3° Sessione

The "SERRATED ZONE"

Moderatori: Vincenzo Matarese (FE), Maria Antonia Bianco (NA)

10.30 Lo spettro delle lesioni serrate: classificazioni e pathways
Paola Cassoni (TO)

UNIVERSITÀ DEGLI STUDI DI TORINO

DIPARTIMENTO di SCIENZE MEDICHE unito.it

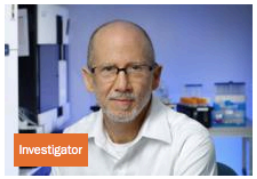
The Molecular Basis of Colorectal Cancer and Its Implications for Patients

Research Summary

Bert Vogelstein is interested in identifying and characterizing the genes that cause cancer and the application of this knowledge to the management of patients.

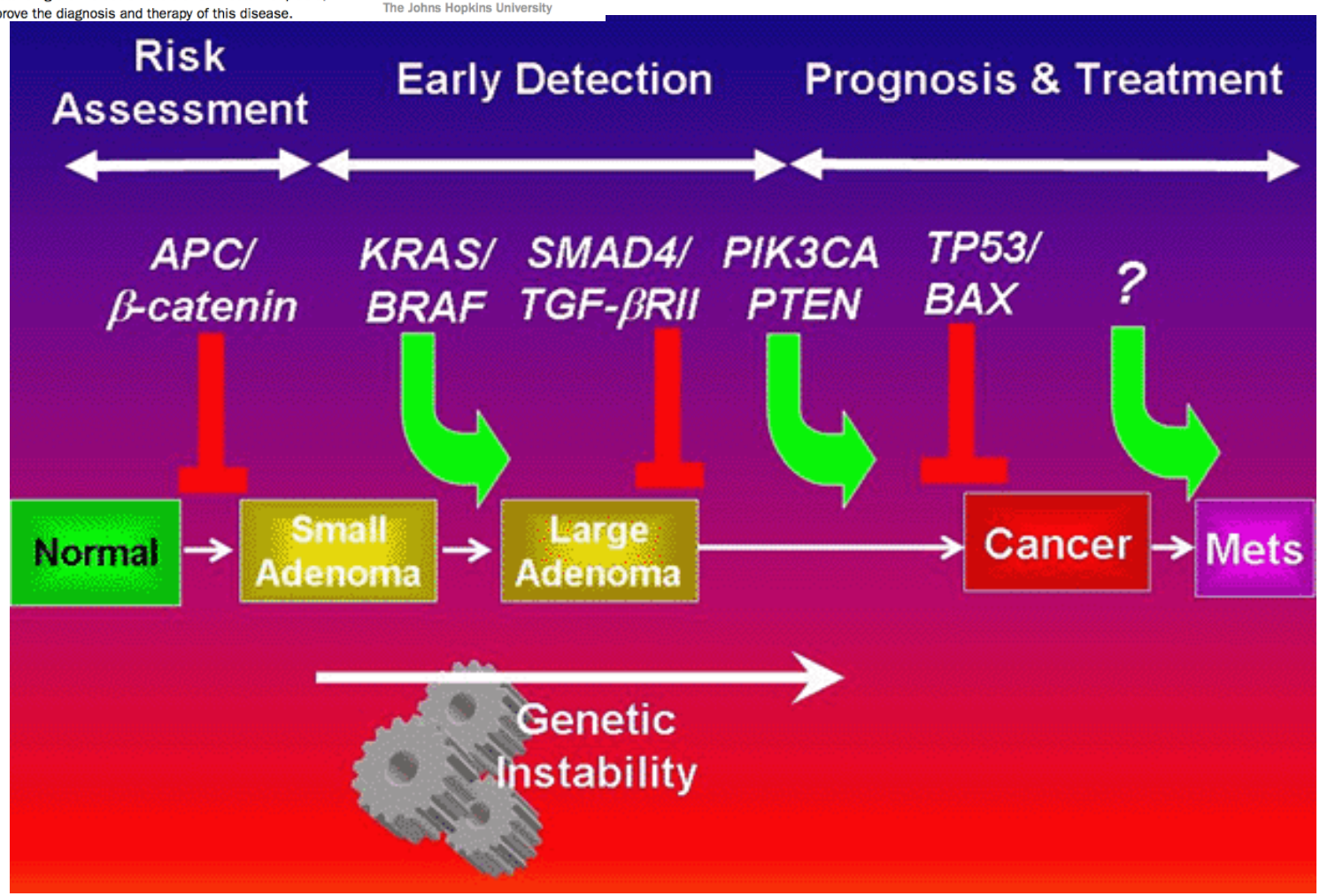
Tumors of the colon and rectum are a major health problem: in 2006 alone, a million new cancer cases occurred in the world, resulting in ~590,000 deaths. Half of the population of the United States will develop at least one benign colorectal tumor, and in one-tenth of these, the tumors will eventually become malignant. Our research is aimed at understanding the molecular basis of colorectal neoplasia, in the hope that this knowledge can be used to improve the diagnosis and therapy of this disease.

Scientist Profile

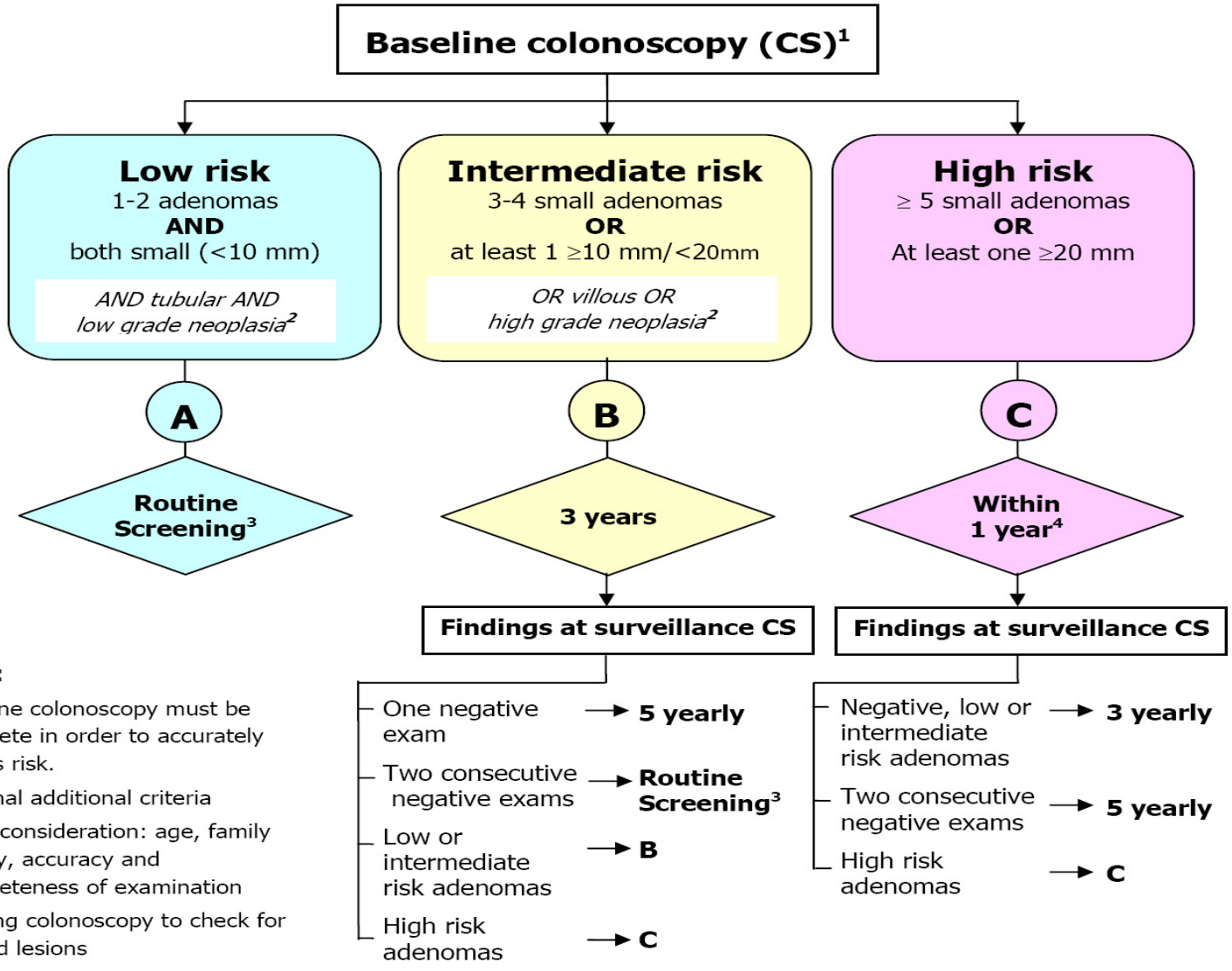


Bert Vogelstein, MD

The Johns Hopkins University



COLONOSCOPIC SURVEILLANCE FOLLOWING ADENOMA REMOVAL (EU 2010)



Notes:

[1] Baseline colonoscopy must be complete in order to accurately assess risk.

