated adenoma		57 (0.9)	18 (32)	22 (39)	17 (30)	10.6 (6.8)
Serrated polyp unclassifiable		20 (0.3)	14 (70)	6 (30)	0 (0)	4.7 (1.5)
Malignant polyp		23 (0.4)	8 (35)	12 (52)	3 (13)	20 (12.7)

*Some percentages do not add to 100 as site data were not supplied in all cases.
HGD indicates high-grade dysplasia; LGD, low-grade dysplasia.

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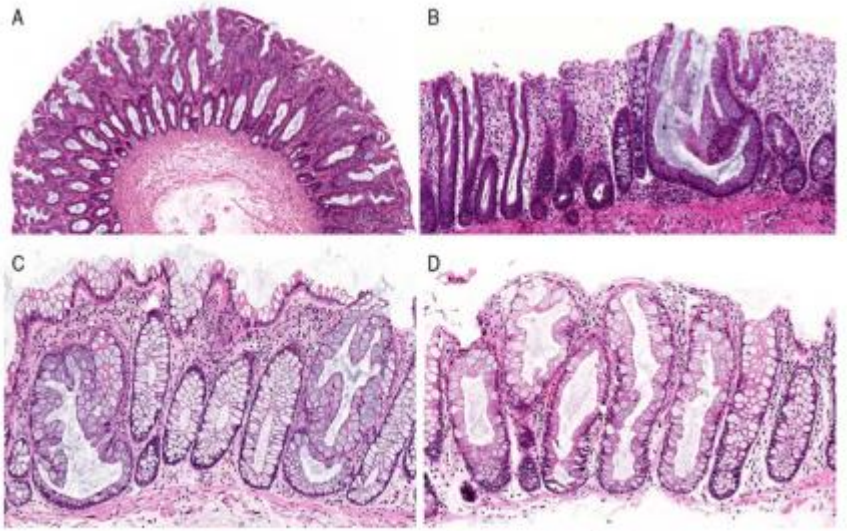

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All adenomatous polyps						
TA (LGD)		2648 (41.8)	1559 (59)	854 (32)	196 (7)	5.8 (3.0)
TA (HGD)		20 (0.3)	10 (50)	9 (45)	1 (5)	7.3 (4.0)
TVA (LGD)		363 (5.7)	168 (46)	123 (34)	68 (19)	12.9 (9.0)
TVA (HGD)		49 (0.8)	15 (31)	22 (45)	12 (24)	17.3 (10.1)
Villous adenoma (LGD)		6 (0.1)	0 (0)	4 (67)	2 (33)	NA
Villous adenoma (HGD)		5 (0.1)	1 (20)	2 (40)	2 (40)	20.0 (NA)
All serrated polyps						
Hyperplastic polyp	GCHP	825 (13)	129 (16)	418 (51)	266 (32)	4.5 (2.4)
	MVHP	1343 (21.2)	202 (15)	593 (44)	533 (40)	4.6 (2.4)
SSA		741 (11.7)	594 (80)	128 (17)	11 (1)	8.5 (4.1)
SSAD		27 (0.4)	21 (78)	3 (11)	0 (0)	7.8 (3.6)
Traditional serrated adenoma		57 (0.9)	18 (32)	22 (39)	17 (30)	10.6 (6.8)
Serrated polyp unclassifiable		20 (0.3)	14 (70)	6 (30)	0 (0)	4.7 (1.5)
Malignant polyp		23 (0.4)	8 (35)	12 (52)	3 (13)	20 (12.7)

*Some percentages do not add to 100 as site data were not supplied in all cases.
HGD indicates high-grade dysplasia; LGD, low-grade dysplasia.

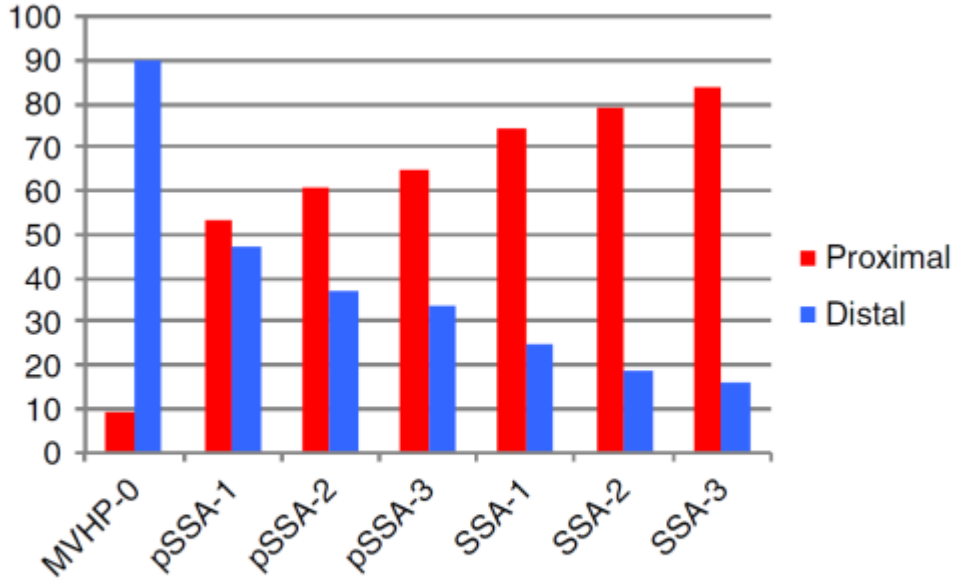


FIGURE 3. Location of subcategories of MVHP, pSSAs, and SSAs by percentage on a per polyp basis.

„We found that serrated polyps (MVHPs or SSAs) with any SSA-like crypts had clinical features more in common with the SSA than the MVHP and that this diagnostic cutoff showed good reproducibility between pathologists.

This supports the position of a recent consensus publication (Rex et al. Am J Gastroenterol 2012) proposing that polyps with as few as 1 SSA-type crypt should be diagnosed as an SSA."

Bettington et al. Am J Surg Pathol 2014

6.1.1.1:

Colorectal serrated lesions and polyps

Pai RK
Makinen MJ
Rosty N

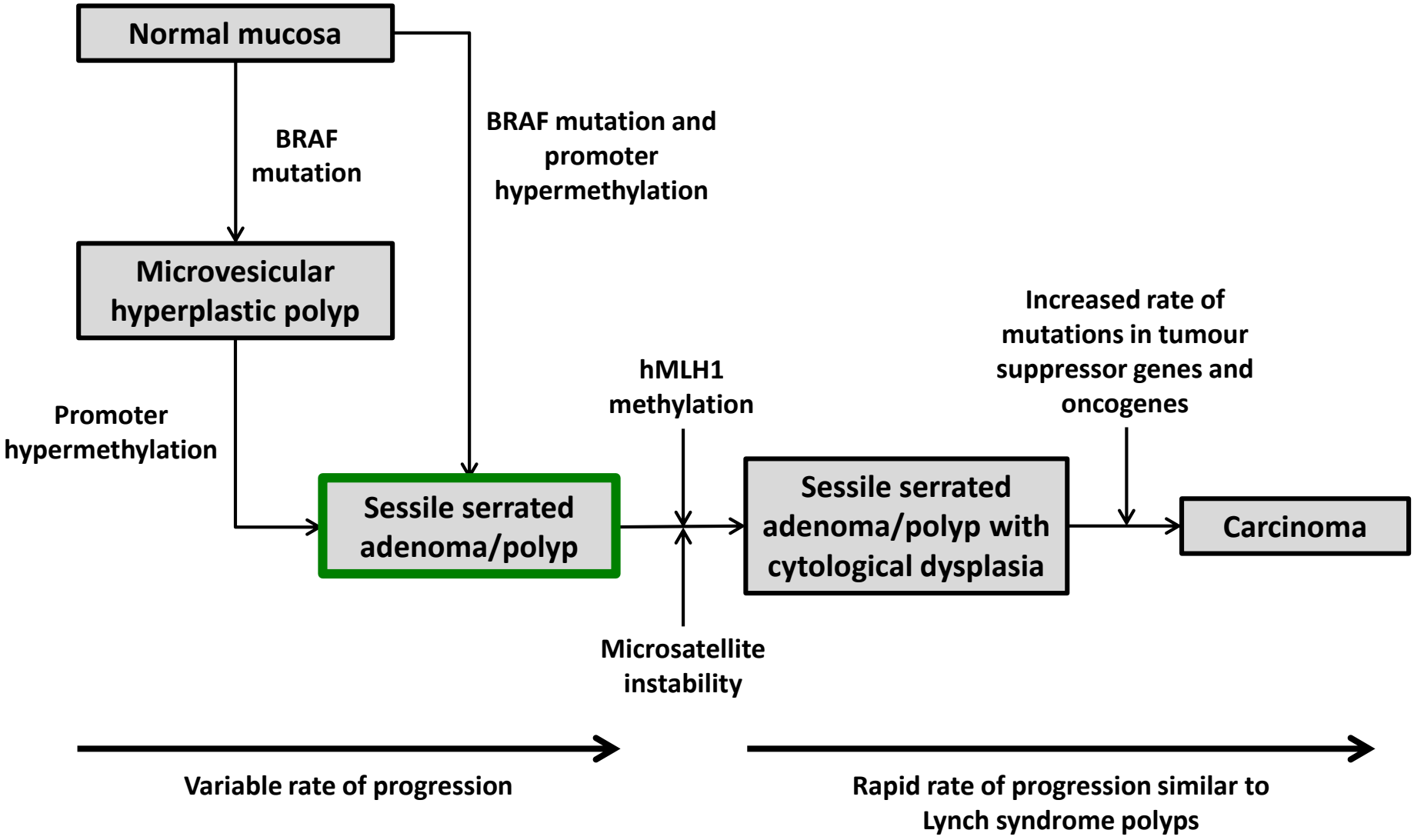
Medizinische Universität Graz

- Recent studies have indicated that **the presence of one unequivocal architecturally distorted serrated crypt** as defined above is sufficient for a diagnosis of SSL. The term "unequivocal" is important, because crypts with only subtle architectural abnormalities should not be regarded as diagnostic of SSL. Mild symmetrical dilatation of crypt bases is not sufficient for SSL diagnosis. Crypts with mature cells, such as goblet cells, in the crypt base are also not diagnostic of SSL.
- Importantly, the **size, location, and endoscopic appearance** alone should not be used to make the diagnosis of SSL; rather, these may be considered **adjunctive features** that may favour the diagnosis for ambiguous cases or poorly oriented sections. Because the diagnosis of SSL is dependent predominantly on crypt architecture, well-oriented sections evaluating crypt bases are essential. Deeper levels may be helpful in sections that are not well oriented.
- The presence of mucosal herniation should not be confused with invasion, particularly when dysplasia is present.

Pai et al. Upcoming WHO Classification

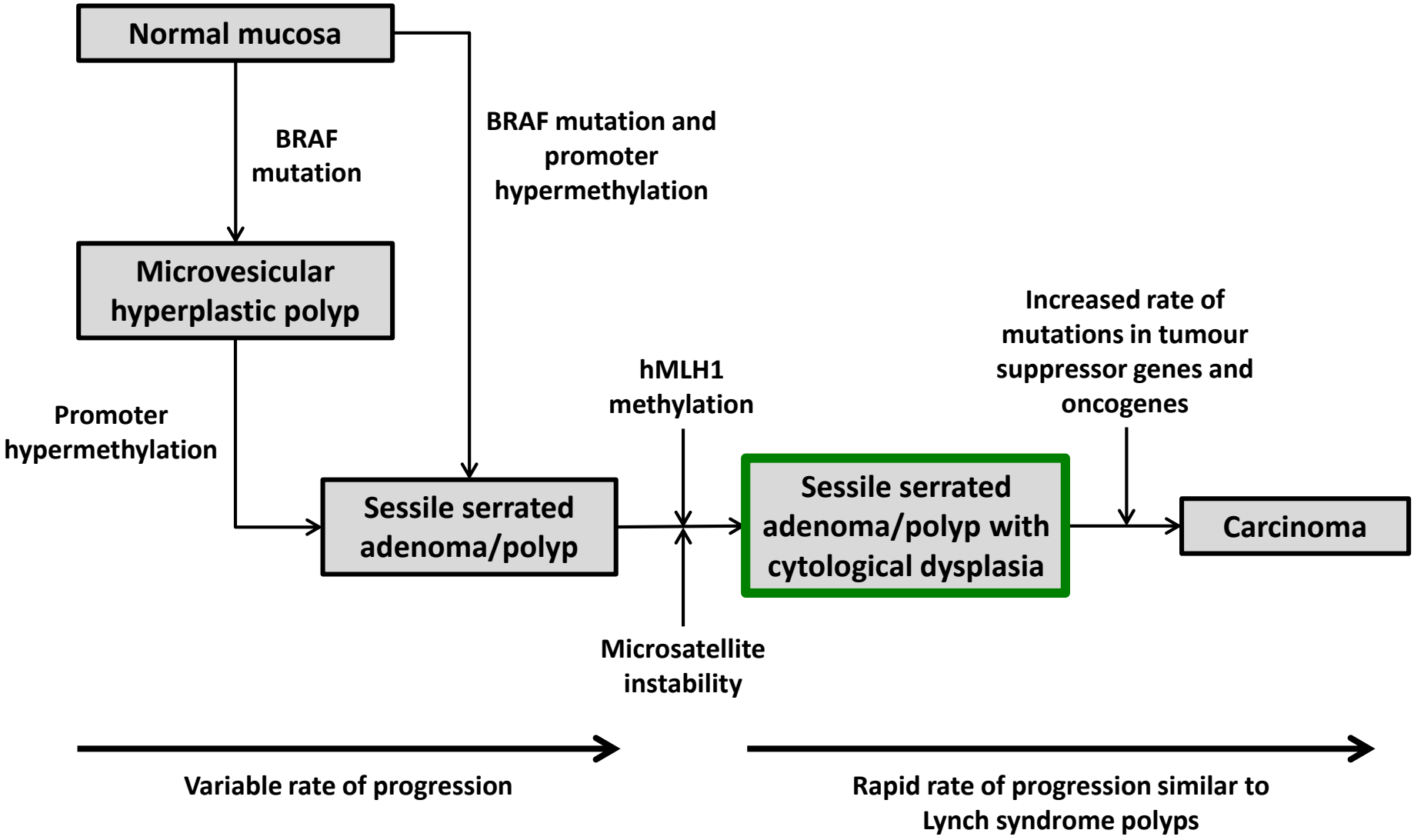
Molecular pathology of sessile serrated adenomas/polyps (sessile serrated lesions)

SSA/P Molecular Pathology



Langner. Dig Dis 2015

SSA/P Molecular Pathology



Langner. Dig Dis 2015

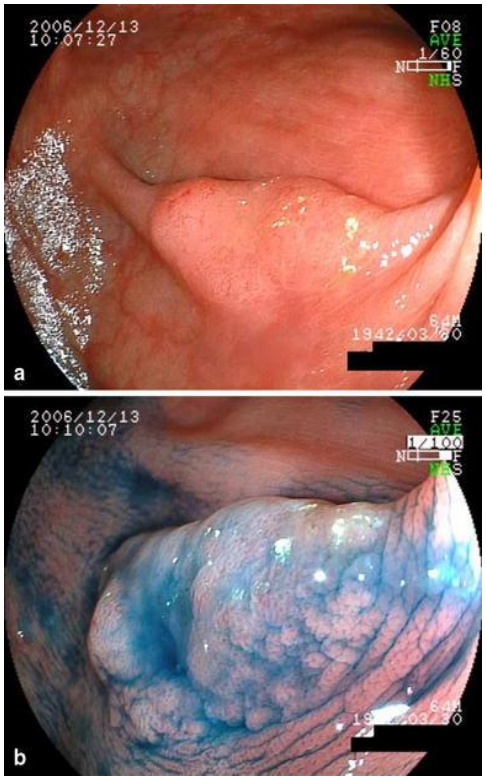
Dig Dis Sci (2009) 54:906–909
DOI 10.1007/s10620-008-0407-7