[2] Optional additional criteria

[3] Other consideration: age, family history, accuracy and completeness of examination

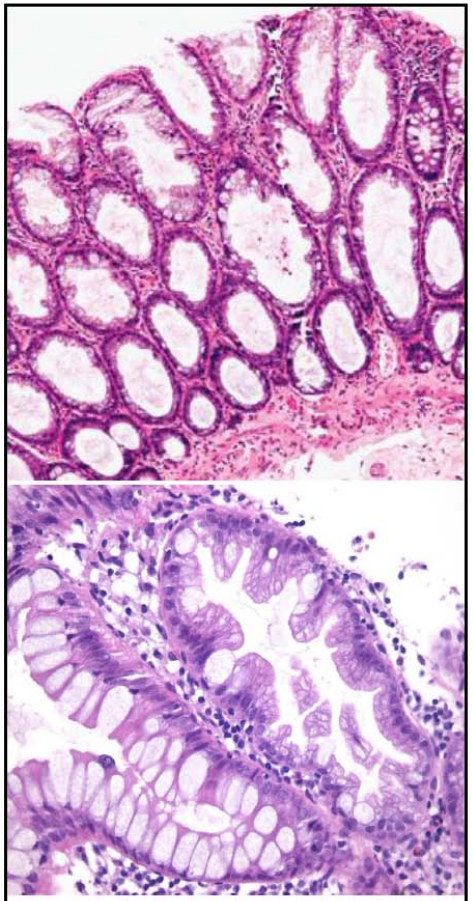
[4] Clearing colonoscopy to check for missed lesions

The background dogma

Morfologia serrata (seghettata)

↓

Classicamente innocuo

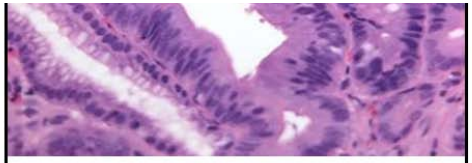


Polipo iperplastico

Morfologia adenomatosa

↓

Neoplastico



Adenoma

MODERN PATHOLOGY (2015) 28, S80–S87

The pathology of serrated colorectal neoplasia: practical answers for common questions

Kenneth P Batts

For the pathologist, endoscopist, gastroenterologist, and colorectal surgeon who were practicing before the year 2000, the emergence of the 'serrated pathway' of colorectal neoplasia has been a fairly momentous development that has stirred up significant emotions in many (disbelief, anger, mistrust, and fear, among likely many others). These emotions have been so strong because a bedrock dogma in medicine, that hyperplastic polyps (HPPs) of the colon are innocuous, has been shaken.

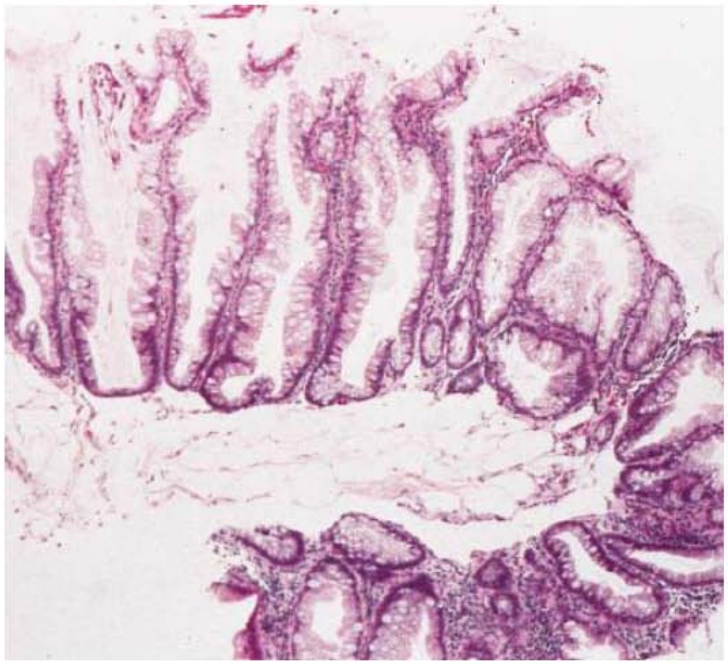
Kenneth P Batts

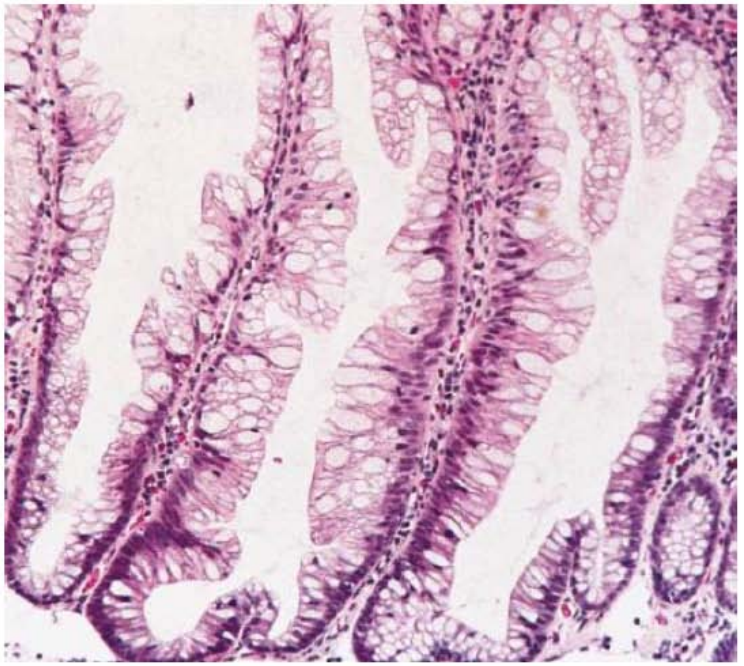
Modern Pathology (2015) **28**, S80–S87

Come abbattere un dogma

Hyperplastic-like Colon Polyps That Preceded Microsatellite-Unstable Adenocarcinomas

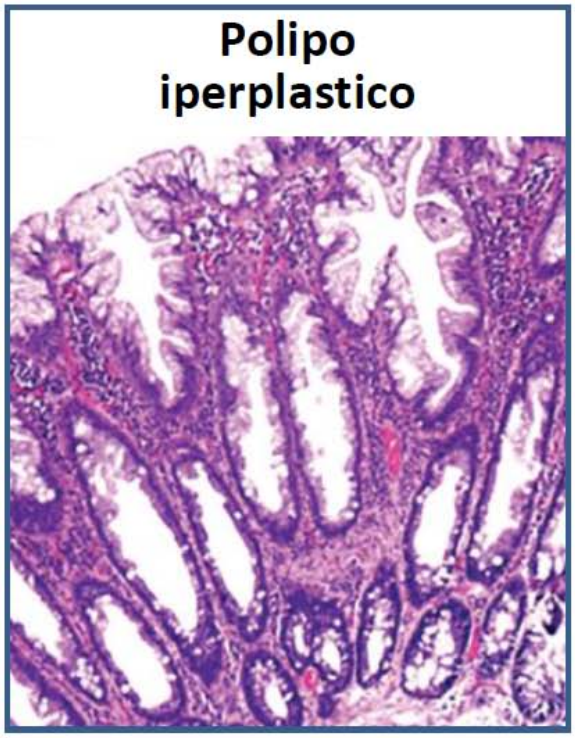
Neal S. Goldstein, MD, Punam Bhanot, MD, Eva Odish, HTL(ASCP), and Susan Hunter, SI(ASCP)

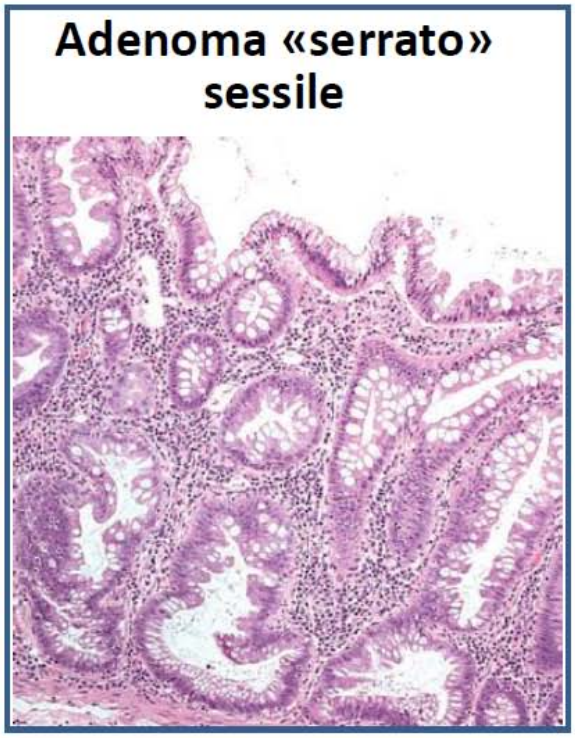




Am J Clin Pathol 2003;119:778-796

The WHO rules

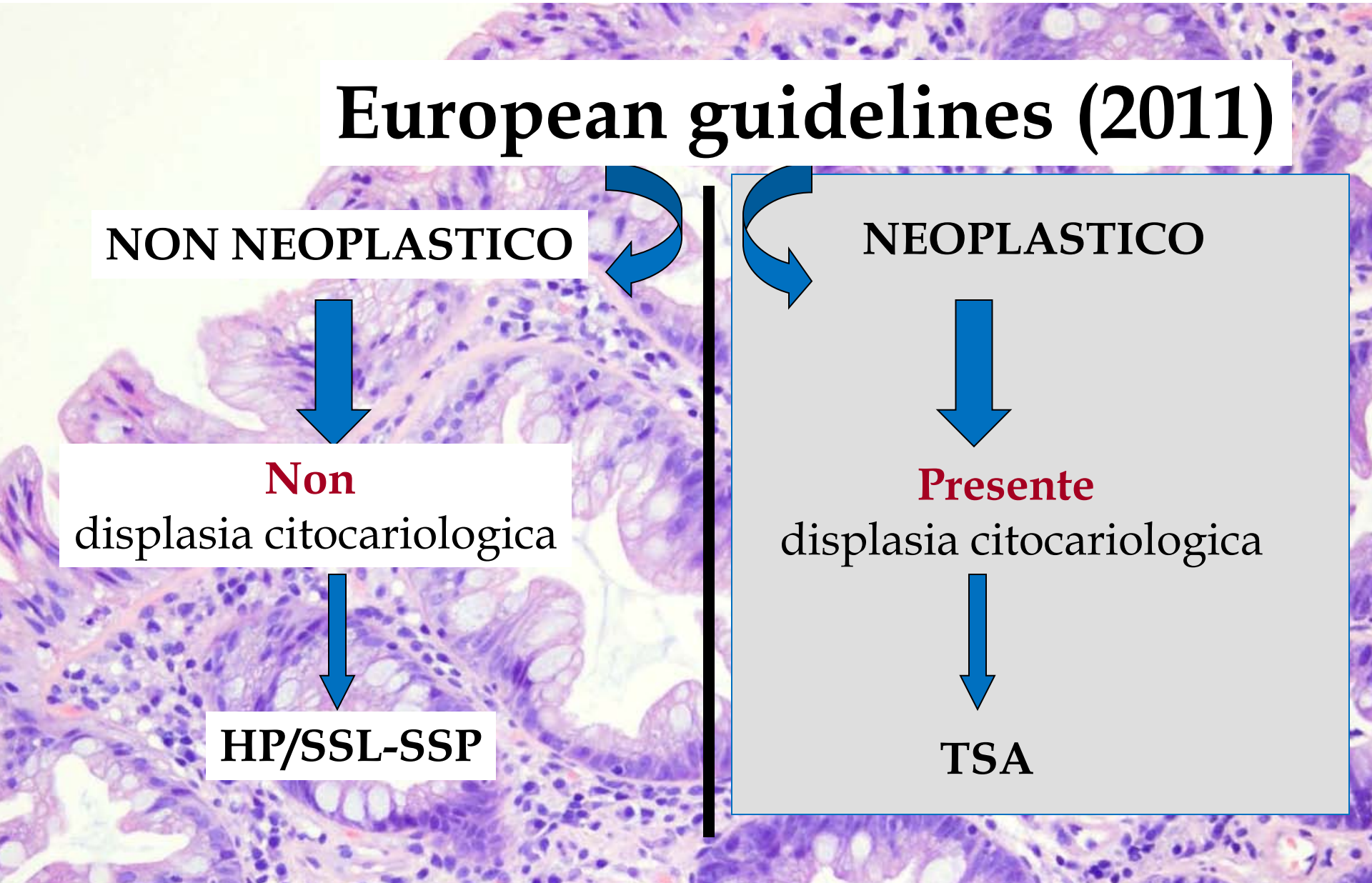




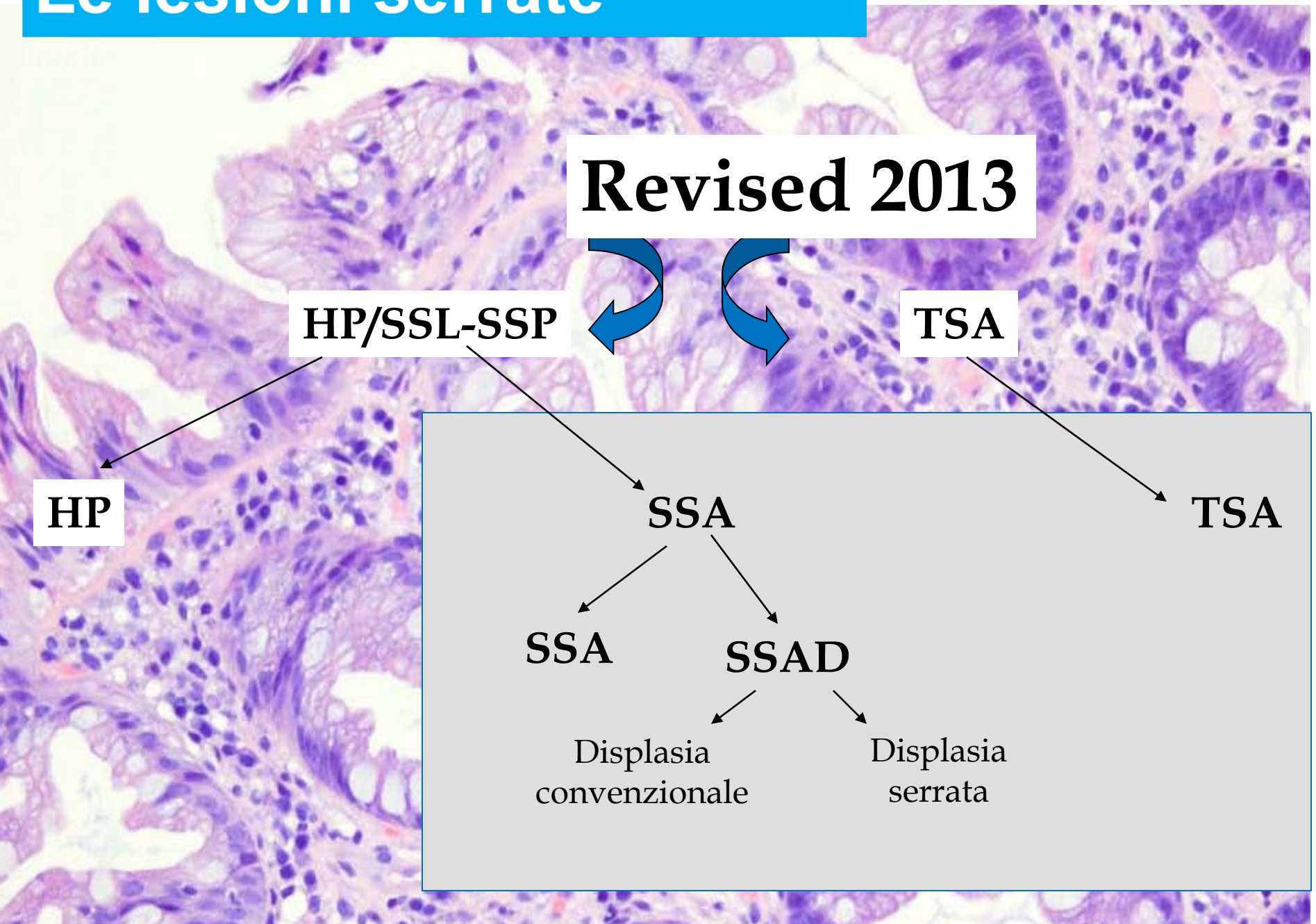
Serrated polyps of the colon and rectum WHO 2010	
Hyperplastic polyps	75% of all serrated polyps
Sessile serrated adenomas/polyps	15-25% of all serrated polyps
Traditional serrated adenoma	<1% of all polyps

«The SSA/P was identified as a subgroup that comprised about 20% of what had previously been called HPPs.» KP Batts 2015