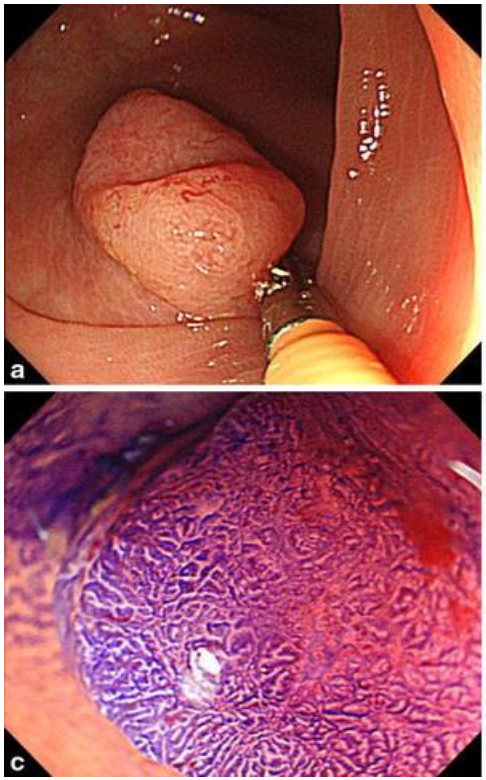
CASE REPORT

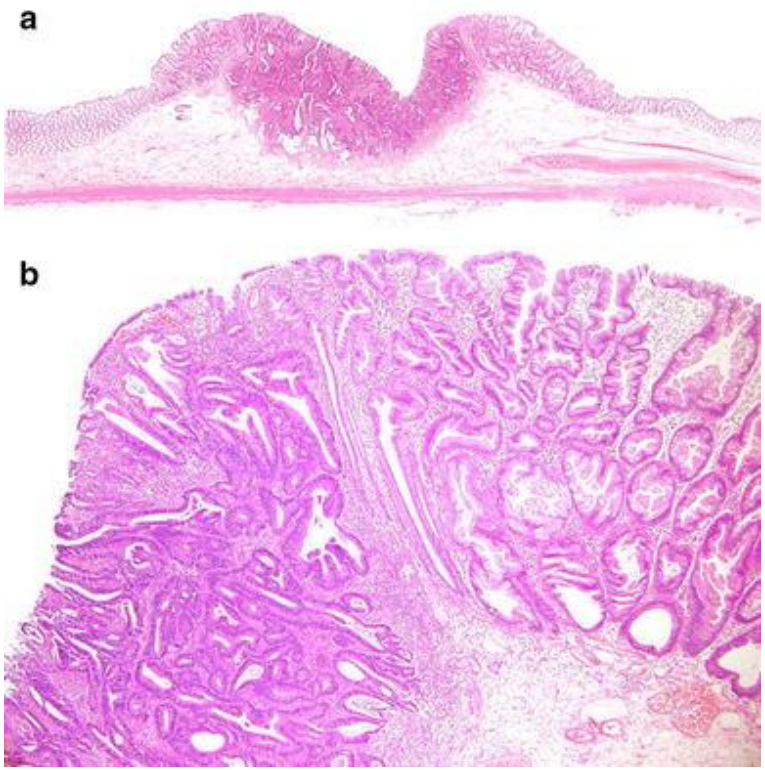
Medizinische Universität Graz

Progression of a Sessile Serrated Adenoma to an Early Invasive Cancer Within 8 Months

Yasuhiro Oono · Kuangi Fu · Hisashi Nakamura · Yosuke Iriguchi · Akihiko Yamamura · Yasuhiro Tomino · Johji Oda · Masaru Mizutani · Satoshi Takayanagi · Daisuke Kishi · Tomoaki Shinohara · Kozo Yamada · Jun Matumoto · Kazuhiro Imamura



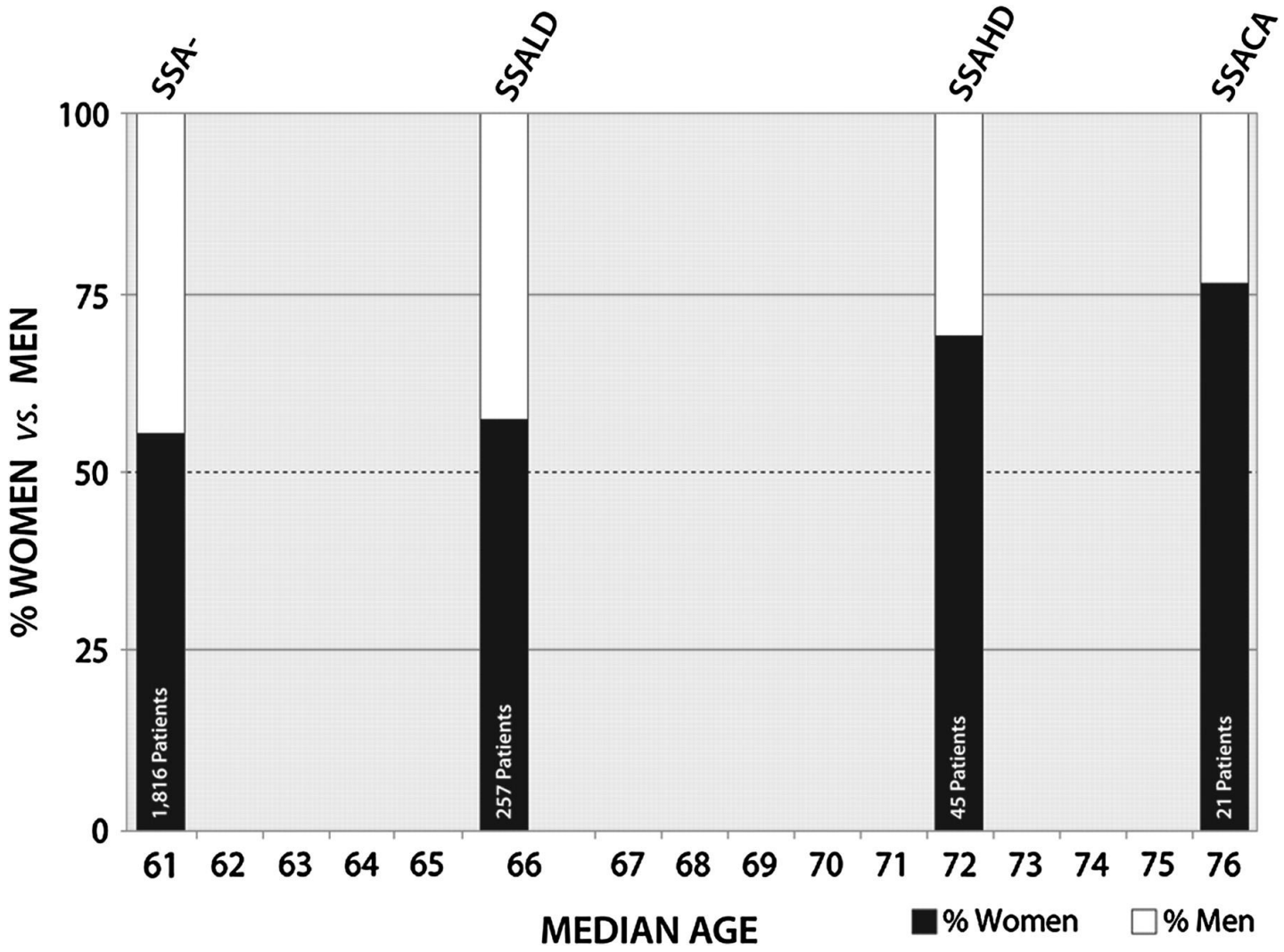




Oono et al. Dig Dis Sci 2009

Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients

Richard H Lash, Robert M Genta, Christopher M Schuler



Lash et al. J Clin Pathol 2010

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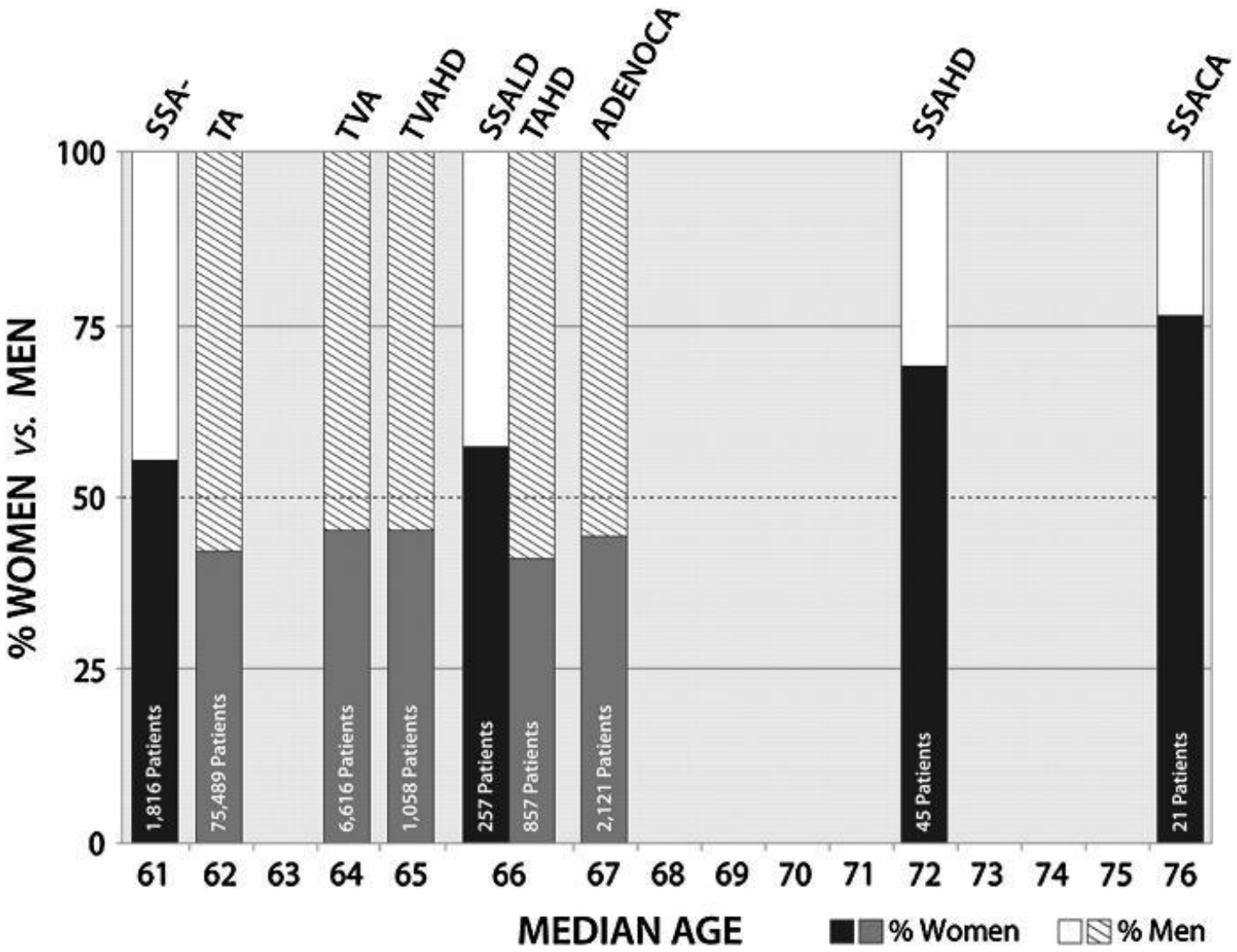

Lash et al. J Clin Pathol 2010

ORIGINAL ARTICLE

Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma

Mark Bettington,[1,2,3] Neal Walker,[1,2] Christophe Rosty,[1,2] Ian Brown,[2] Andrew Clouston,[1,2] Diane McKeone,[3] Sally-Ann Pearson,[3] Barbara Leggett,[1,3,4] Vicki Whitehall[1,3,5]

Medizinische Universität Graz

Table 1 Clinicopathological features of study lesions

Feature	All cases	*MMRD (all) (n=102)*	MMRD SSAD (n=66)	MMRD SSADC/C (n=36)	*MMRP (all) (n=35)*	MMRP SSAD (n=30)	MMRP SSADC/C (n=5)	p Values (MMRD vs MMRP)
Age	75.2	76.7	77.4	75.5	71.0	70.8	72.0	**0.0029**
Gender (female)	61%	70%	71%	69%	36%	39%	20%	**0.0008**
Location* (proximal)	109/126 (87%)	86/94 (91%)	55/58 (95%)	31/36 (86%)	23/32 (72%)	18/27 (67%)	5/5 (100%)	**0.0130**
Median size†	9	9	9	11	8.5	9	8	
Mean size†	10.7	11.1	11.1	11.1	9.5	9.3	11.0	0.1950
Size <10 mm†	70/129 (54%)	47/95 (49%)	36/66 (55%)	12/29 (41%)	22/34 (65%)	18/29 (62%)	4/5 (80%)	0.1668

Bold values indicate a p-value of less than 0.05.
*Eleven cases did not have location data.
†Excludes eight cases presenting clinically as a carcinoma.
MMRD, mismatch repair deficient; MMRP, mismatch repair proficient; SSAD, sessile serrated adenoma with dysplasia; SSADC/C, sessile serrated adenoma with dysplasia and carcinoma or sessile serrated adenoma with carcinoma.

- SSA/Ps with dysplasia or cancer are predominantly small (<10mm), flat polyps of the proximal colon
- SSA/Ps progress to malignancy via a mismatch repair deficient (MMRD, 75%) or mismatch repair proficient (MMR, 25%) pathway

Bettington et al. Gut. 2017

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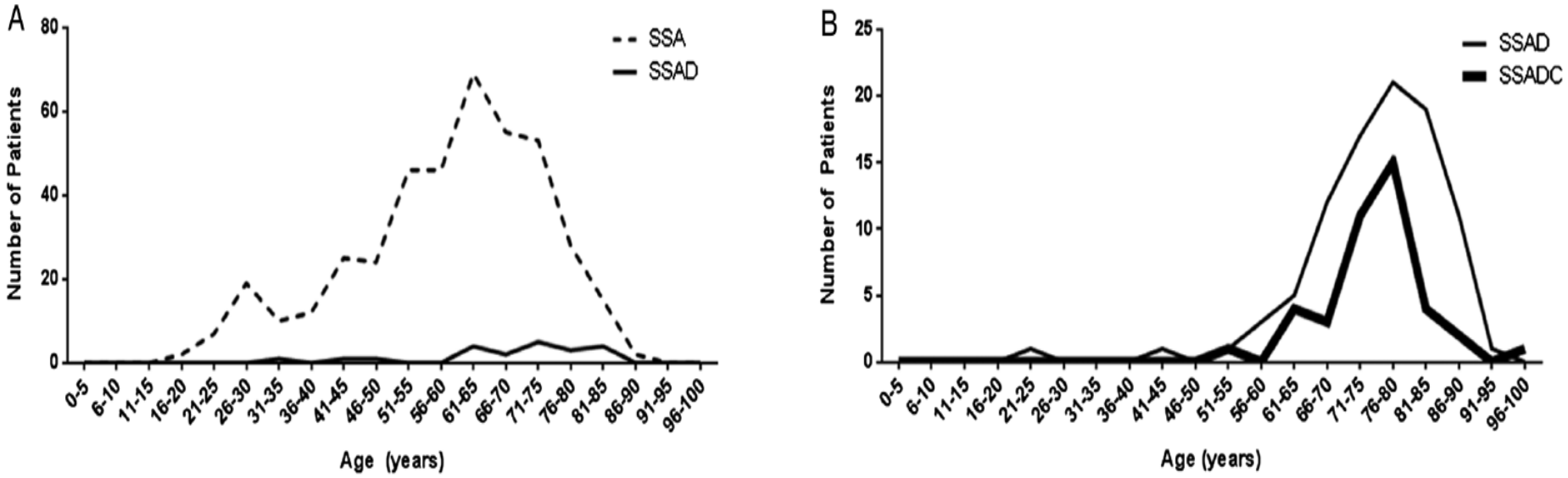

The mean age of patients with SSA/P with dysplasia only and those with SSA/P with carcinoma (indicating **rapid conversion from dysplasia to carcinoma**) is the same, but this is 17 years older than patients with SSA/P without dysplasia

Bettington et al. Gut. 2017

How does dysplasia develop in sessile serrated adenomas/polyps (sessile serrated lesions)?

MODERN PATHOLOGY (2017) 30, 1728–1738
1728 Official journal of the United States and Canadian Academy of Pathology

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Sessile serrated adenomas with dysplasia: morphological patterns and correlations with MLH1 immunohistochemistry

Cheng Liu[1,2], Neal I Walker[2,3], Barbara A Leggett[1,2,4], Vicki LJ Whitehall[1,2,5], Mark L Bettington[2,3,7] and Christophe Rosty[2,3,6,7]

Table 1 Clinicopathological characteristics of patterns of dysplasia

Dysplasia pattern	*Total* N (%)	*Patient age, years* Mean (range)	*Proximal colonic location* N (%)	*Polyp size, mm* Median (range)	*MLH1 loss of expression* N (%)	*Association with other patterns* N (%)	*Association with invasive carcinoma* N (%)
Minimal deviation	50 (19)	76 (44–86)	43 (90)	11.5 (5–55)	43 (91)	36 (72)[a]	4 (8)
Serrated	31 (12)	71 (35–89)[a]	20 (71)[a]	9 (5–20)	4 (13)[a]	9 (29)	4 (13)
Adenomatous	21 (8)	72 (36–89)[a]	15 (75)	15 (6–27)	1 (5)[a]	4 (19)	0 (0)[a]
Not otherwise specified	211 (79)	77 (34–97)	174 (88)	13 (4–70)	175 (83)	44 (21)	47 (22)
All lesions	266 (100)	75 (34–97)	210 (85)	12 (4–70)	193 (73)	46 (17)	50 (19)

[a]Indicates significance difference ($P < 0.05$) when compared with characteristic of dysplasia not otherwise specified.

We found that dysplasia can be divided morphologically into **four major patterns**, comprising minimal deviation (19%), serrated (12%), adenomatous (8%) and not otherwise specified (79%) groups.

Minimal deviation dysplasia is defined by minor architectural and cytological changes that typically requires loss of MLH1 immunohistochemical expression to support the diagnosis.

Serrated dysplasia and **adenomatous dysplasia** have distinctive histological features and are less frequently associated with loss of MLH1 expression (13 and 5%, respectively).

Dysplasia not otherwise specified encompasses most cases and shows a diverse range of morphological changes that do not fall into the other subgroups and are frequently associated with loss of MLH1 expression (83%).

Liu et al. Mod Pathol 2017

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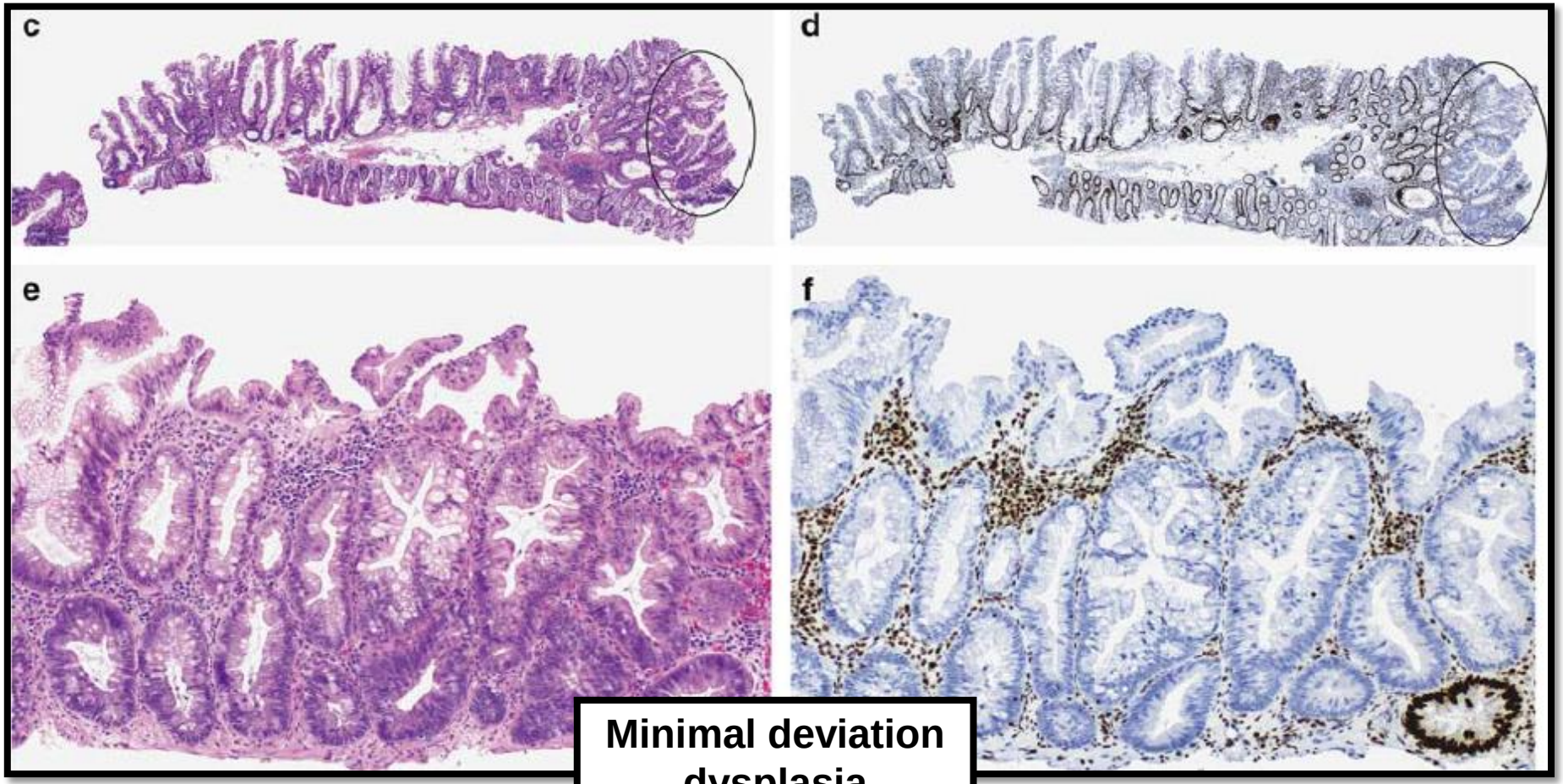

Minimal deviation dysplasia

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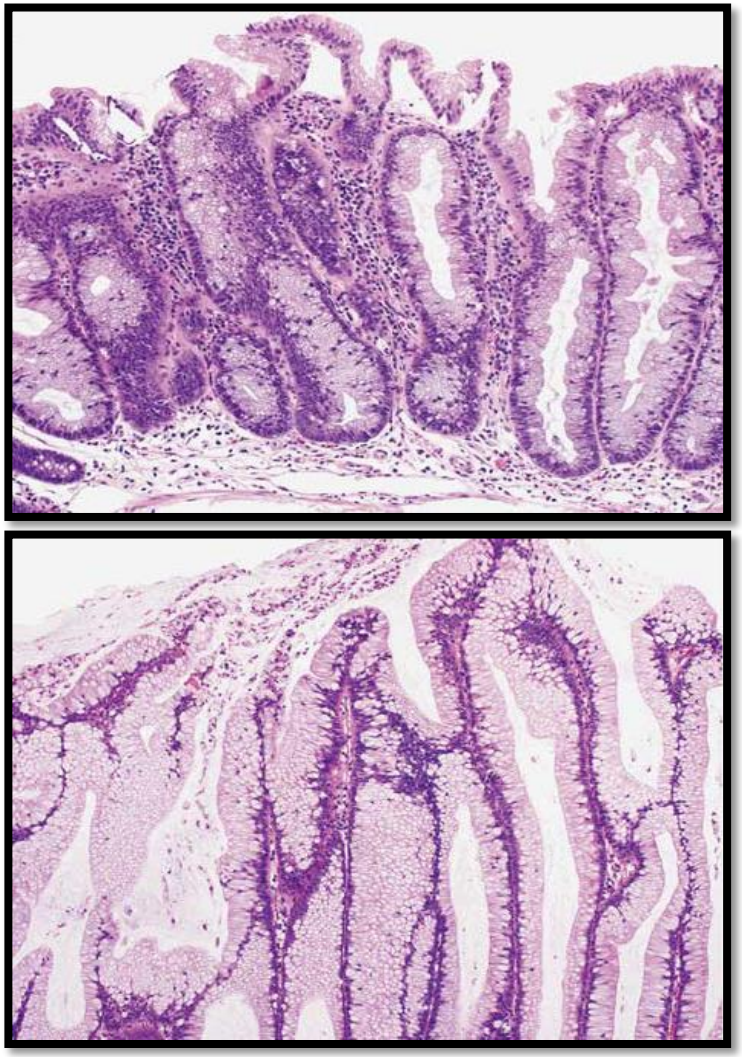
Minimal deviation dysplasia exhibits minimal architectural and cytological changes and is difficult to identify histologically.

At low magnification, there is mild crypt disorganization, crypt crowding and reduced luminal serration compared with the background SSA/P.

The cells frequently have a hypermucinous appearance with compressed, basally located nuclei showing mild hyperchromasia, compared with the nuclei of the adjacent SSA/P component.



Liu et al. Mod Pathol 2017

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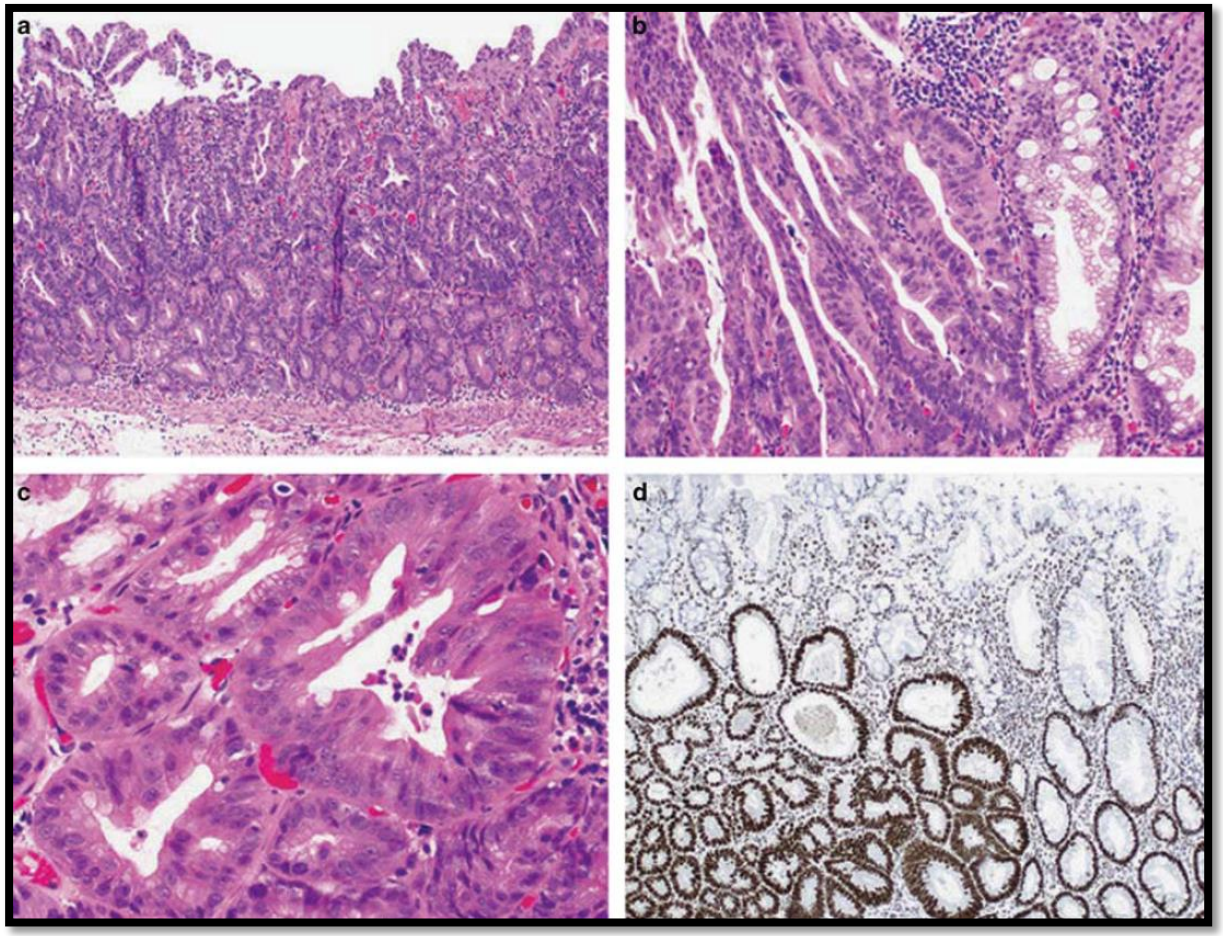

Serrated dysplasia is characterized by closely packed small glands with abundant eosinophilic cytoplasm that occupy the full thickness of the mucosa. Serration is less prominent. The cells are cuboidal to low columnar with evident dysplasia, containing round vesicular nuclei, prominent nucleoli.

The majority of SSA/P with serrated dysplasia demonstrate retained MLH1 expression by immunohistochemistry.

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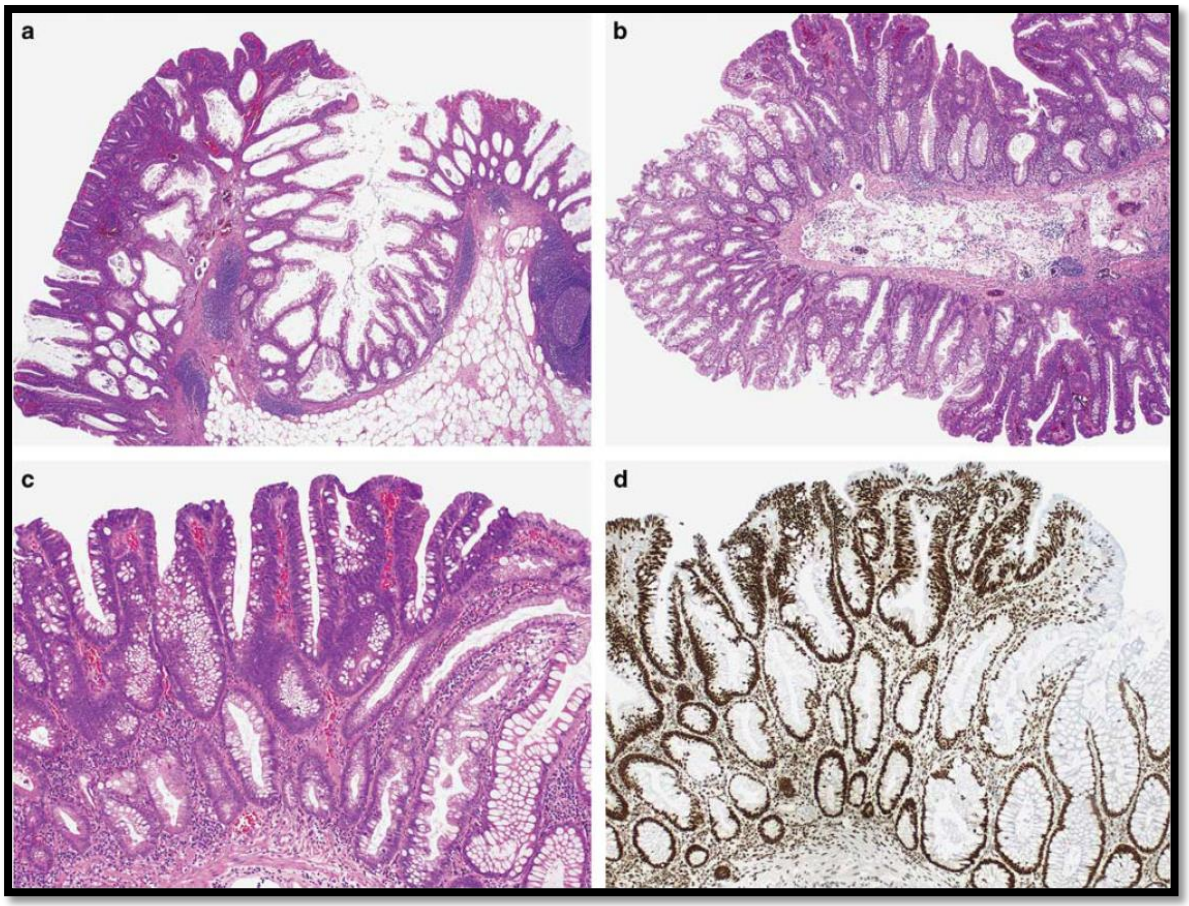

The main characteristics of **adenomatous dysplasia** are the predominant location of the dysplastic component on the surface ('top–down') with preserved non-dysplastic SSA/P at the base of the lesion and the complete similarity to the dysplasia of conventional adenomas. There is no serration. The cells are columnar with at least focal goblet cell differentiation, elongated nuclei and pseudo-stratification. This pattern also had a strong predilection to retain staining for MLH1.

Liu et al. Mod Pathol 2017

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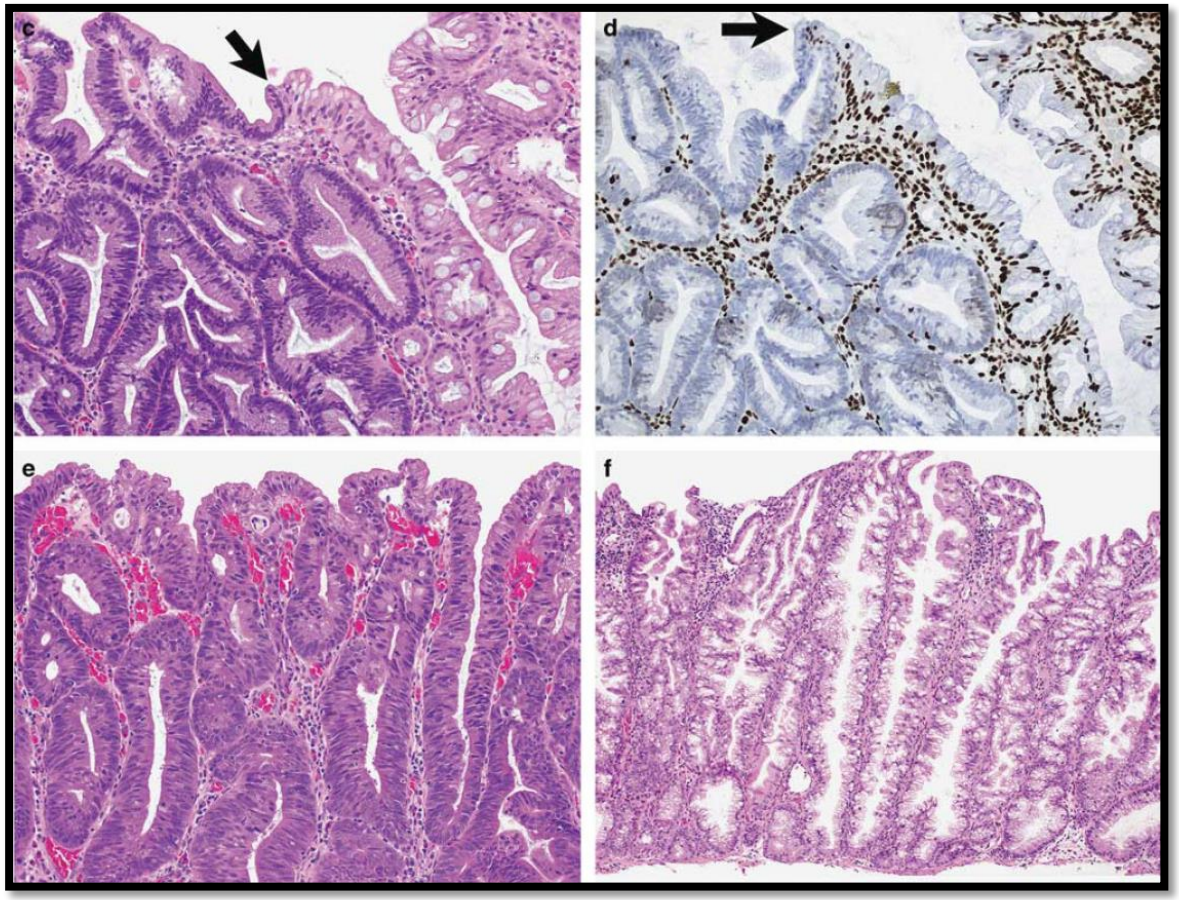

Dysplasia not otherwise specified shows obvious architectural and cytological abnormalities in all cases ("prototypical SSA/P-D"). *Architectural dysplasia* includes crypt elongation, crypt crowding, excessive serration and complex branching or cribriform growth. *Cytological dysplasia* occupies the full thickness of the epithelium. The morphological appearance is often heterogeneous ("waste basket") with often more than one architectural pattern in one lesion.