Le lesioni serrate

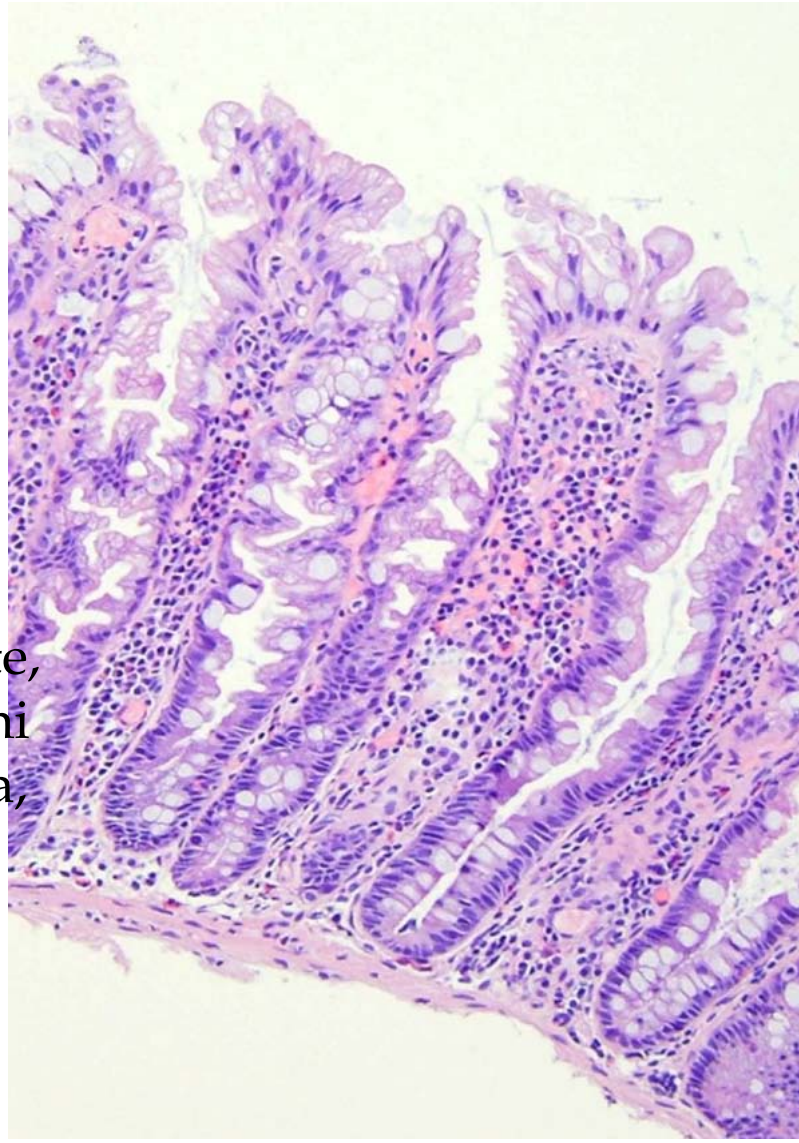


Le lesioni serrate



HP – Caratteristiche istologiche

- **Ghiandole regolari non ramificate** che si dilatano progressivamente verso la superficie
- Compartimento **proliferativo**, cellule immature e mitosi nella **porzione basale**
- **Serrazione nella porzione superiore** delle cripte



Si distinguono tre sottotipi:

– **Microvescicolare**, con serrazione più evidente, muco in microvescicole e rare cellule caliciformi
– **A cellule caliciformi**, con serrazione modesta, numerose cellule caliciformi, molto più frequente nel colon sinistro e retto
– **A scarsa produzione di muco**, raro, sempre localizzato nel colon sinistro e retto, con serrazione evidente ed ipercromasianucleare

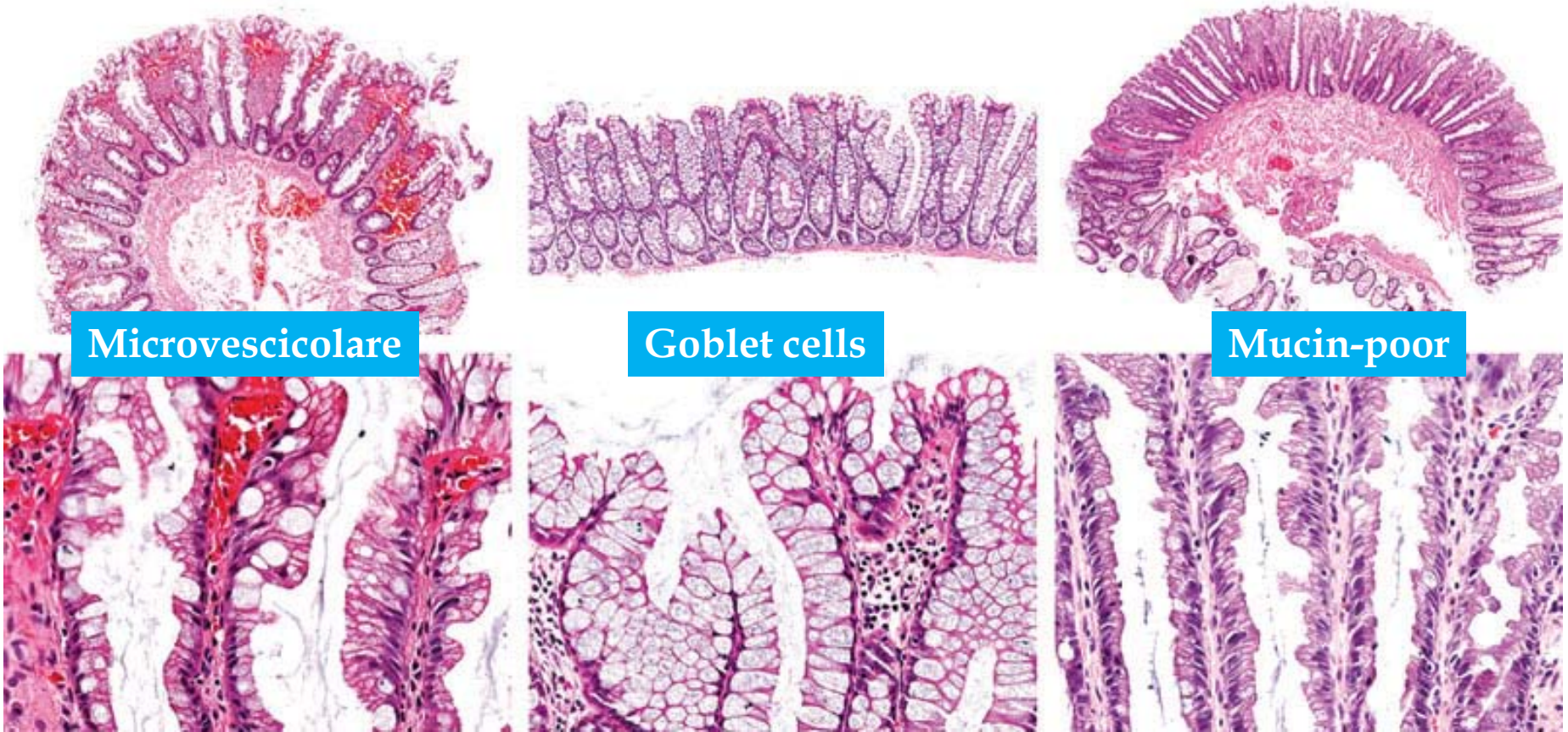
Histopathology

Histopathology 2013, **62**, 367–386. DOI: 10.1111/his.12055

REVIEW

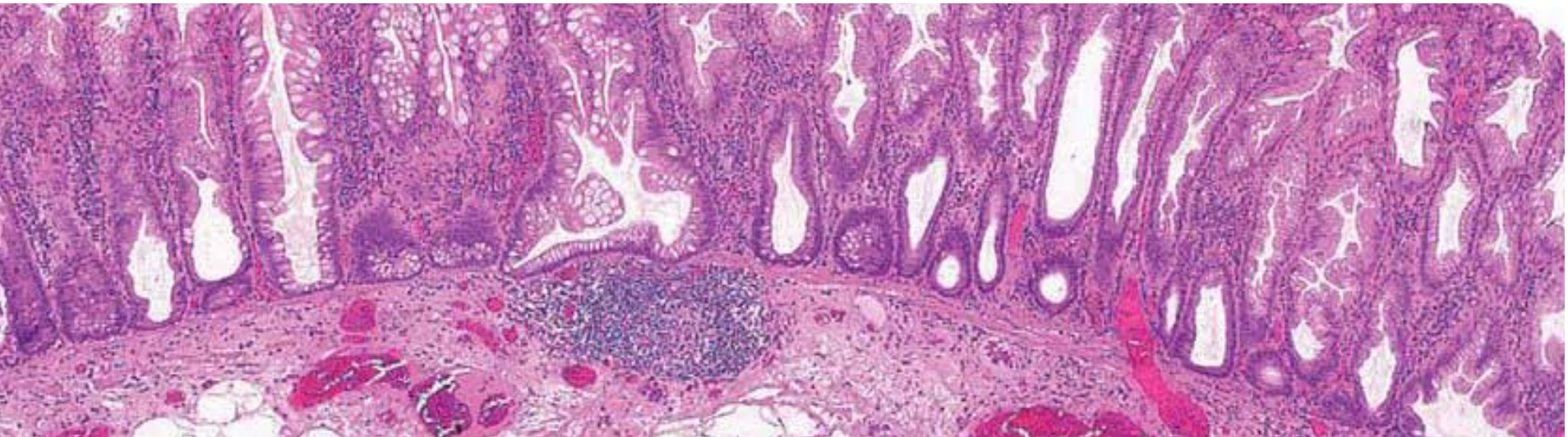
The serrated pathway to colorectal carcinoma: current concepts and challenges

Mark Bettington,[1,2,3] Neal Walker,[1,3] Andrew Clouston,[1,3,4] Ian Brown,[3,4] Barbara Leggett[1,2,5] & Vicki Whitehall[2,4]