Liu et al. Mod Pathol 2017

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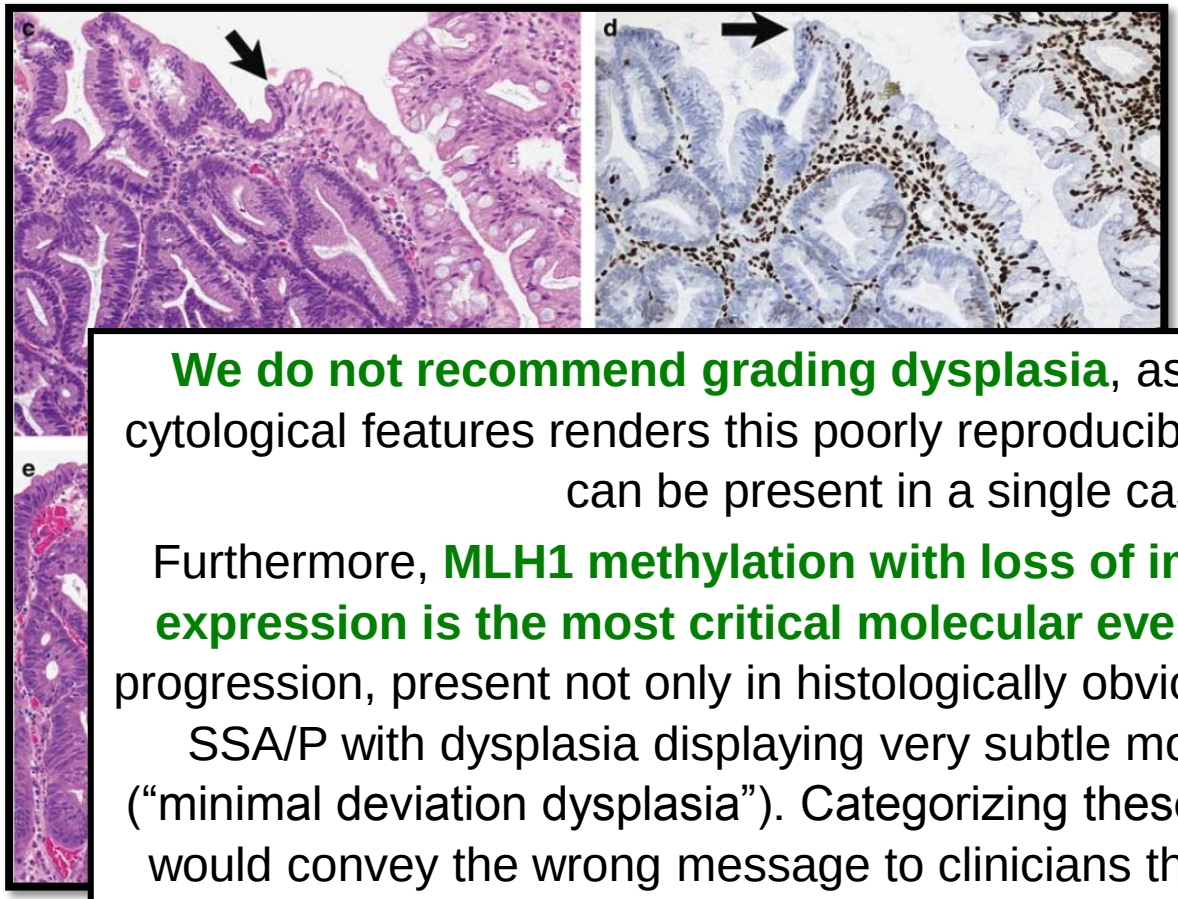


Dysplasia not otherwise specified shows obvious architectural and cytological abnormalities in all cases ("prototypical SSA/P-D"). *Architectural dysplasia* includes crypt elongation, crypt crowding, excessive serration and complex

We do not recommend grading dysplasia, as the architectural and cytological features renders this poorly reproducible, and several patterns can be present in a single case.

Furthermore, **MLH1 methylation with loss of immunohistochemical expression is the most critical molecular event** underpinning lesion progression, present not only in histologically obvious dysplasia but also in SSA/P with dysplasia displaying very subtle morphological changes ("minimal deviation dysplasia"). Categorizing these lesions as "low grade" would convey the wrong message to clinicians that they are innocuous.

Liu et al. Mod Pathol 2017

Modern Pathology
https://doi.org/10.1038/s41379-019-0280-2

USCAP

REVIEW ARTICLE

Medizinische Universität Graz

An update on the morphology and molecular pathology of serrated colorectal polyps and associated carcinomas

Rish K. Pai[1] · Mark Bettington[2,3,4] · Amitabh Srivastava[5] · Christophe Rosty[2,3,6]

Table 2 Morphologic patterns of dysplasia in sessile serrated polyps

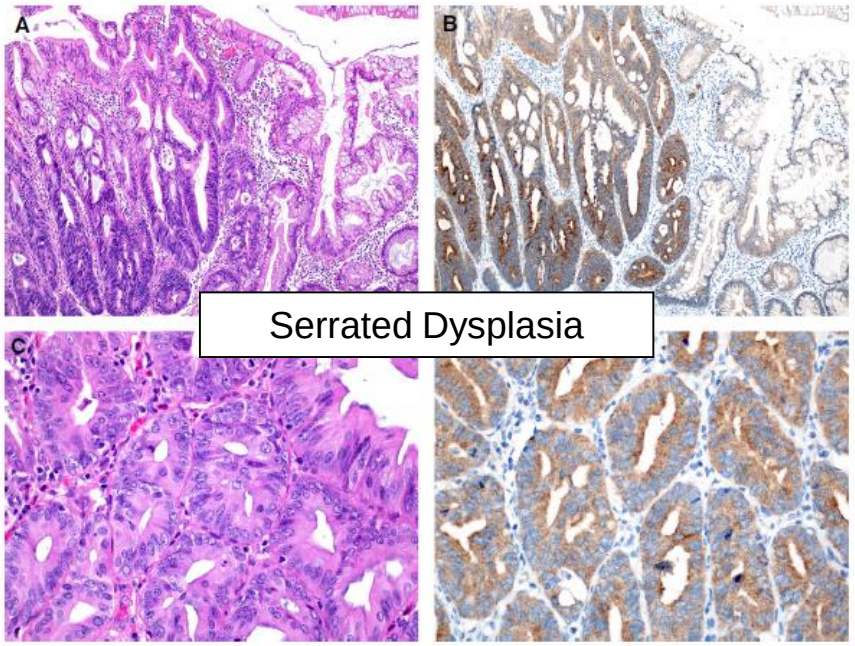
Patterns	Architectural changes	Cytologic features	MLH1 loss	Frequency[a]
Dysplasia not otherwise specified	Easily identifiable and varied in appearance: crypt elongation, crowding, complex branching, change in serration	Obvious atypia with amphophilic or eosinophilic cytoplasm, hyperchromatic nuclei with pseudostratification, frequent mitotic figures and loss of polarity	Frequent (>80%)	79%
Minimal deviation	Subtle changes with crypt crowding, change in crypt branching pattern and often reduced serration	Cells with hypermucinous cytoplasm or slightly eosinophilic with gastric phenotype, basally located nuclei showing mild hyperchromasia and mitotic figures not restricted to the lower part of the crypts.	Required for the diagnosis	19%
Serrated dysplasia	Closely packed small glands with reduced serration and cribriforming	Cuboidal cells with eosinophilic cytoplasm, frequent mitotic figures, marked nuclear atypia with vesicular nuclei and prominent nucleoli	Rare	12%
Adenomatous dysplasia	Absence of crypt serration, same appearance as conventional adenomas; dysplastic component on the upper part of the lesion	Cells with amphophilic or basophilic cytoplasm, elongated hyperchromatic nuclei and variable amount of goblet cell differentiation resembling cells from conventional adenomas	Rare	8%

[a]Frequency of each pattern from Liu et al. [28] Multiple patterns can be present in a single lesion.

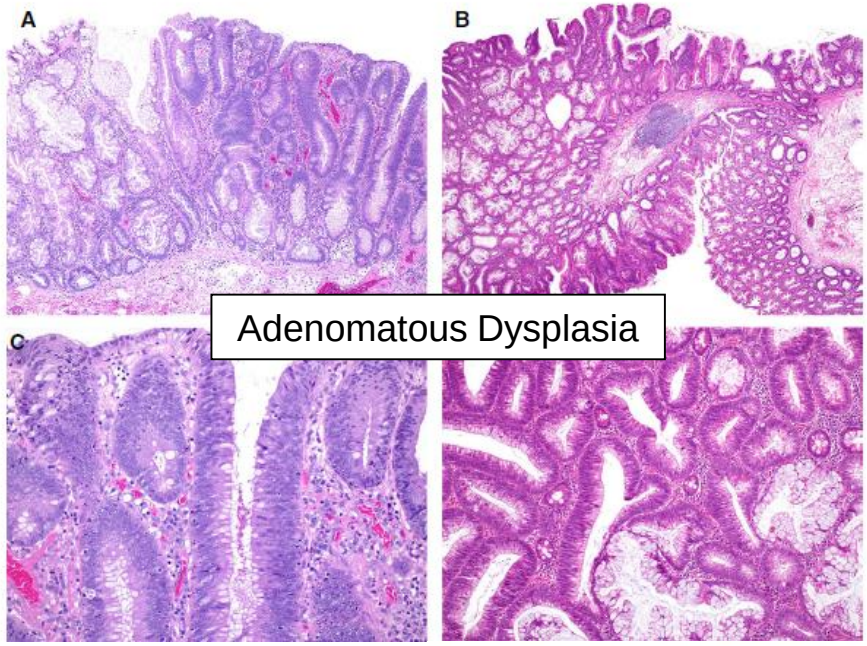
Pai et al. Mod Pathol 2019

BRAF V600E immunohistochemistry demonstrates that some sessile serrated lesions with adenomatous dysplasia may represent collision lesions

Mark Bettington,[1,2,3] Cheng Liu,[1,2,3] Anthony Gill,[4,5,6] Neal Walker,[1,2] Barbara Leggett,[2,3,7] Vicki Whitehall[2,3,8] & Christophe Rosty[1,3,9]



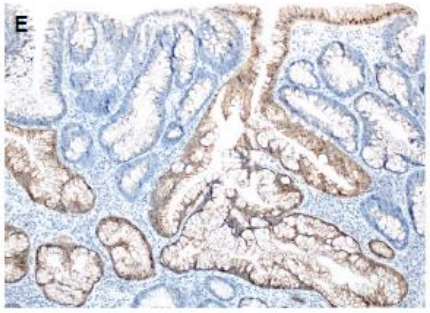
Serrated Dysplasia



Adenomatous Dysplasia

Table 2. *BRAF* mutation status by allelic discrimination and immunohistochemistry

	SSLs with adenomatous dysplasia *n* = 19	SSLs with serrated dysplasia *n* = 18	SSLs with dysplasia NOS *n* = 43
BRAF mutated by allelic discrimination	13 (68%)	16 (89%)	38 (88%)
BRAF-V600E immunohistochemistry results in the *BRAF*-mutated cases (as assessed in the dysplastic component)*			
Positive	2 (17%)	14 (100%)	36 (97%)
Negative	10 (83%)	0 (0%)	1 (3%)



Bettington et al. Histopathology 2019

BRAF V600E immunohistochemistry demonstrates that some sessile serrated lesions with adenomatous dysplasia may represent collision lesions

Mark Bettington,[1,2,3] Cheng Liu,[1,2,3] Anthony Gill,[4,5,6] Neal Walker,[1,2] Barbara Leggett,[2,3,7] Vicki Whitehall[2,3,8] & Christophe Rosty[1,3,9]

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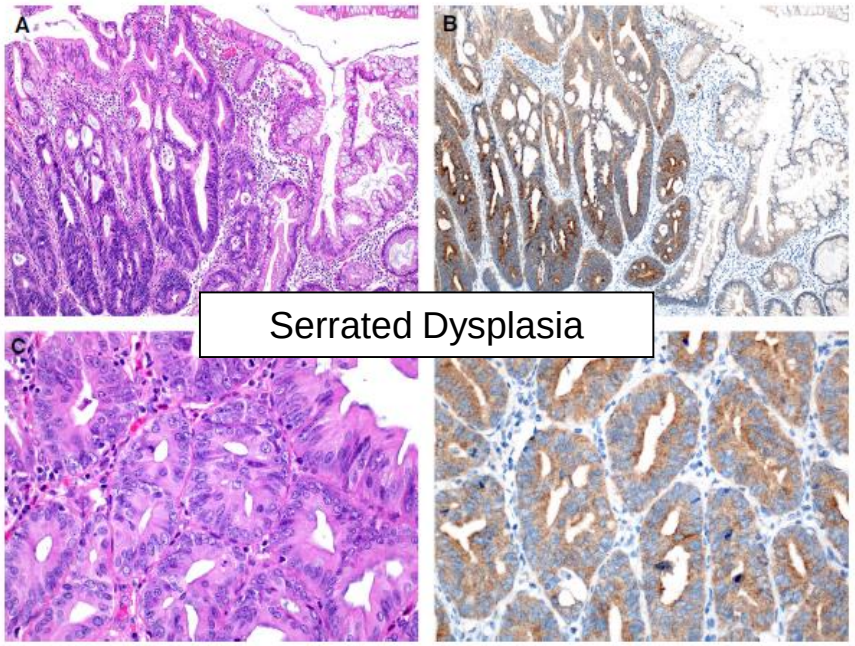
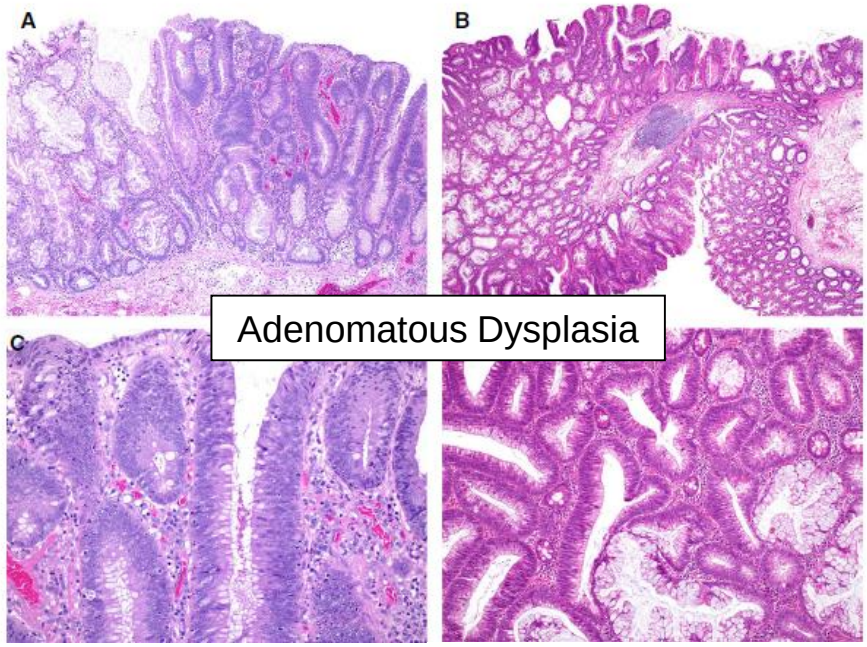
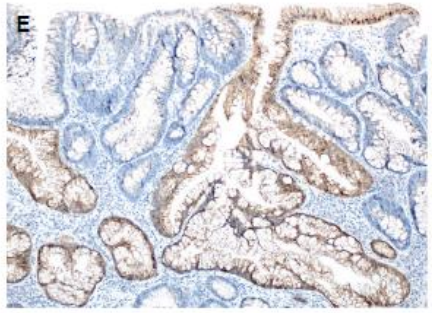


Serrated Dysplasia



Adenomatous Dysplasia



Does adenomatous dysplasia in sessile serrated lesions (previously SSA/P) really exist?

Bettington et al. Histopathology 2019

Medizinische Universität Graz

What to do with multiple sessile serrated adenomas/polyps (sessile serrated lesions)?

GASTROENTEROLOGY 1996;110:748–755

Medizinische Universität Graz

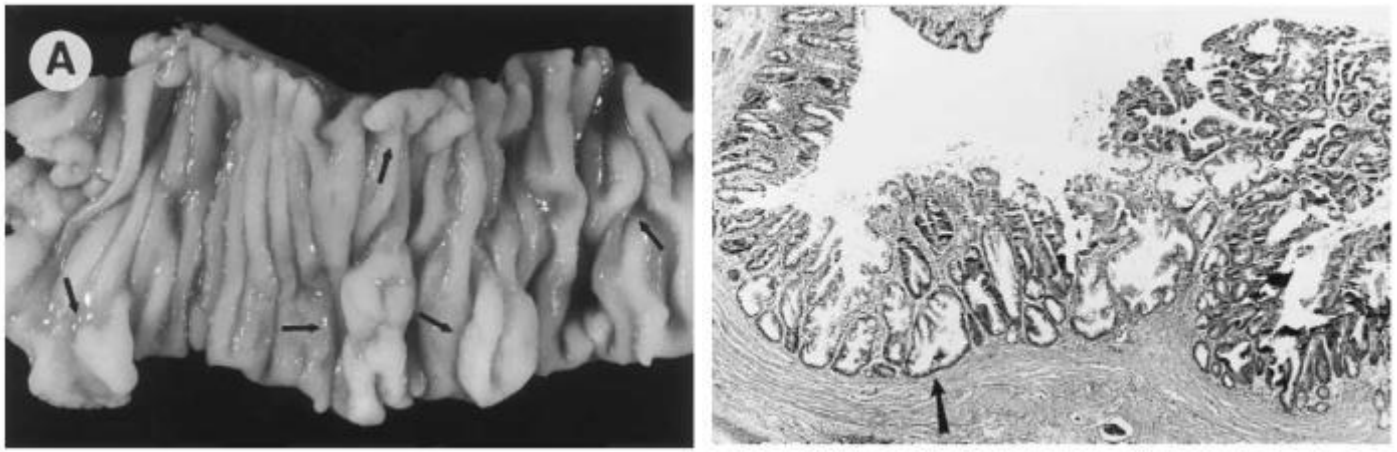
Serrated Adenomatous Polyposis in Humans

EMINA TORLAKOVIC and DALE C. SNOVER
Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota

Table 1. Clinical and Gross Features of Cases Studied

		Polyps				Cancer	
Patient	Sex/age (*yr*)	No.	Size (*cm*)	Shape	Distribution	Present	Synchronous versus metachronous
1	M/53	Numerous	0.5–1.5	S	Left colon	Yes	Synchronous
2	M/43	Numerous	0.5–2.0	S	Diffuse	Yes	Synchronous
3	F/85	>50	0.3–1.5	S > P	Diffuse	Yes	Synchronous
4	M/39	>50	0.5–4.0	S > P	Left colon	No	—
5	M/63	Numerous	0.5–4.5	S, P	Diffuse	Yes	Metachronous
6	M/57	Numerous	0.5–4.0	S > P	Right colon	No	—

NOTE. Numerous indicates either more than 100 polyps and/or large areas of the thickened mucosa (carpet-like lesions).
P, pedunculated; S, sessile.



Torlakovic and Snover. Gastroenterology 1996

Serrated Polyposis (Previously: Hyperplastic Polyposis)

Medizinische Universität Graz

Serrated polyposis syndrome: a silent killer when undetected

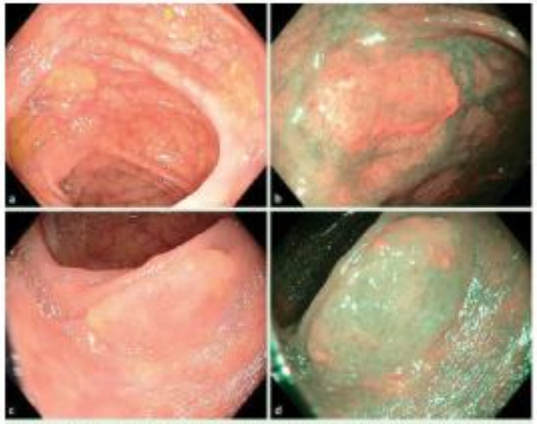


Fig. 1 Representative images of sessile serrated polyps that were missed during the initial colonoscopy. a High-resolution white-light endoscopy (HR-WLE) image of the transverse colon showing sessile serrated polyps in the left and right upper quadrants; b narrow-band imaging (NBI) of the polyp situated in the left upper quadrant showing the characteristic appearance with a covering mucus cap; c HR-WLE image of a large sessile serrated polyp located on a fold (often erroneously described as a thickened fold); d the corresponding NBI image showing typical features of a sessile serrated polyp including clouded surface, indistinct borders, irregular shape, and dark spots inside the crypts.

The second-look colonoscopy showing 6 out of the 14 previously missed sessile serrated polyps, using first white-light imaging then narrow-band imaging.

This report describes the clinical course of a 59-year-old woman who was diagnosed with metachronous colorectal cancer (CRC). She was diagnosed with a T3 N0 M0 sigmoid carcinoma in 2002 (at the age of 46) for which she underwent a sigmoid resection and received follow-up at another hospital. Follow-up colonoscopies in 2003 and 2004 did not show any colonic abnormalities, while colonoscopy in 2006 showed a flat polyp in the cecum, which was biopsied. Histopathologic examination revealed a sessile serrated polyp with a focus of dysplasia and surveillance colonoscopy was advised in 3 years. At a subsequent ileocolonoscopy in 2009, no abnormalities were detected in the cecum or elsewhere in the colon and a 5-year surveillance interval was recommended.

During colonoscopy 5 years later (2014), a cecal tumor was detected. Further inspection of the colon did not reveal any other lesions. The patient underwent a right-sided hemicolectomy; histopathologic examination of the resection specimen showed a T2 N0 Mx adenocarcinoma. Furthermore, seven serrated polyps were identified, of which at least five were larger than 10 mm.

The patient was referred to a clinical genetics outpatient clinic elsewhere for analysis of an underlying hereditary cancer syndrome. The clinical geneticist accurately analyzed the family history, which was negative, and requested molecular analysis on the tumor tissue of both CRCs.

The tumor resected in 2002 was microsatellite stable and showed normal expression of the mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2). The tumor resected in 2014 was microsatellite instable and showed loss of function of both MLH1 and PMS2 due to promoter hypermethylation of the *MLH1* gene, indicating that this carcinoma had developed via the serrated neoplasia pathway. On the basis of these findings, the patient was diagnosed with serrated polyposis syndrome. Subsequent DNA analysis showed no germline mutation in the *MutYH* gene [1].

The patient was referred for a second-look colonoscopy, which was performed at our center and demonstrated 14 sessile serrated polyps and 2 hyperplastic polyps up to 15 mm in size, which were confirmed by histopathology (◎ **Fig. 1**; ○ **Video 1**). Surveillance colonoscopy within 1 year was advised.

Serrated polyposis syndrome (SPS), clinically characterized by multiple serrated polyps throughout the colorectum, is accompanied by an increased lifetime risk of CRC [2]. A recent large retrospective study demonstrated that, once cleared from all polyps and under close surveillance, CRC risk in these patients is only moderately increased [3]. However, most cases of SPS remain unrecognized and as a consequence patients do not receive proper surveillance intervals, significantly increasing their risk of developing CRC [4, 5]. For this reason it is important that endoscopists become acquainted with the diagnosis, risk, and optimal treatment strategies for SPS [6].

Endoscopy_UCTN_Code_CPL_1AJ_2AB

Competing interests: None

- **Clinical criteria for diagnosis**

Criterion 1: ≥ 5 serrated lesions/polyps proximal to the rectum, all being ≥ 5 mm in size, with ≥ 2 being ≥ 10 mm in size

Criterion 2: > 20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥ 5 being proximal to the rectum

Any histological subtype of serrated lesion/polyp (hyperplastic polyp, sessile serrated lesion without or with dysplasia, traditional serrated adenoma, and unclassified serrated adenoma) is included in the final polyp count. The polyp count is cumulative over multiple colonoscopies.

- **About 25% present with type 1 phenotype, 45% with type 2, and 30% have both phenotypes**
- **Molecular features and cancer risk**
  - **Type 1:** SSA/P > HP, BRAF > KRAS, cancer risk substantially increased (MSI-H, CIMP)
  - **Type 2:** HP > SSA/P, KRAS > BRAF, cancer risk modestly increased (MSS)

Ijspeert et al. Endoscopy 2015
Rosty et al. Upcoming WHO Classification

ORIGINAL ARTICLE

Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study

Sabela Carballal,[1] Daniel Rodríguez-Alcalde,[2] Leticia Moreira,[1] Luis Hernández,[2] Lorena Rodríguez,[3] Francisco Rodríguez-Moranta,[3] Victoria Gonzalo,[4] Luis Bujanda,[5] Xavier Bessa,[6] Carmen Poves,[7] Joaquin Cubiella,[8] Inés Castro,[8] Mariano González,[9] Eloísa Moya,[10] Susana Oquiñena,[11] Joan Clofent,[12] Enrique Quintero,[13] Pilar Esteban,[14] Virginia Piñol,[15] Francisco Javier Fernández,[16] Rodrigo Jover,[17] Lucía Cid,[18] María López-Cerón,[1] Miriam Cuatrecasas,[19] Jorge López-Vicente,[2] Maria Liz Leoz,[1] Liseth Rivero-Sánchez,[1] Antoni Castells,[1] María Pellisé,[1] Francesc Balaguer,[1] for the Gastrointestinal Oncology Group of the Spanish Gastroenterological Association

Medizinische Universität Graz

Table 2 Characteristic of serrated polyps according to histological subtype

	Hyperplastic polyps	Sessile serrated adenomas/polyps
Total number, n (%)	6458 (72.5%)	2398 (27%)
Size ≥10 mm, n (%)	359 (5.4%)	647 (28.7%)
Location, n (%)		
▶ Proximal to splenic flexure	1520 (23.5%)	1330 (55.4%)
▶ Descending colon	902 (14%)	446 (18.6%)
▶ Rectosigmoid	4036 (62.5%)	622 (25.9%)
Cytological dysplasia, n (%)		
▶ Any dysplasia		469 (19.5%)
▶ Low-grade dysplasia		438 (18.2%)
▶ High-grade dysplasia		31 (1.4%)

Table 1 Baseline characteristics of patients with SPS (n=296)

Demographic and clinical features	
Age at diagnosis SPS (years), mean±SD	57.2±9.9
Female, n (%)	130 (43.9%)
BMI*, mean±SD	27.5±4.6
Overweight/obesity (BMI ≥25), n (%)	146 (69.5%)
Smoking history, n (%)†	207 (74.5%)
First-degree relative with CRC, n (%)	87 (29.4%)
First-degree relative with SPS, n (%)	13 (4.4%)
WHO criteria‡, n (%)	
I	79 (26.7%)
III	134 (45.3%)
I+III	83 (28%)
Follow-up since SPS diagnosis (months), median (IQR)	45 (26–79.7)
Number of total colonoscopies, median (IQR)	3 (2–4)
Cumulative number of serrated polyps (per patient)	
Serrated polyps, median (IQR)	26 (18.2–40.7)
Location, median (IQR)	
Proximal to splenic flexure	7 (4–14)
Descending colon	3 (1–6)
Rectosigmoid	11 (5–23.5)
Size, median (IQR)	
Serrated polyps ≥10 mm	2 (0–4)
Histology, median (IQR)	
Serrated polyp subtypes	
Hyperplastic polyp	17.5 (6–30.2)
Sessile serrated adenoma/polyp	3 (0–9)
Traditional serrated adenoma	0 (0–0)
Serrated polyp with dysplasia§	
Any dysplasia	0 (0–1)
LGD	0 (0–1)
HGD	0 (0–1)
Adenoma features	
Patients with ≥1 adenoma, n (%)	238 (80.4%)
Patients with ≥1 advanced adenoma¶, n (%)	131 (44.2%)
Number of adenomas (per patient), median (IQR)	3 (1–6)
Number of advanced adenomas¶ (per patient), median (IQR)	0 (0–1)

Carballal et al. Gut. 2016

ORIGINAL ARTICLE

Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study

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Table 6 Multivariate logistic regression of variables associated with colorectal cancer in patients with SPS

Variable	Adjusted OR	95% CI	Adjusted p value
Age at SPS diagnosis	1.02	0.98 to 1.05	0.256
Gender (female)	0.83	0.42 to 1.61	0.586
Number of SSA/Ps	0.97	0. 91 to 1.02	0.267
Number of SSA/Ps with HGD	0.76	0.29 to 2.92	0.678
Number of SSA/Ps proximal to the splenic flexure (per polyp)	**1.04**	**1.01 to 1.07**	**0.016**
Number of proximal (to splenic flexure) SSA/Ps with HGD (per polyp)	**2.12**	**1.01 to 4.50**	**0.049**

Statistically significant results are represented in bold.
HGD, high-grade dysplasia; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp.

Table 3 Colorectal features of CRCs diagnosed in patients with SPS

N=47 (15%)	
Age at CRC diagnosis (years), mean±SD	53.9±12.8
WHO criteria*, n (%)	
▸ Criterion I	14 (29.7%)
▸ Criterion III	19 (40.6%)
▸ Criteria I+III	14 (29.7%)
Tumour location, n (%)	
▸ Caecum	3 (6.4%)
▸ Ascending colon	6 (12.8%)
▸ Hepatic flexure	3 (6.4%)
▸ Transverse colon	10 (21.3%)
▸ Descending colon	1 (2.1%)
▸ Sigmoid colon	18 (38.3%)
▸ Rectum	6 (12.8%)
TNM tumour stage, n (%)	
▸ I	24 (51%)
▸ II	12 (25.5%)
▸ III	6 (12.8%)
▸ IV	5 (10.7%)
Time at CRC diagnosis, n (%)	
▸ Before SPS diagnosis	8 (17%)
▸ At the time of SPS diagnosis	35 (74.5%)
▸ During SPS surveillance	4 (8.5%)

*WHO criteria: (I) patients who fulfil criterion I only; (III) patients who fulfil criterion III only; (I+III): patients who fulfil both I and III criteria.
CRC, colorectal cancer; SPS, serrated polyposis syndrome; TNM, tumour, node, metastases.

Carballal et al. Gut. 2016

Traditional Serrated Adenoma (TSA)

Medizinische Universität Graz

- **Incidence**
  - Rare: <1% of all colorectal polyps
- **Gross morphology**
  - Location: left > right (distal colon and rectum)
  - Macroscopy / Endoscopy: polypoid > flat lesion
- **Histology**
  - **Complex villiform growth pattern with prominent „slit-like“ serration**
  - **Tall columnar cells with intensively eosinophilic cytoplasm and pencillate nuclei** (referred to by some authors as „serrated dysplasia“)
  - Ectopic crypt foci (epithelial buds not anchored to the muscularis mucosae)

Pai et al. Upcoming WHO Classification

Ectopic crypt foci in conventional and serrated colorectal polyps

Sara A Väyrynen,[1,2] Juha P Väyrynen,[1,2] Kai Klintrup,[2,3] Jyrki Mäkelä,[2,3] Anne Tuomisto,[1,2] Markus J Mäkinen[1,2]

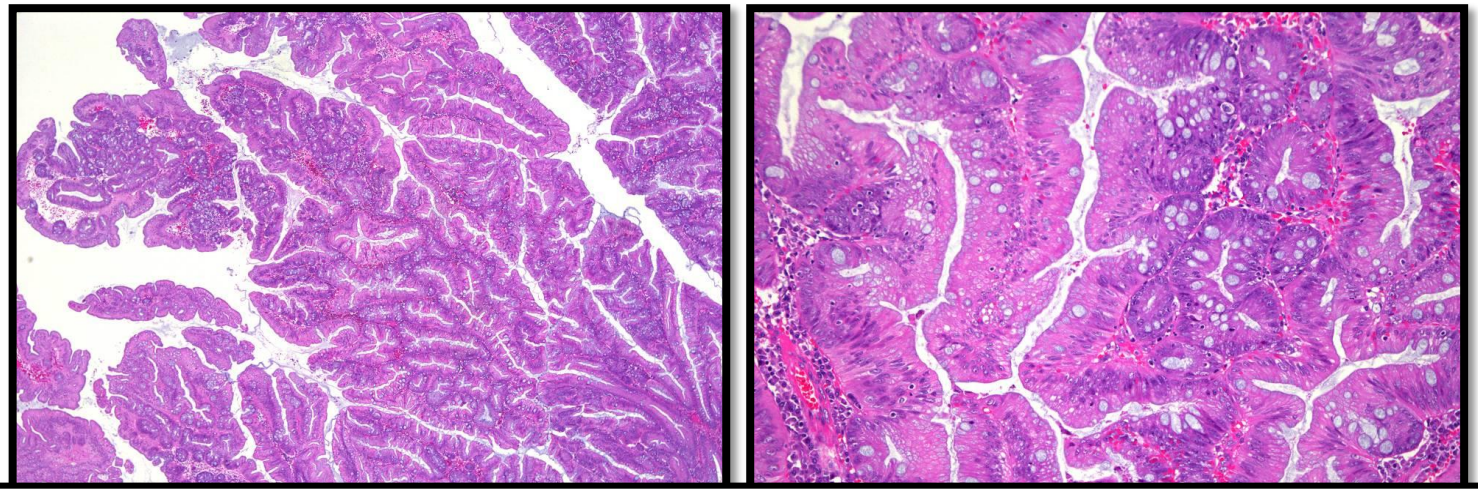
Table 1 Characteristics of colorectal polyps in the study

Polyp type	TA	TVA	VA	HP	SSA	TSA	p Value
n (%)	428 (46.4)	26 (2.8)	2 (0.2)	412 (44.7)	45 (4.9)	9 (1.0)	
Age, mean (SD)	65.2 (12.9)	69.2 (9.0)	84.0 (0.0)	58.5 (12.9)	57.4 (13.5)	69.6 (14.4)	<0.001*
Gender (%)							
Male	245 (57.2)	14 (53.8)	2 (100.0)	241 (58.5)	24 (53.3)	4 (44.4)	0.813†
Female	183 (42.8)	12 (46.2)	0 (0.0)	171 (41.5)	21 (46.7)	5 (55.6)	
Polyp location (%)‡							
Proximal colon	158 (41.5)	11 (44.0)	0 (0.0)	68 (18.0)	18 (45.0)	3 (33.3)	<0.001†
Distal colon	149 (39.1)	6 (24.0)	0 (0.0)	125 (33.1)	12 (30.0)	3 (33.3)	
Rectum	74 (19.4)	8 (32.0)	1 (100.0)	185 (49.8)	10 (25.0)	3 (33.3)	
The presence of ECF (%)							
No	400 (93.5)	12 (46.2)	0 (0.0)	412 (100.0)	45 (100.0)	0 (0.0)	<0.001†
Yes	28 (6.5)	14 (53.8)	2 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)	

*t test.
†χ^2 or Fisher's exact test.
‡Information of the exact polyp location was not available in 88 (9.5%) cases.
ECF, ectopic crypt foci; HP, hyperplastic polyps; SSA, serrated precursor lesions, sessile adenoma; TA, tubular adenoma; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma; VA, villous adenomas.