SSA – Caratteristiche istologiche

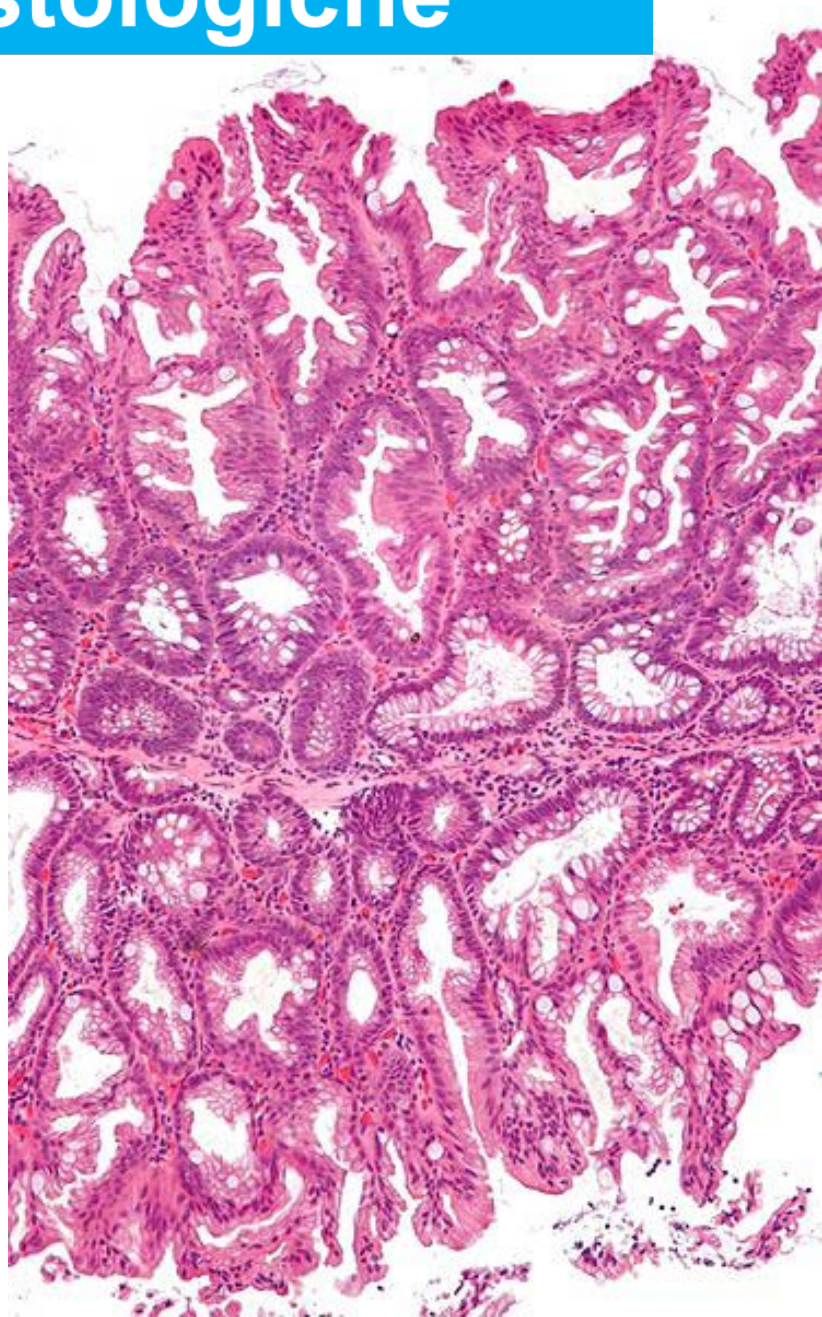
- **Alterazioni architetturali**
  - Architettura più **complessa** e meno organizzata rispetto ai HP
  - **Ramificazione,** dilatazione della porzione basale ed orizzontalizzazione delle
- **Aspetti dismaturativi**
  - Presenza di **cellule mature** con fenotipo caliciforme o foveolare e di serrazione nella **porzione basale** delle cripte
  - **Spostamento verso l'alto** del compartimento proliferativo con mitosi nella parte superiore delle cripte
  - **Asimmetria** maturativa



SSA – Caratteristiche istologiche

- **Altri aspetti**

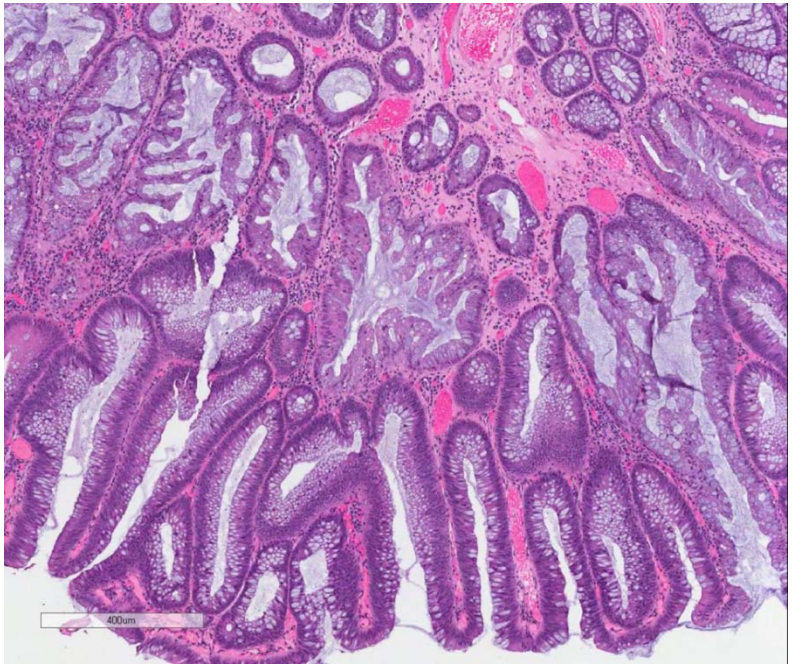
– Presenza di piccoli focolai di pseudostratificazione e di **modificazione eosinofila** dell' epitelio superficiale
– Alterazioni nucleari (disegno cromatinico aperto, piccoli nucleoli prominenti, irregolarità del contorno nucleare)
– Cellule caliciformi distrofiche
– Abbondante muco nel lume ghiandolare
– Aree indistinguibili da HPMV

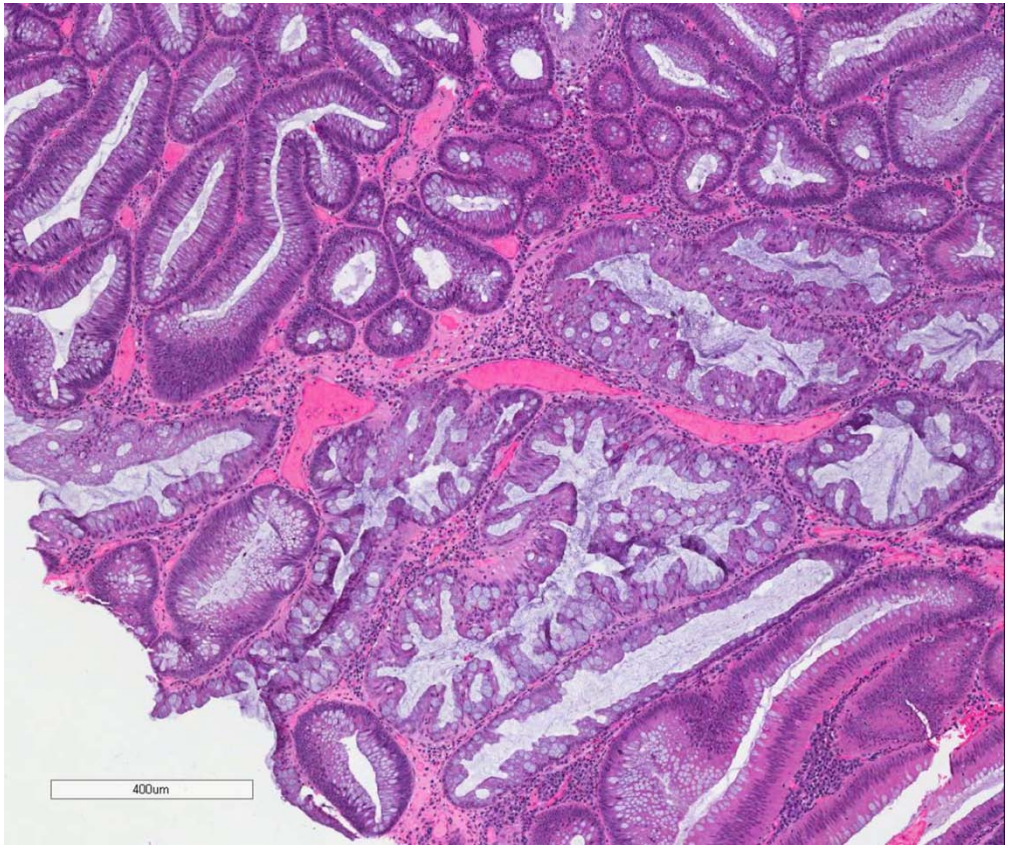


La Transizione Displasia Architetturale – Nucleare: Adenoma Serrato Sessile con Displasia (SSAD)

DISPLASIA CONVENZIONALE

- Mitosi e Mitosi Atipiche
- Nuclei Ipercromici
- Nuclei Pseudostratificati
- Citoplasma Anfofilo



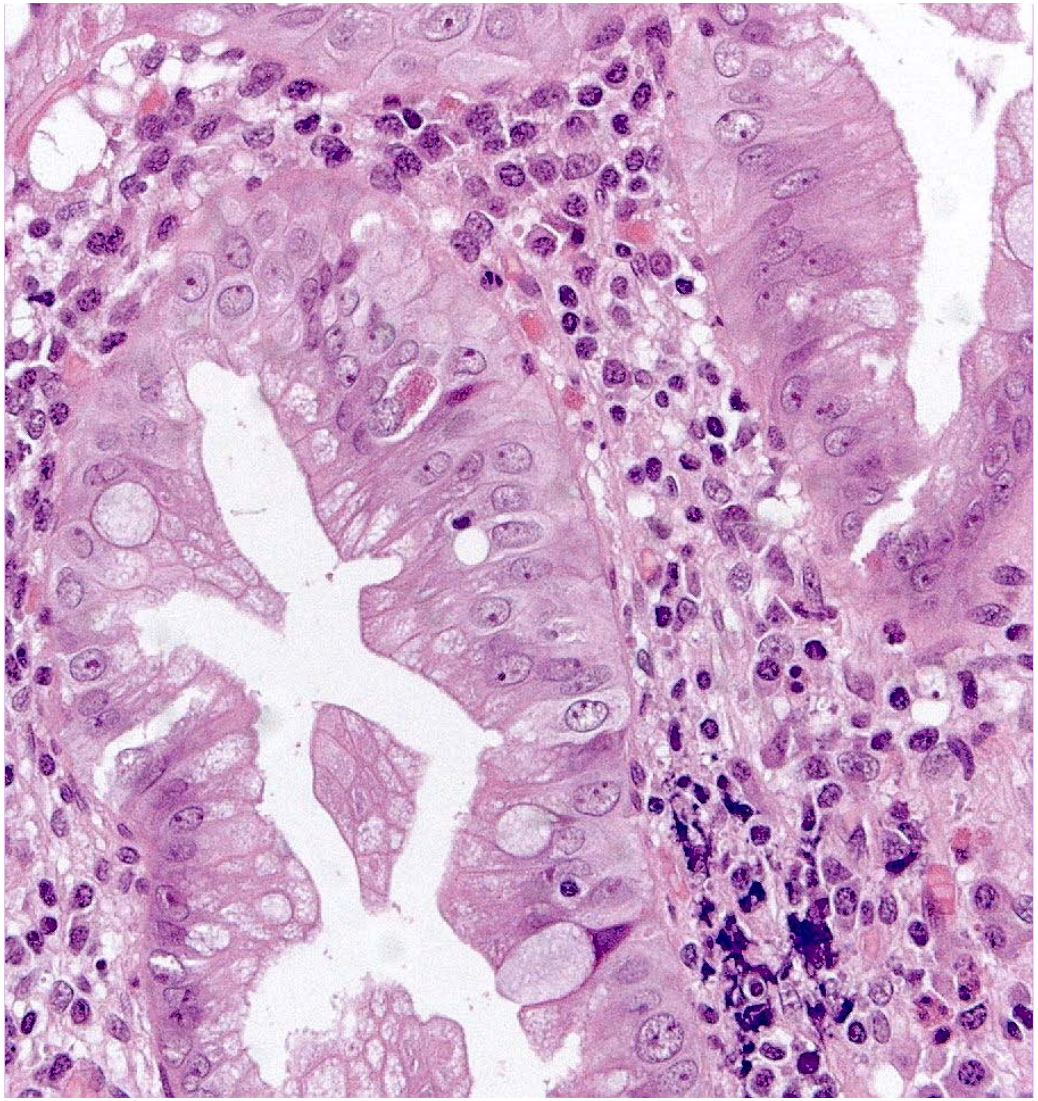


[Rex et al, 2012]

La Transizione Displasia Architetturale – Nucleare: Adenoma Serrato Sessile con Displasia (SSAD)

DISPLASIA SERRATA

- **Profilo Serrato**
- **Nuclei Vescicolosi e Nucleolati**
- **Nuclei Oligostratificati o Monostratificati alla Base**
- **Progressiva Eosinofilia del Citoplasma**



[WHO 2010; Fujita et al, 2011; Bettington 2013]

La pathway serrata in numeri

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]

The serrated neoplasia pathway is a major contributor to colorectal carcinoma, with approximately 25% of cases arising via this route.[1–4] These cancers have their origins in serrated polyps, including sessile serrated adenomas (SSAs) and traditional serrated adenomas (TSAs).[4 5] Of these, the SSA is by far the most prevalent and accounts for most serrated neoplasia pathway carcinomas.

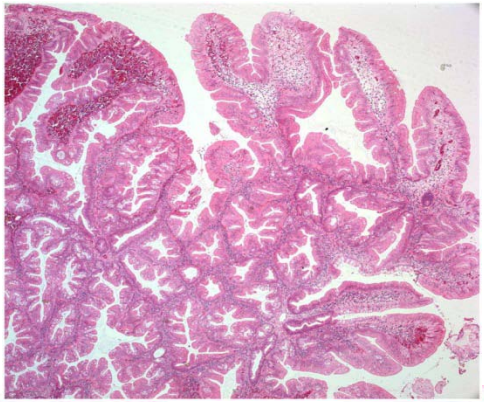
SSAs are subtle polyps that can be difficult to detect colonoscopically, are frequently incompletely excised and have the hypothesised potential for rapid malignant degeneration.[4 6–8] series. For the pathologist, misdiagnosis or underdiagnosis of SSA as a microvesicular hyperplastic polyp remains an issue.[11–15] This combination of factors has clinical implications, the most significant being interval carcinoma. This can occur due to missed lesions, incompletely excised lesions, rapid progression of de novo lesions or inadequate surveillance due to misdiagnosis by the pathologist. Several studies have demonstrated that serrated pathway carcinomas are over-represented among interval cancers, confirming that some, if not all, of these factors contribute to this occurrence.[16 17]

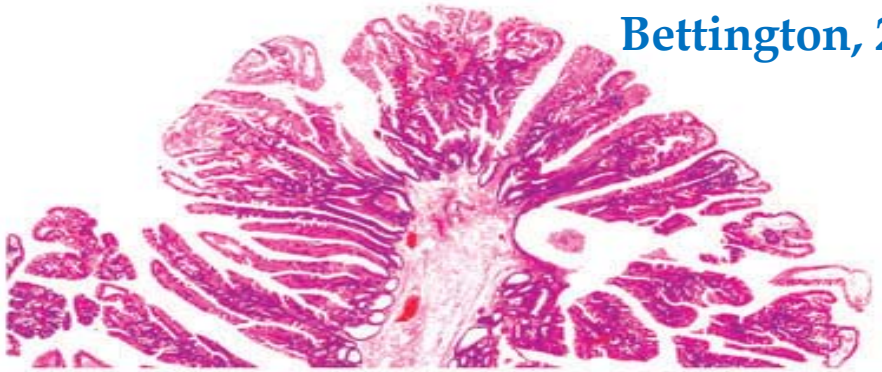
SSAs occur predominantly in the proximal colon and in older women.[11 18] Histologically, they are characterised by abnormal crypt architecture, but without cytological dysplasia.[18 19]

Gut 2015;**0**:1–10. doi:10.1136/gutjnl-2015-310456

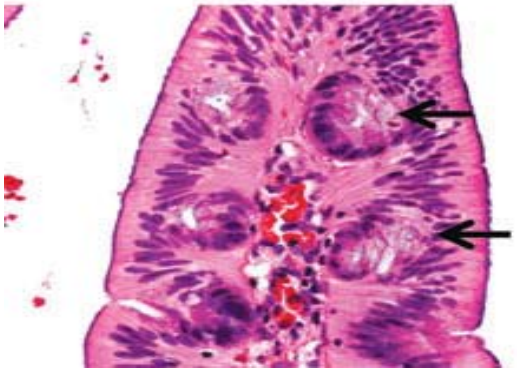
TSA – Caratteristiche istologiche

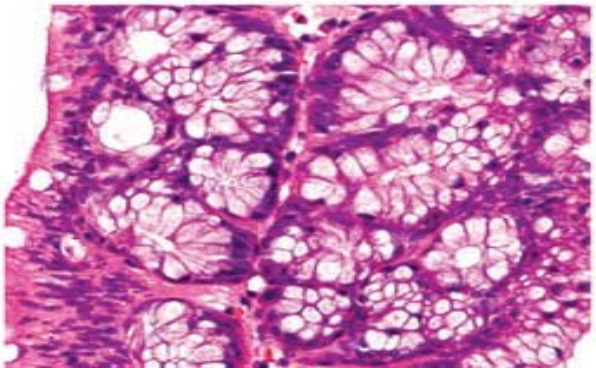
- **Struttura villosa**, architettura complessa con serrazione prominente
- Principalmente composto da **cellule colonnari con citoplasma eosinofilo**, nucleo centrale allungato, ipercromico
- Modesta pseudostratificazione nucleare
- **Micropapille superficiali** con nuclei molto allungati
- Ectopic crypt foci (**ECF**)