Väyrynen et al. J Clin Pathol 2016

Traditional Serrated Adenoma (TSA)



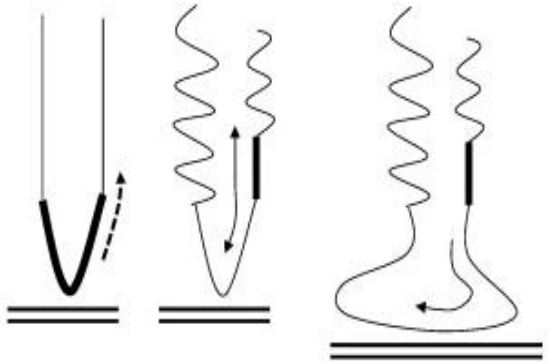
For the diagnosis of TSA, polyps need to show at least two of the following three features, with at least one feature evident in >50% of the polyps (Bettington et al. Am J Surg Pathol 2014 / Mod Pathol 2014):

(1) Slit-like epithelial serration (referred to narrow slits in the epithelium similar to normal small intestinal mucosa)

(2) Typical cytology (abundant brightly eosinophilic cytoplasm with centrally placed, pencillate nuclei)

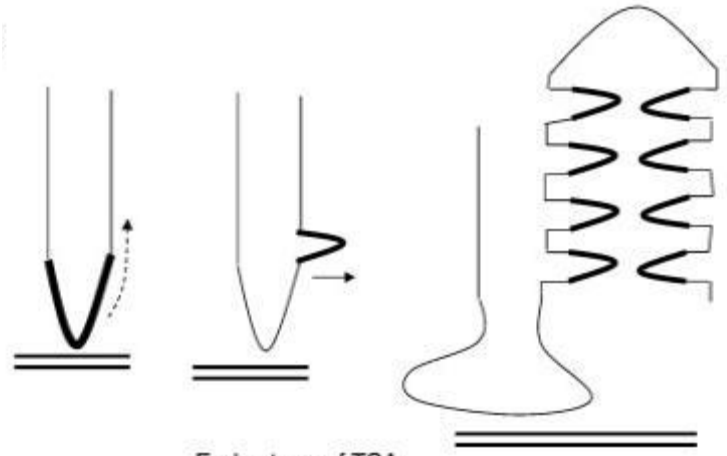
(3) Ectopic crypt formation referred to epithelial buds with their bases not seated adjacent to the muscularis mucosae

Traditional Serrated Adenoma (TSA)



Early stage of SSA/P with movement of proliferative zone to side of crypt (dotted arrow) and bidirectional maturation (solid arrow)

Progression of SSA/P with downward growth of mature epithelium leading to distorted crypt

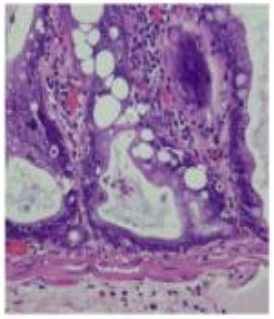


Normal crypt

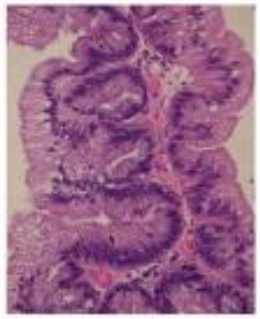
Early stage of TSA with proliferative zone on side of crypt. Outward growth creates ectopic crypt (arrow)

Fully developed TSA with multiple ectopic crypts lining villi

Sessile serrated adenoma/polyp (SSA/P)



Traditional serrated adenoma (TSA)



Snover Hum Pathol 2011

Modern Pathology (2015) 28, 414–427

Medizinische Universität Graz

A clinicopathological and molecular analysis of 200 traditional serrated adenomas

Mark L Bettington[1,2,3], Neal I Walker[2,3], Christophe Rosty[2,3,4], Ian S Brown[3,5], Andrew D Clouston[2,3,5], Diane M McKeone[1], Sally-Ann Pearson[1], Kerenaftali Klein[6], Barbara A Leggett[1,2,7] and Vicki LJ Whitehall[1,2,8]

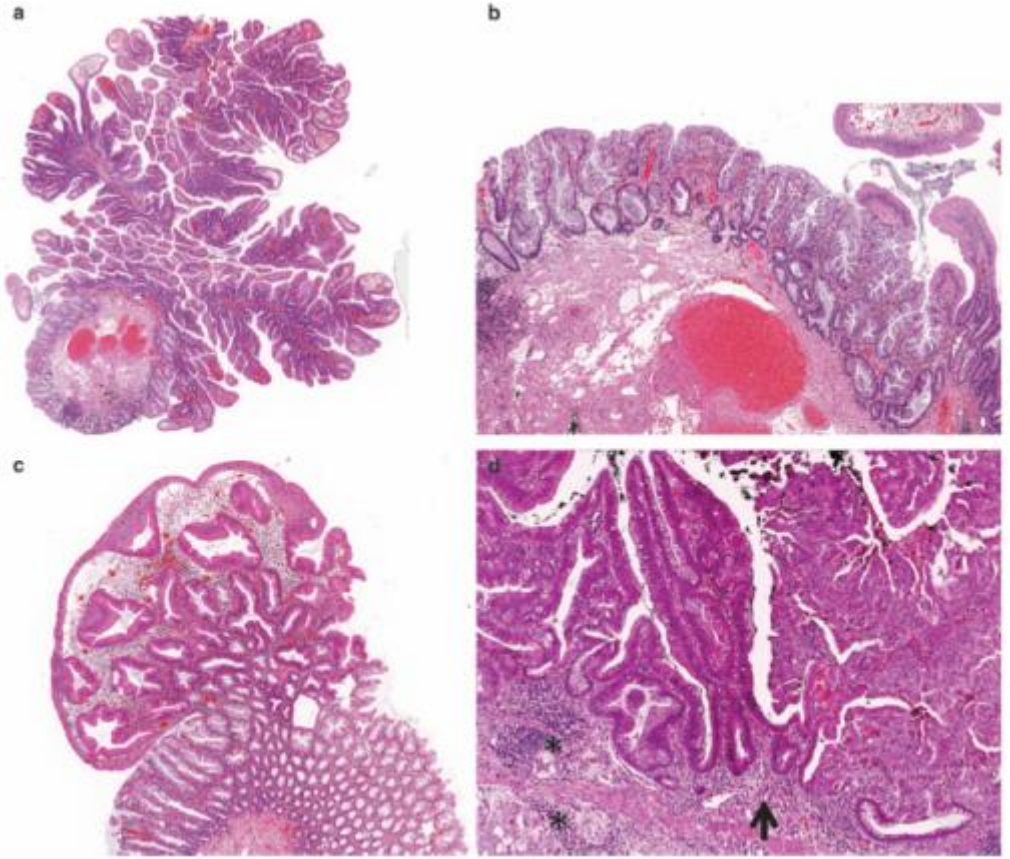


Figure 2 (a, b). A protuberant *BRAF* mutant traditional serrated adenoma from the sigmoid colon with adjacent sessile serrated adenoma better demonstrated at higher power in (b). (c) A small but protuberant *BRAF* mutant traditional serrated adenoma from the rectum arising from a microvesicular hyperplastic polyp. (d) An advanced *BRAF* mutant traditional serrated adenoma from the transverse colon (left) with abrupt transition (arrow) to high-grade serrated dysplasia (right). This polyp also had a small focus of invasive carcinoma (not shown); however, note the carcinoma within the lymphatics of the mucosa and submucosa (asterisks).

Bettington et al. Mod Pathol 2015

MODERN PATHOLOGY (2015) 28, 414–427

Medizinische Universität Graz

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Table 1 Clinicopathological features by advanced histology

	All traditional serrated adenomas (n = 200)	*Ordinary traditional serrated adenomas (n = 162)*	*Advanced traditional serrated adenomas (n = 38)*	*P-value (ordinary versus advanced)*
Age	64 (27–89)	64 (27–89)	65 (27–85)	0.8069
Female	50%	51%	45%	0.5891
Mean size (mm)	16 (3–95) (median 12)	14 (3–95) (median 11)	25 (5–70) (median 21)	**<0.0001**
Distal location	71%	68%	82%	0.1153
Precursor polyp	38%	44%	13%	**0.0003**
Sessile serrated adenoma	31%	36%	11%	**0.0018**
Microvesicular hyperplastic polyp	7%	8%	3%	0.4769

P-values <0.05 are indicated in bold.

Bettington et al. Mod Pathol 2015

Modern Pathology (2015) 28, 414–427

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Table 2 Clinicopathological features by mutation status

Feature	*BRAF mutation (n = 134)*	*KRAS mutation (n = 43)*	*BRAF/KRAS wild type (n = 23)*	P-*value (BRAF versus KRAS)*
Age	64 (27–89)	65 (36–86)	62 (36–87)	0.8611
Female	49%	49%	57%	1.000
Mean size (mm)	14 (3–70) (median 12)	18 (3–60) (median 13)	20 (4–95) (median 13)	0.0550
Distal location	61%	98%	74%	**<0.0001**
Precursor polyp	57%	0%	0%	**<0.0001**
Sessile serrated adenoma	46%	0%	0%	**<0.0001**
Microvesicular hyperplastic polyp	10%	0%	0%	**0.0233**

P-values <0.05 are indicated in bold.

Bettington et al. Mod Pathol 2015

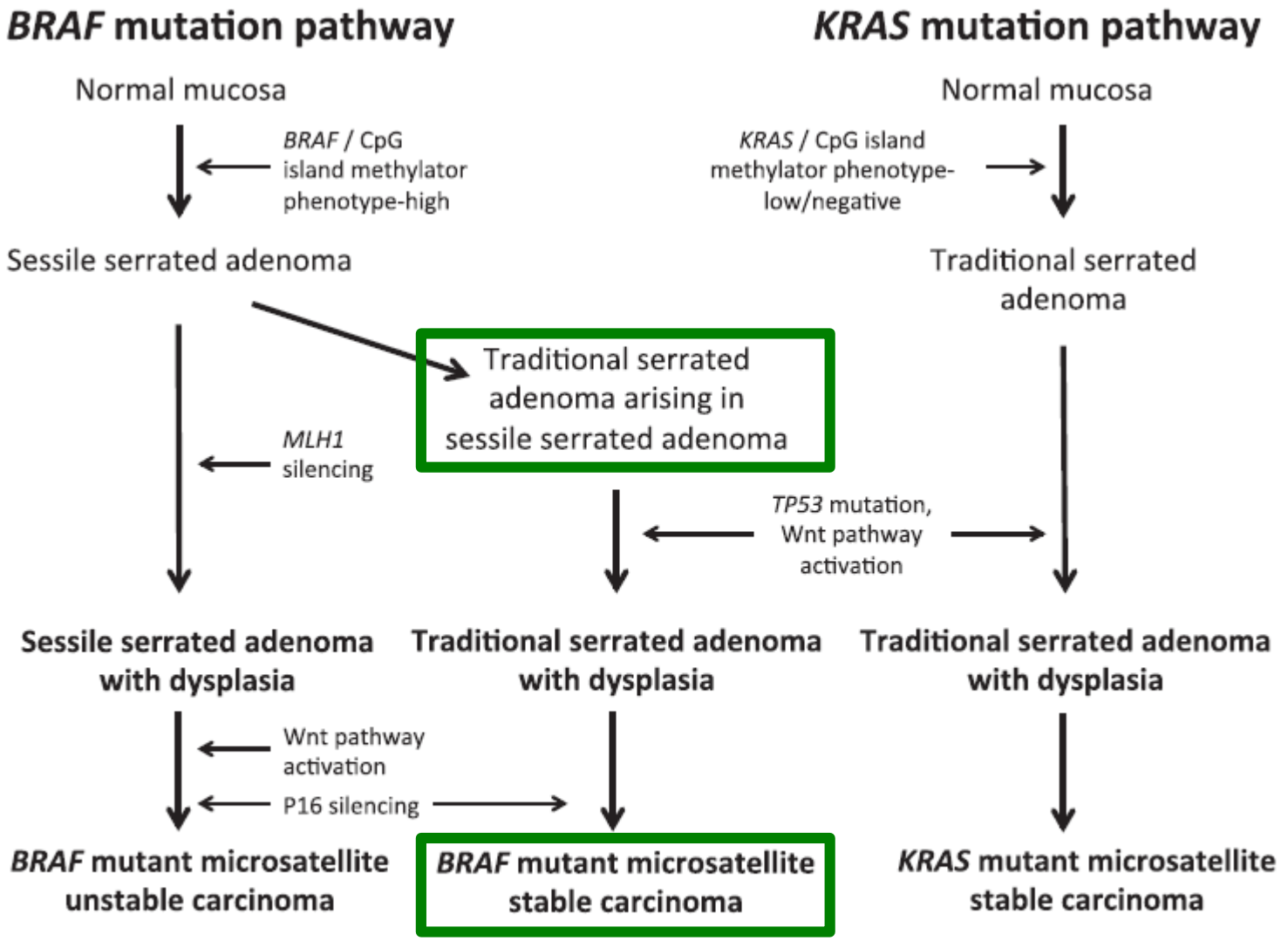

Figure 4 Proposed molecular pathways of malignant progression in *BRAF* and *KRAS* mutant traditional serrated adenoma.

Bettington et al. Mod Pathol 2015

Modern Pathology
https://doi.org/10.1038/s41379-019-0280-2

USCAP

Medizinische Universität Graz

REVIEW ARTICLE

An update on the morphology and molecular pathology of serrated colorectal polyps and associated carcinomas

Rish K. Pai[1] · Mark Bettington[2,3,4] · Amitabh Srivastava[5] · Christophe Rosty[2,3,6]

Table 1 Histologic and molecular features of serrated polyps

	Histologic features				Molecular features		
Type	Crypt architecture	Proliferation zone	Cytologic features	Mucin type	BRAF mutation	KRAS mutation	CpG island methylation
Microvesicular hyperplastic polyp	Funnel-shaped crypts with serrations limited to upper two-thirds	Located uniformly in the basal portion of crypts	Small basally located nuclei, no dysplasia	Mixed Micro-vesicular and Goblet cell	70–80%	0%	+
Goblet cell hyperplastic polyp	Elongated crypts that resemble enlarged normal crypts; Little to no serrations	Located uniformly in the basal portion of crypts	Small basally located nuclei, no dysplasia	Goblet cell only	0%	50%	–
Sessile serrated polyp	Horizontal growth along the muscularis mucosae, dilation (often asymmetric) of the crypt base (basal third of the crypt), and/or serrations extending into the crypt base	Proliferation may be abnormally located away from the crypt base, variable from crypt to crypt	Small basally located nuclei with occasional larger nuclei with inconspicuous nucleoli, no dysplasia	Mixed Micro-vesicular and Goblet cell	>90%	0–5%	++
Sessile serrated polyp with dysplasia	As for sessile serrated polyp	As for sessile serrated polyp with more proliferation in dysplastic component	Varied morphologic appearance to dysplastic component	Varied type	>90%	0%	+++
Traditional serrated adenoma	Slit-like serrations, often ectopic crypt foci	Present within ectopic crypt foci and crypt base	Elongated pencillate nuclei with nuclear stratification and cytoplasmic eosinophilia; may develop overt (conventional or serrated) dysplasia	Occasional scattered goblet cells; rare goblet cell variant has been described	20–40%	50–70%	BRAF mutated ++ KRAS mutated +
Serrated adenoma-unclassified	Varied	Varied	Unequivocal dysplasia must be present	Varied	Uncertain	Uncertain	Uncertain

Pai et al. Mod Pathol 2019 [and Pai et al. in the upcoming WHO Classiciation]