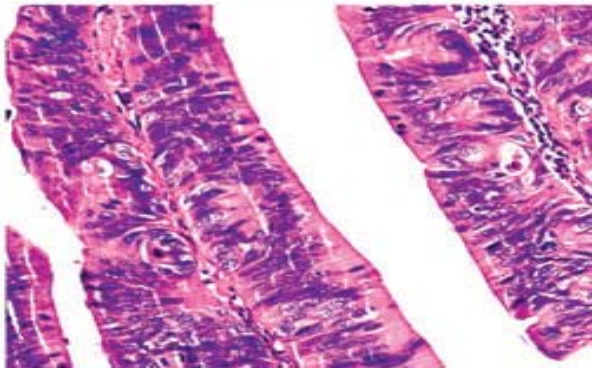




Bettington, 2013



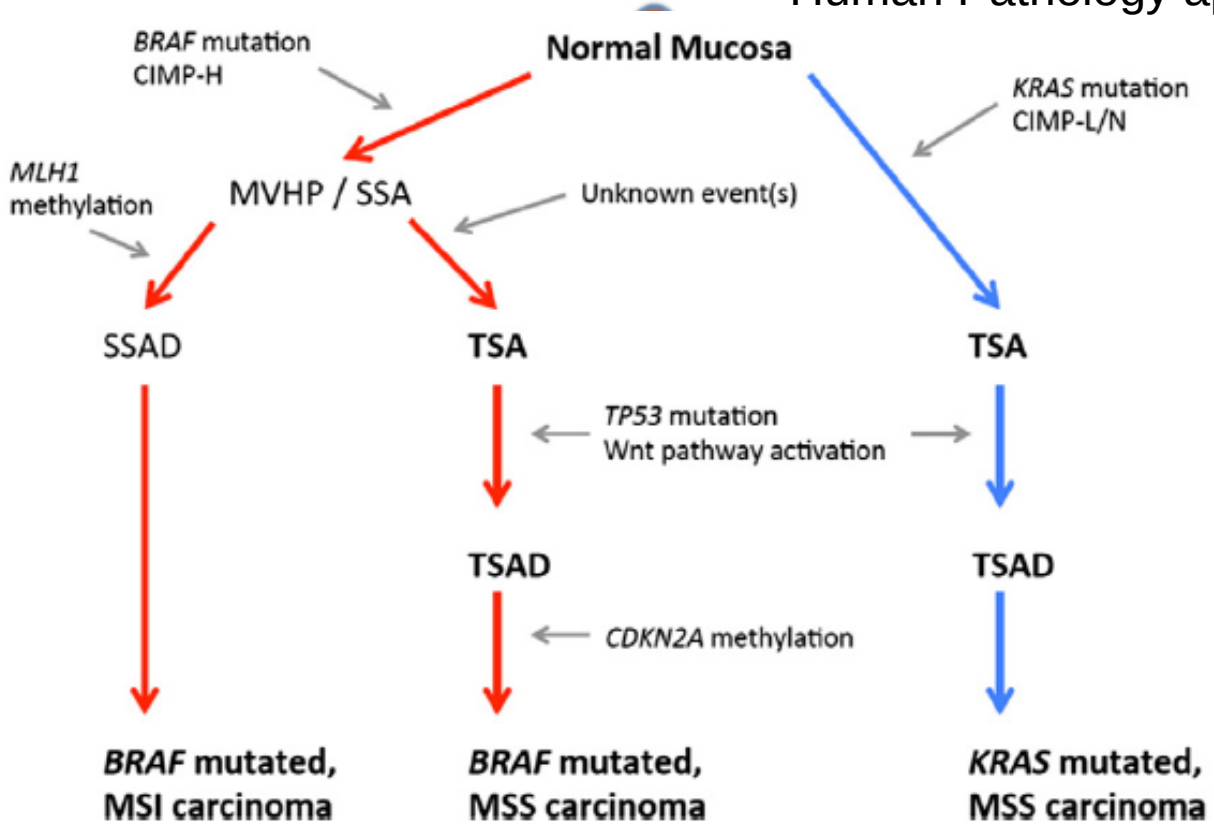




TSA: c’ è sempre qualcosa di nuovo –step1

Progress in pathology

Human Pathology april 2015



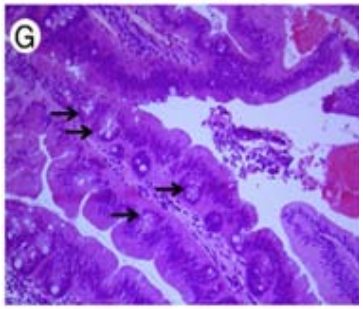


Table Comparison of serrated polyps

Polyp	Location	Endoscopy	Cancer risk	Molecular alteration	Surveillance
HP	Mainly right	Sessile pale, starlike pit pattern	None/minimal	Microvesicular HP *BRAF*	<10 mm, 5 y
SSA	Mainly right	Sessile, flat on crest of mucosal fold, mucus cap, cloudlike surface	1 with dysplasia, 2×; ≥10 mm, 3×	*BRAF*	1: <10 mm, 5 y; >1: <10 mm, 3-5 y; 1-3: ≥10 mm, 3 y
TSA	Mainly left	Pine cone, fernlike, stellate pit pattern	Yes	*BRAF* and *KRAS*	Every 3 y

Abbreviations: HP, hyperplastic polyp; SSA, sessile serrated adenoma; TSA, traditional serrated adenoma.

Un altro dogma abbattutto: il TSA dysplasia free

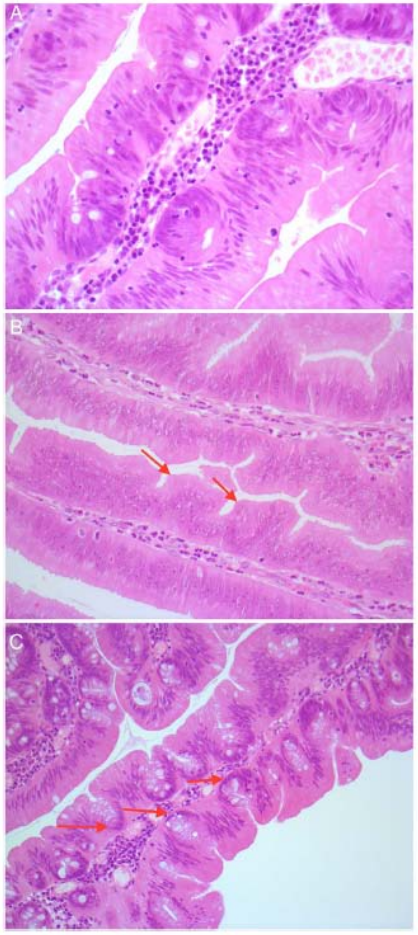
- In our view, although the ordinary TSA is undoubtedly neoplastic, it ***does not have inherent cytologic dysplasia***.
- Although specific surveillance guidelines for this scenario have not been developed, it ***may be prudent to follow these patients closely***.

Nondysplastic-dysplastic-carcinoma sequence in the TSA

TSA: c’ è sempre qualcosa di nuovo -step2

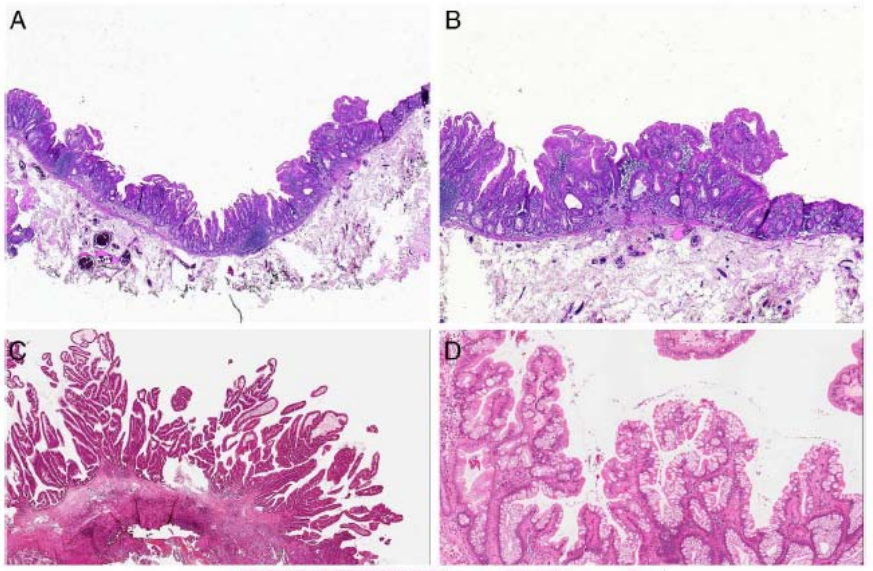
Traditional serrated adenoma (TSA): morphological questions, queries and quandaries

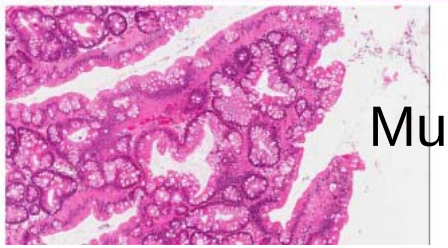
Runjan Chetty



Flat TSA:
more *BRAF*
than *KRAS*

Filiform TSA





Mucin-rich

Take home messages

- Traditional serrated adenoma (TSA) represents a unique polyp that falls within the spectrum of serrated polyps.
- It has a very characteristic constellation of morphological features with an exophytic growth pattern, cytoplasmic eosinophilia and ectopic crypt foci being characteristic.
- Morphological variants are flat, filiform and mucin-rich.
- Coexistence with other polyp types can occur.
- Not all TSAs show adenomatous dysplasia.
- It is controversial whether all TSA contain serrated dysplasia ab initio.

JCP Online First, published on November 9, 2015

However, the **current estimate (5% of all serrated lesions)** is likely to increase with the widespread implementation of bowel cancer screening programmes, *better endoscopy and increasing awareness of TSA among diagnostic pathologists.*

It is therefore reasonable to anticipate that TSA will be encountered more frequently.

JCP Online First, published on November 9, 2015

Una visione non univoca….ancora!