Modern Pathology
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USCAP

REVIEW ARTICLE

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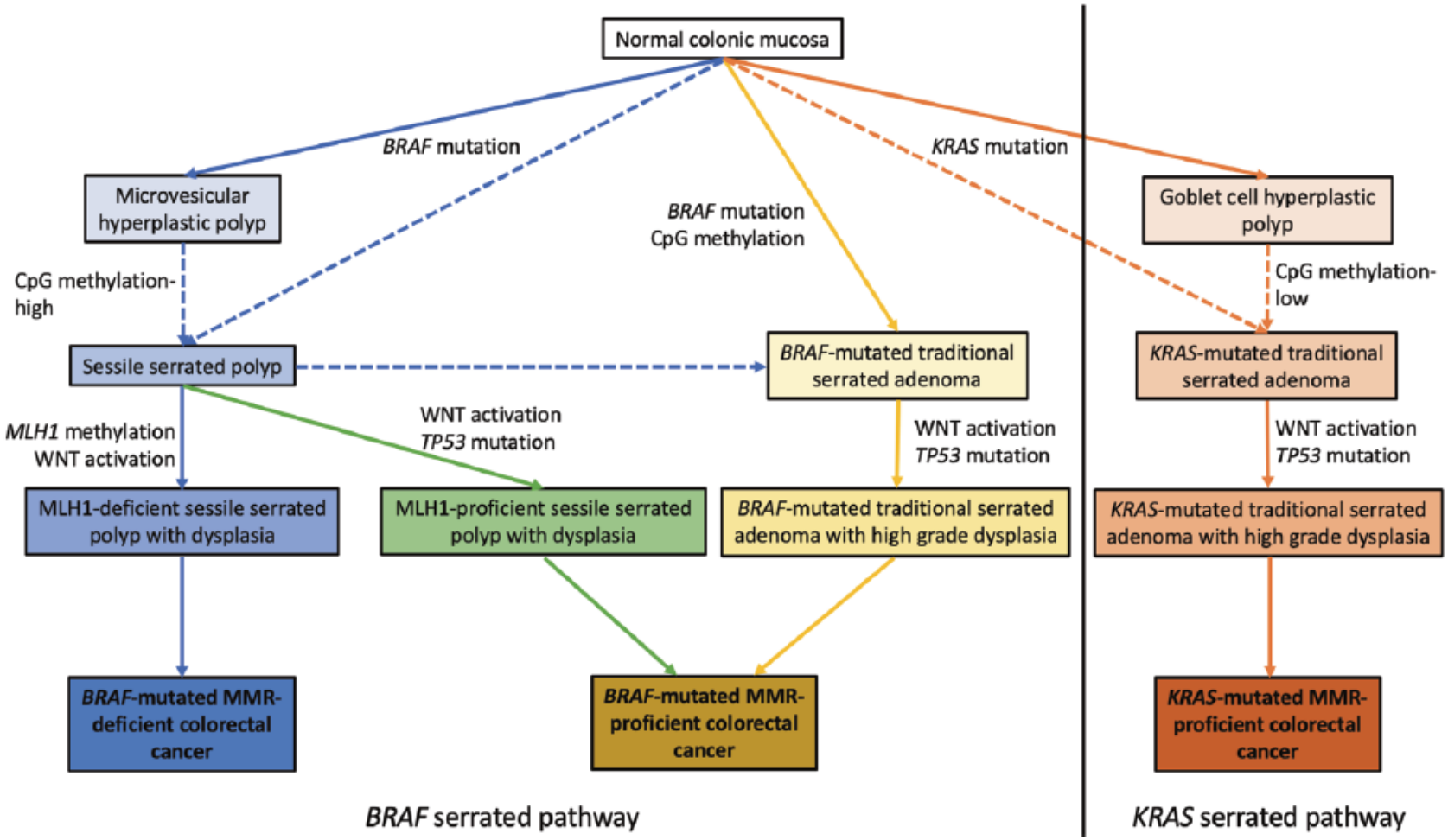

Pai et al. Mod Pathol 2019 [and Pai et al. in the upcoming WHO Classiciation]

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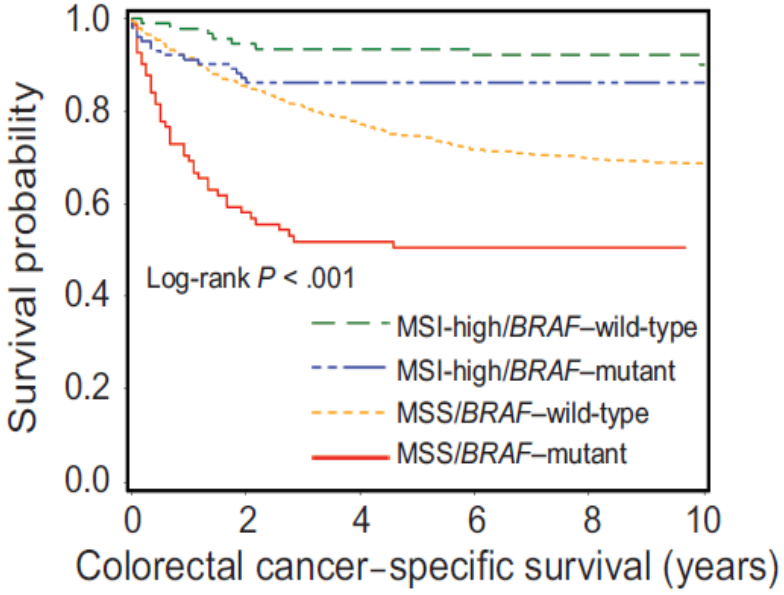
Microsatellite Instability and *BRAF* Mutation Testing in Colorectal Cancer Prognostication

Paul Lochhead, Aya Kuchiba, Yu Imamura, Xiaoyun Liao, Mai Yamauchi, Reiko Nishihara, Zhi Rong Qian, Teppei Morikawa, Jeanne Shen, Jeffrey A. Meyerhardt, Charles S. Fuchs, Shuji Ogino

A



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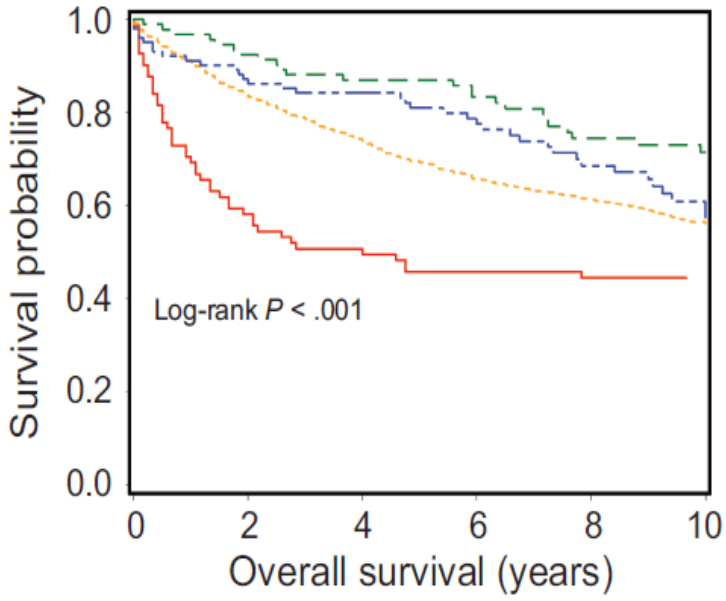

Lochhead et al. J Natl Cancer Inst 2013

Modern Pathology
https://doi.org/10.1038/s41379-019-0280-2

USCAP

REVIEW ARTICLE

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An update on the morphology and molecular pathology of serrated colorectal polyps and associated carcinomas

Rish K. Pai[1] · Mark Bettington[2,3,4] · Amitabh Srivastava[5] · Christophe Rosty[2,3,6]

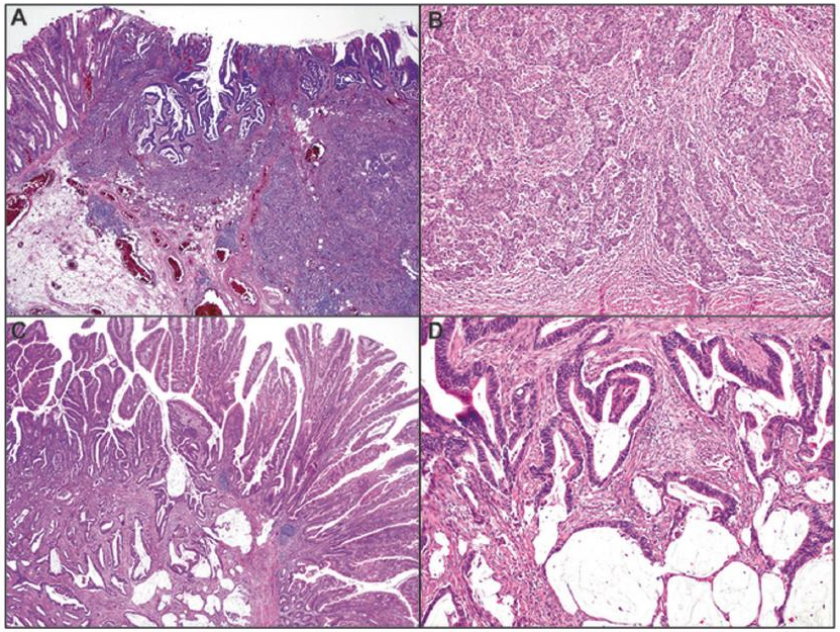


Fig. 11 Invasive carcinoma arising from serrated precursors. **a, b** An invasive carcinoma arising from a sessile serrated polyp with pushing margin, poor differentiation and conspicuous tumor infiltrating lymphocytes. **c, d** An invasive carcinoma arising from a traditional serrated adenoma showing infiltrative margin, serration in glands, focal mucin and eosinophilic tumor cells

Table 4 Colorectal carcinomas associated with serrated precursors

Type	CpG methylation	Prognosis	Precursor	Prevalence
BRAF mutated, mismatch repair deficient	+++	Good	Sessile serrated polyp	10–15%
KRAS mutated, mismatch repair proficient	+	Intermediate	Traditional serrated adenoma	Unknown
BRAF mutated, mismatch repair proficient	+++	Poor	Sessile serrated polyp or traditional serrated adenoma	5%
BRAF/*KRAS* wild-type, mismatch repair deficient	+++	Good	Sessile serrated polyp	5–0%

Pai et al. Mod Pathol 2019

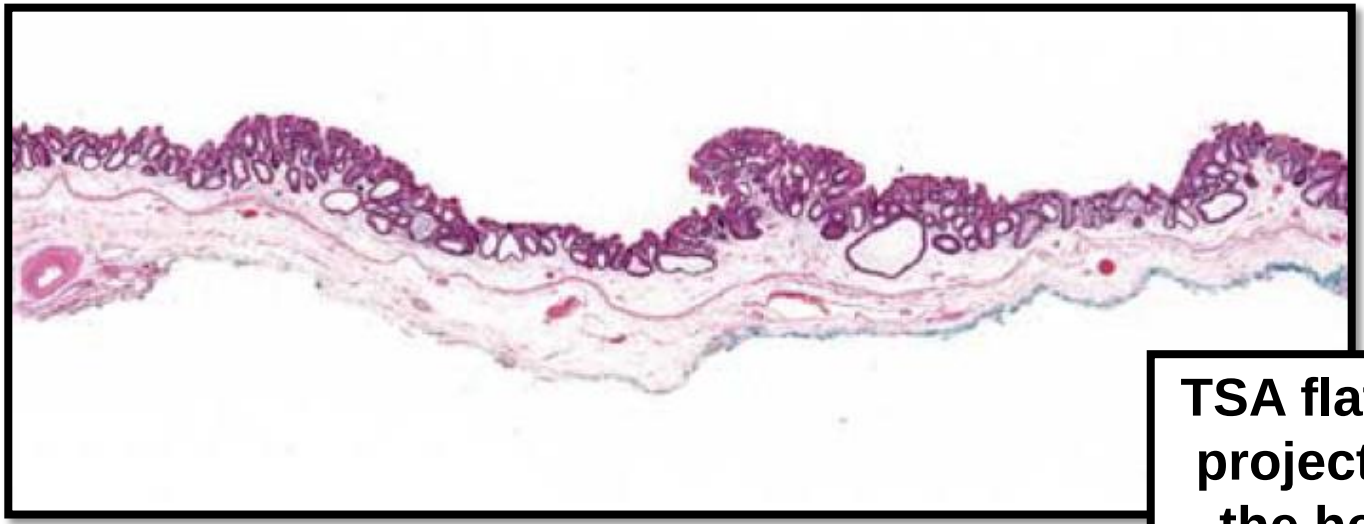
Unfortunately…

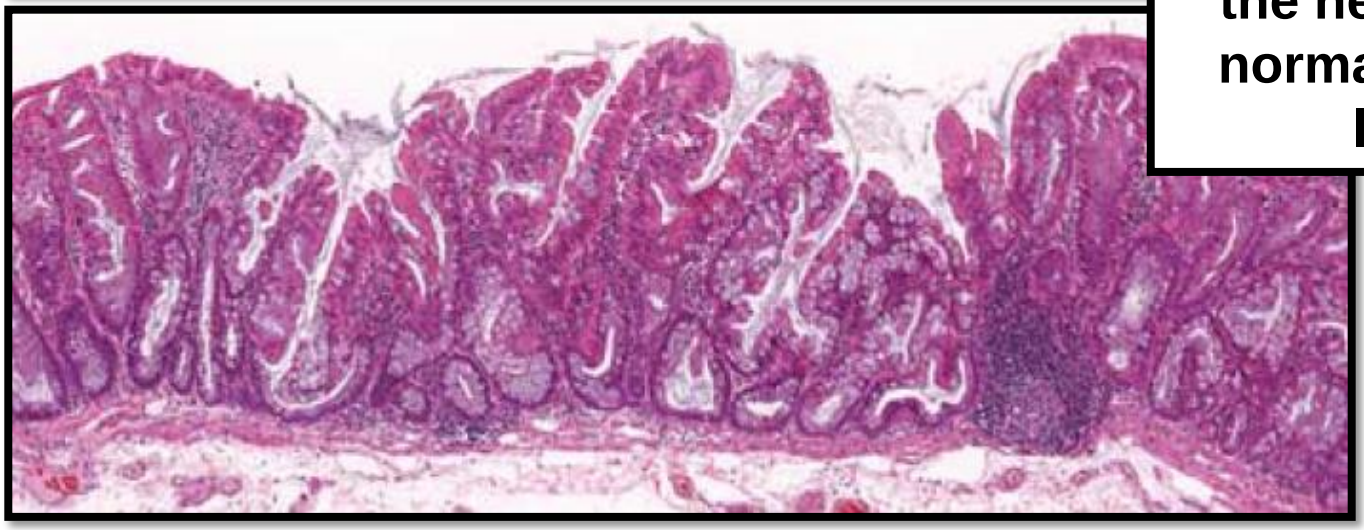
…typing of colorectal (serrated) adenomas is even more complex

Traditional serrated adenoma (TSA): morphological questions, queries and quandaries

Runjan Chetty

Medizinische Universität Graz





TSA flat type: should not project more than twice the height of adjacent normal mucosa, often lacks ECFs

Bettington et al. Mod Pathol 2015
Chetty. J ClinPathol 2016

Traditional serrated adenoma (TSA): morphological questions, queries and quandaries

Runjan Chetty

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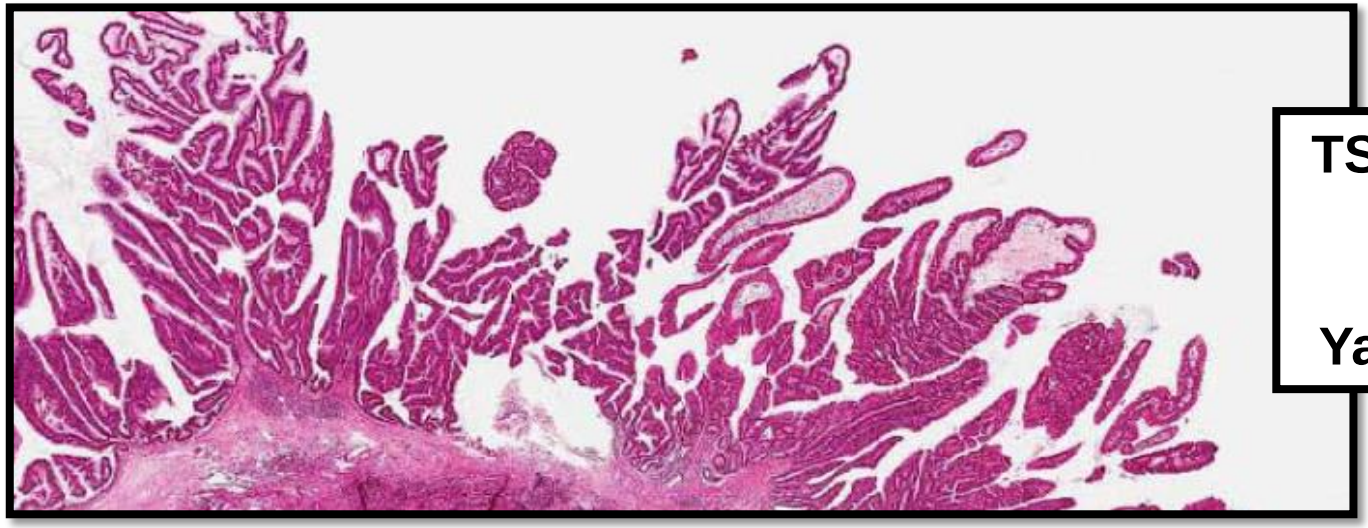
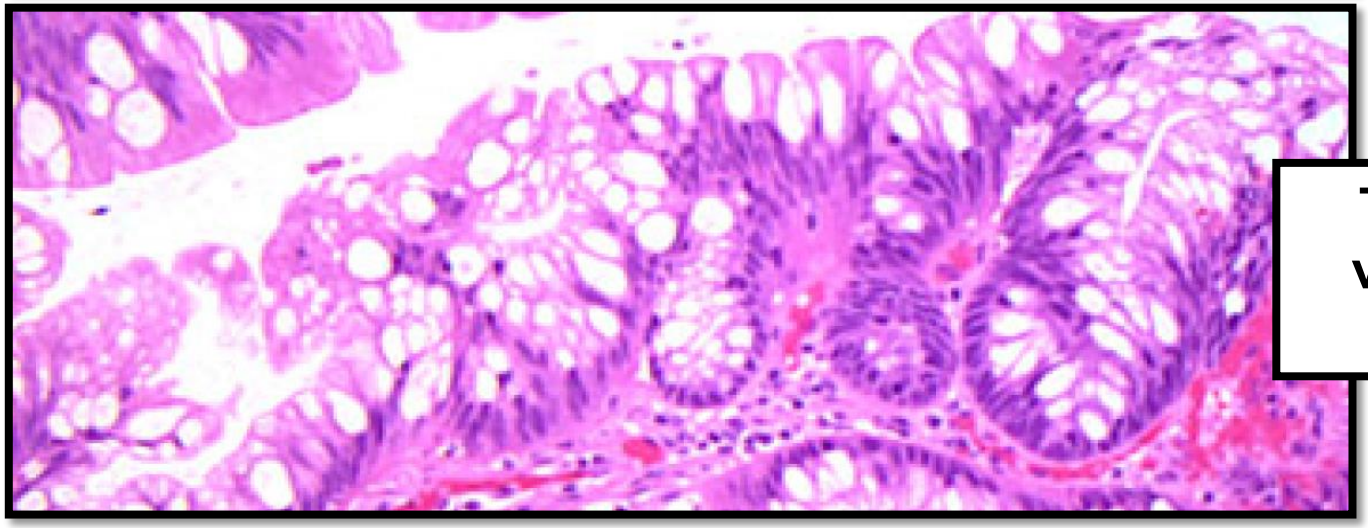


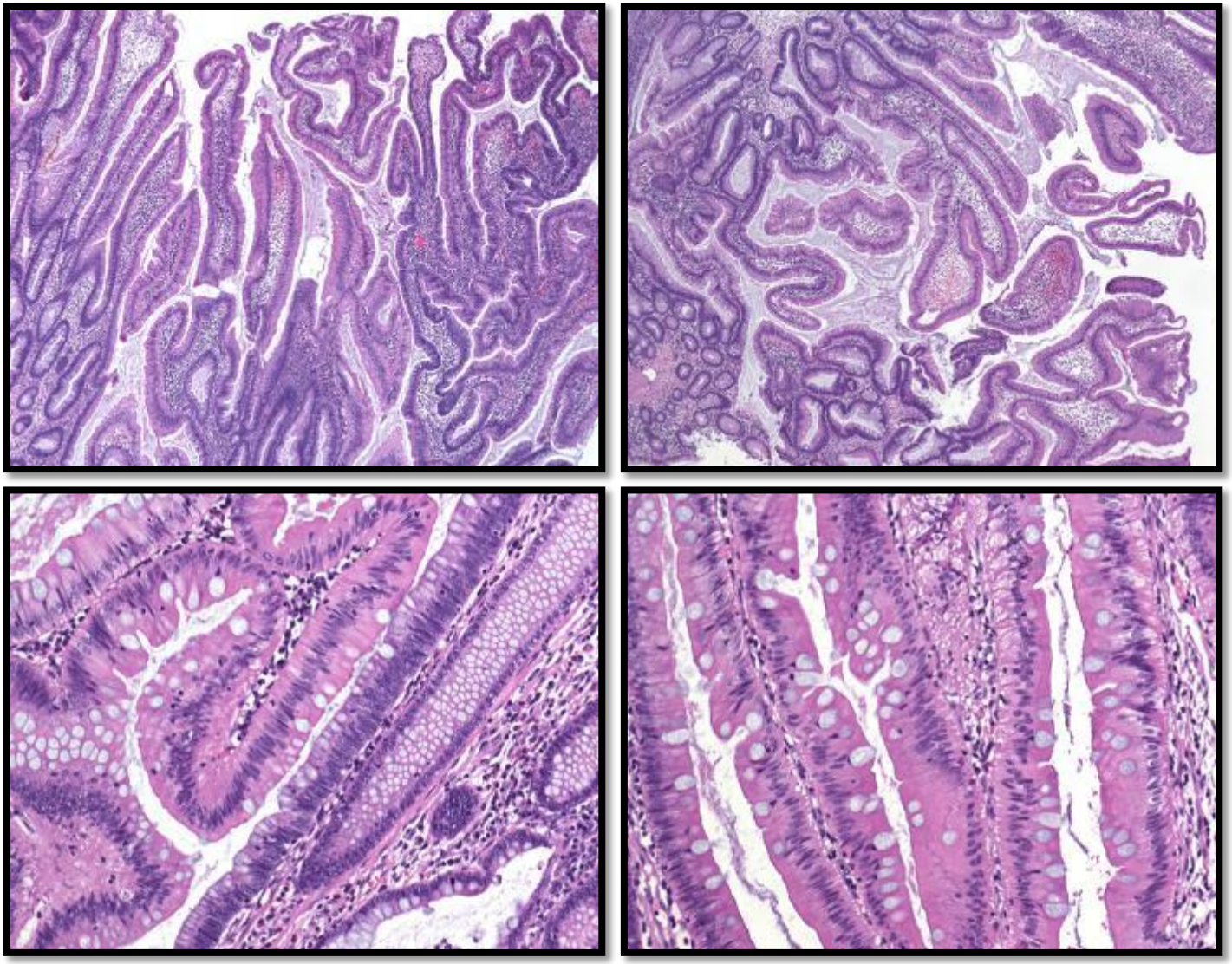
TSA filiform variant (originally described by Yantiss et al. 2007)



TSA mucin-rich variant: ≥50% of goblet cells

Chetty. J ClinPathol 2016
Kalimuthu et al. Histopathology 2017
Hiromoto et al. Histopathology 2018

Polyp (max diameter 1.8 cm) at the Right Flexure (62-year-old female)



Histopathology

Histopathology 2015, **66**, 308–313. DOI: 10.1111/his.12555

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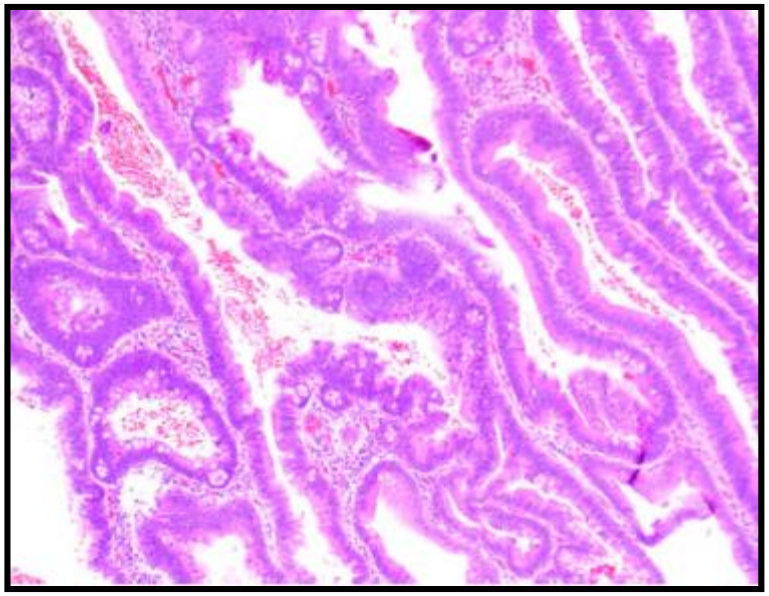
Histological overlap between colorectal villous/tubulovillous and traditional serrated adenomas

Sara Hafezi-Bakhtiari, Lai Mun Wang,[1] Richard Colling,[1] Stefano Serra & Runjan Chetty

Department of Pathology, Laboratory Medicine Program, University Health Network and University of Toronto, Toronto, ON, Canada, and [1]*Department of Cellular Pathology, Oxford University Hospitals, Oxford, UK*



Luminal serration as noted in TSA was not seen in any VA/TVA, but **ectopic crypt foci** were noted in 55/160 (34%) cases.

Cytoplasmic eosinophilia (constituting <50% of the adenoma) was noted in 10/160 (6%) cases.

Hafezi-Bakhtiari et al. Histopathology 2015

Histopathology

Histopathology 2015 DOI: 10.1111/his.12788

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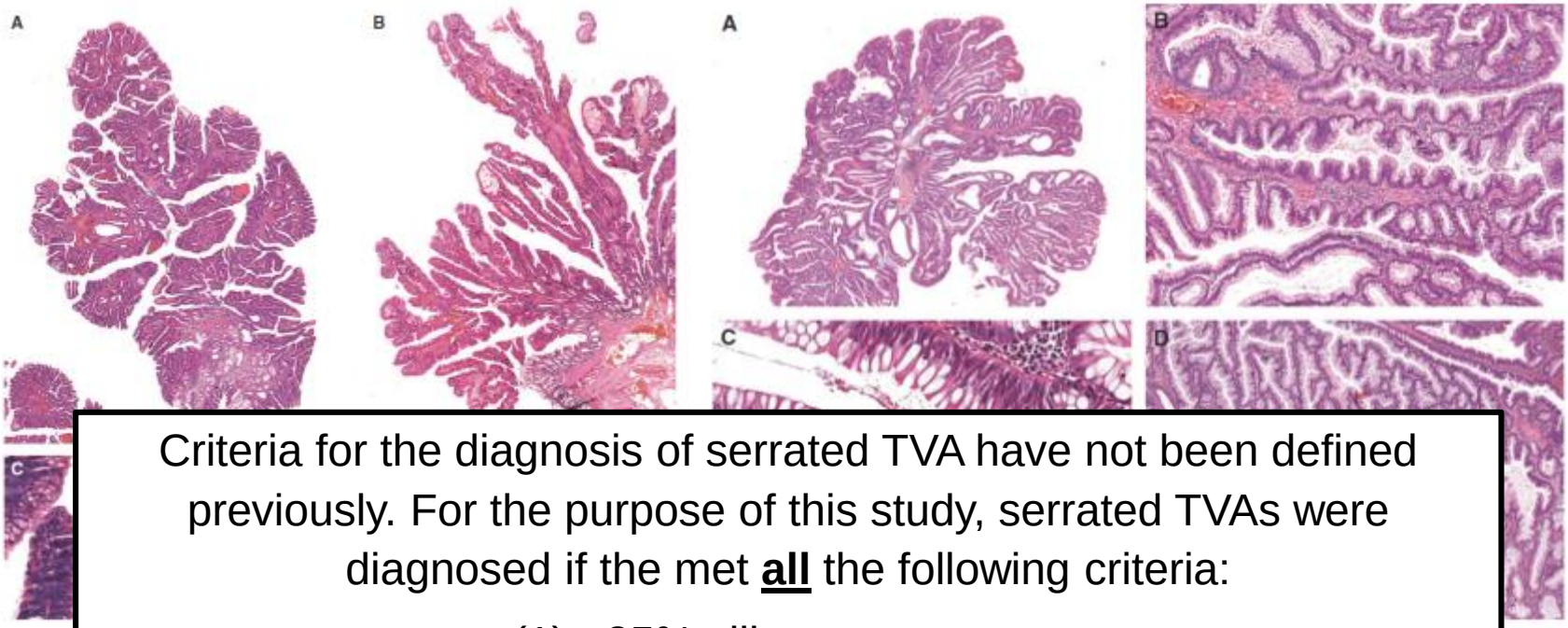
Serrated tubulovillous adenoma of the large intestine

Mark Bettington,[1,2,3] Neal Walker,[2,3] Christophe Rosty,[2,3,4] Ian Brown,[3,5] Andrew Clouston,[2,3,5] Diane McKeone,[1] Sally-Ann Pearson,[1] Kerenaftali Klein,[6] Barbara Leggett[1,2,7] & Vicki Whitehall[1,2,8]



Criteria for the diagnosis of serrated TVA have not been defined previously. For the purpose of this study, serrated TVAs were diagnosed if the met **all** the following criteria:

(1) >25% villous component

(2) Morphological serration in >50% of the polyp

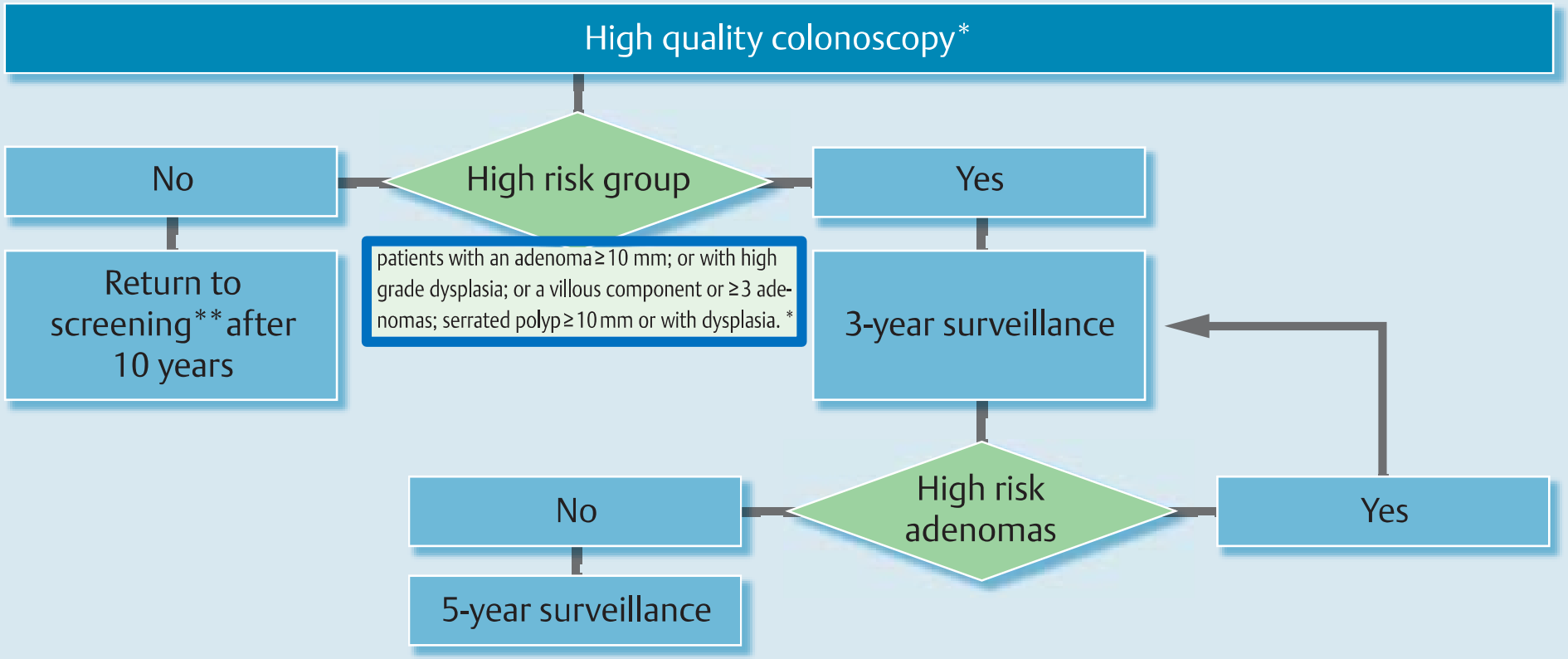
(3) TSA-type cytology and slit-like serrations in <10% of the polyp

Bettington et al. Histopathology 2016

Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

Authors

Cesare Hassan[1], Enrique Quintero[2,3], Jean-Marc Dumonceau[4], Jaroslaw Regula[5], Catarina Brandão[6], Stanislas Chaussade[7], Evelien Dekker[8], Mario Dinis-Ribeiro[6], Monika Ferlitsch[9], Antonio Gimeno-García[2,3], Yark Hazewinkel[8], Rodrigo Jover[3,10], Mette Kalager[11,12], Magnus Loberg[12,13], Christian Pox[14], Bjorn Rembacken[15], David Lieberman[16]



Take Home Messages I

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- **Tubular adenomas, tubulovillous adenomas and villous adenomas** are the precursor lesions of the classical pathways to colorectal cancer, leading to microsatellite stable (MSS, BRAF wild type), preferably left-sided tumours
- **Serrated lesions** include hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSA/Ps; upcoming WHO classification: sessile serrated lesions [SSL]) and traditional serrated adenomas (TSAs)
- The differential diagnosis may be challenging as **overlapping morphological features** exist and transition from HP to SSA/P as well from SSA/P to TSA may occur

Take Home Messages II

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- The serrated lesions progress through two different **molecular pathways** (BRAF or KRAS dependent)
- **SSA/Ps** are the prototypic precursor lesions of microsatellite instable (MSI), BRAF mutated, preferably right-sided cancers (favourable prognosis)
- **TSAs** are the prototypic precursors of microsatellite stable (MSS), BRAF mutated cancers (poor prognosis)
- Accurate typing of (serrated and non-serrated) colorectal polyps is the basis for accurate risk classification of affected patients and has immediate clinical consequences (**timing of follow-up strategies**)

Thank you very much for your kind attention!

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