Review

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

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

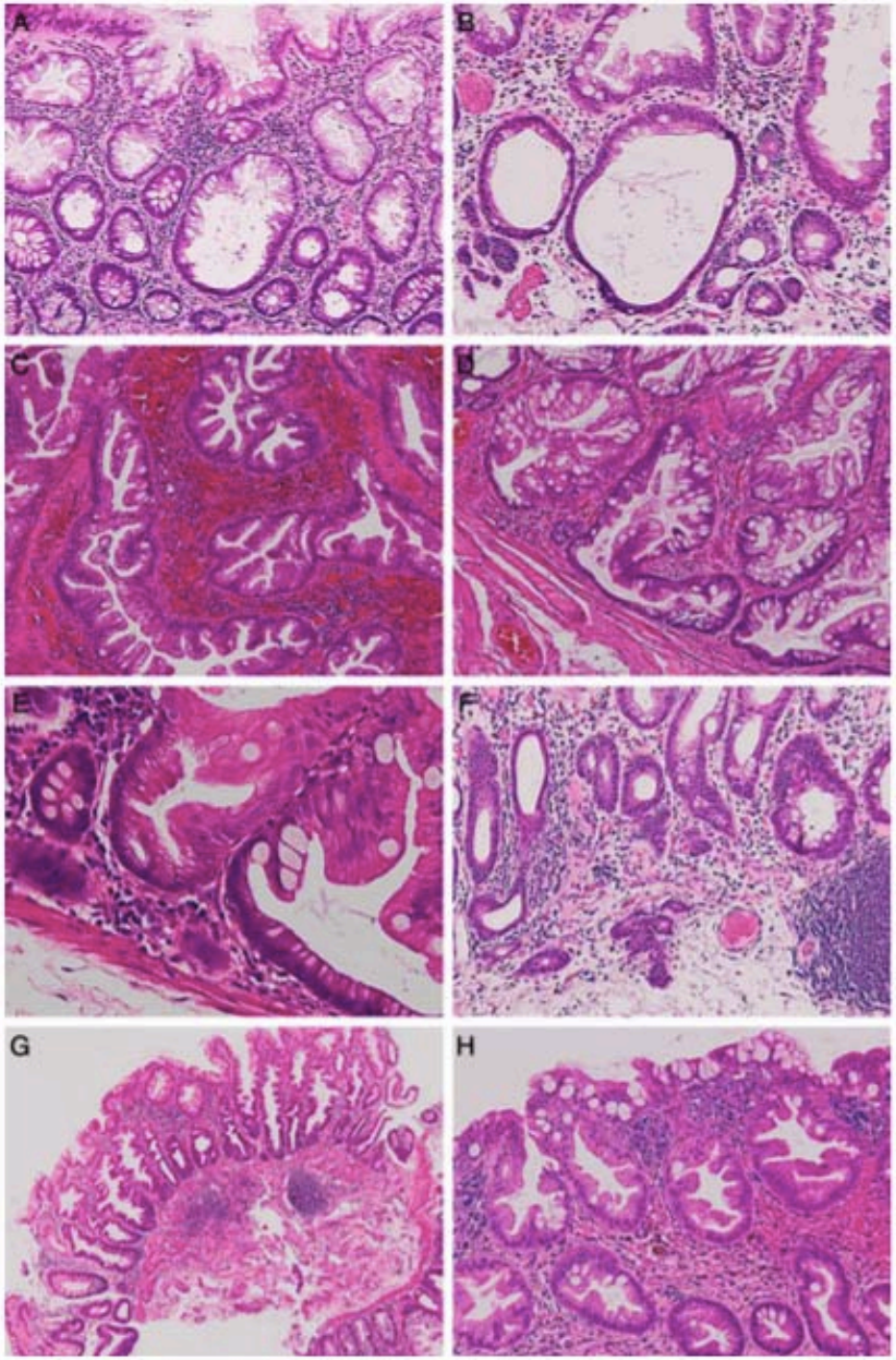
Box 1 Recommended terminology for (non-invasive) serrated lesions of the colon and rectum

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

Box 2 Key histological features of sessile serrated lesions (SSL)

- 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 SSL
- American Gastroenterology Association criteria: one crypt showing the characteristic features is sufficient for the diagnosis of SSL

Key: *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 SSL by highlighting epithelial cell proliferation within the superficial half of crypts. However, such immunohistochemistry, while sometimes helpful, does not revea features that are alone diagnostic of SSL.



Cosa è facile sbagliare e cosa non sbagliare

CONCLUSION

The key diagnostic difficulties within this spectrum of lesions relate to the differentiation of HPs from SSLs (especially those without dysplasia).[22] We have made recommendations for the use of a simplified terminology system for serrated lesions. The minimum criteria for diagnosis of SSLs are still the focus of uncertainty and debate. In contrast, TSAs would not usually be mistaken for HPs or SSLs, as the 'classical' dysplasia within them is more immediately obvious. Therefore, the differential diagnosis between 'classical' adenomas and TSAs is of less importance to patient management than the accurate identification of SSLs with and without dysplasia.

Cosa abbiamo imparato

Int J Colorectal Dis
DOI 10.1007/s00384-015-2404-6

ORIGINAL ARTICLE

Factors associated with reclassification of hyperplastic polyps after pathological reassessment from screening and surveillance colonoscopies

Christoph Schramm[1] · Moritz Kaiser[1] · Uta Drebber[2] · Inga Gruenewald[3] · Jeremy Franklin[4] · Fabian Kuetting[1] · Andrea Bowe[1] · Vera Hoffmann[1] · Sebastian Gatzke[2] · Ulrich Toex[1] · Hans-Michael Steffen[1]

Table 2 Initial histological diagnosis of all detected polypoid lesions, n (%)

Tubular adenoma	862 (45.3)
Tubulovillous adenoma	39 (2.0)
Villous adenoma	2 (0.1)
HP	536 (28.1)
SSA	0 (0)
TSA	0 (0)
Adenocarcinoma	7 (0.4)
Others	429 (22.5)
Missing	29 (1.5)
Total	1904 (100)

Table 3 Definite diagnosis of all 536 initially diagnosed HPs, *n* (%)

HP	474 (88.5)
SSA	41 (7.6)
TSA	6 (1.1)
Unspecified SL	2 (0.4)
Tubular adenoma	9 (1.7)
Others	4 (0.7)
Total	536 (100)

HP hyperplastic polyps, *SSA* sessile serrated adenomas, *TSA* traditional serrated adenomas

Le zone di grigio che rimangono

Table 2. Differing diagnostic criteria for sessile serrated adenoma (SSA), borderline SSA, and microvesicular hyperplastic polyp (MVHP)

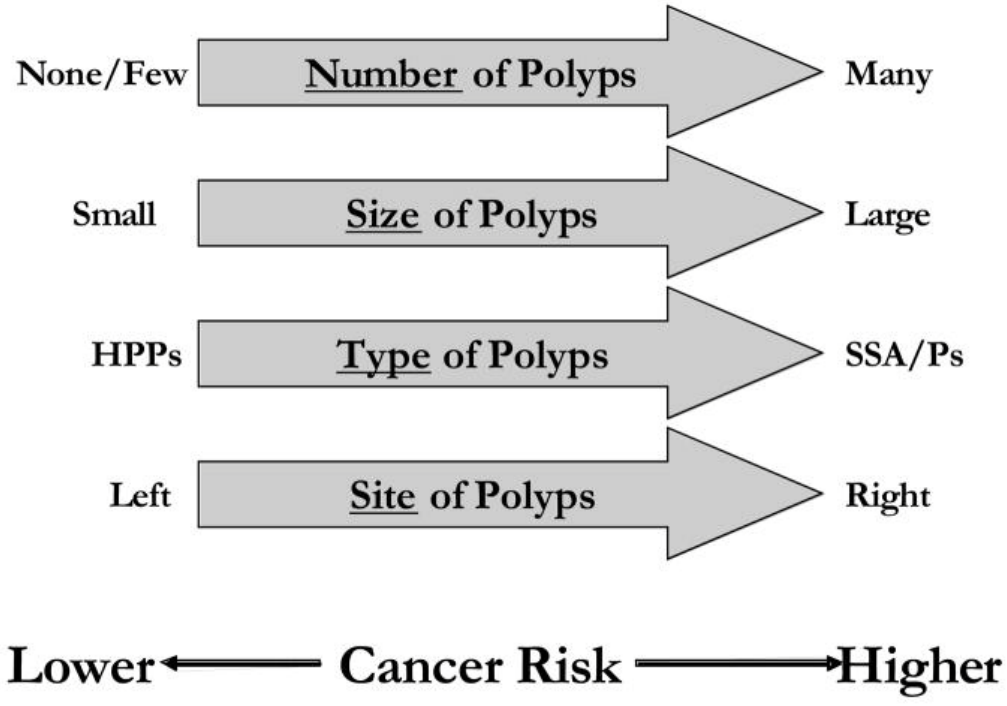
Study[51,65,70]	Polyp category	Diagnostic criteria
Chung *et al.*	SSA	Polyp >10 mm
		Polyp proximal to the hepatic flexure, and at least four of: exaggerated serration, crypt dilation, increased crypt branching/horizontal growth, cytological atypia, mitoses in upper half of the crypt, increased cytoplasmic mucin, and epithelial/stromal ratio of >50%
	Intermediate between MVHP and SSA	Polyp <10 mm
		Polyp anywhere in the large bowel
		At least four of the above criteria
	MVHP	Three or fewer of the above criteria
Mohammadi *et al.*	SSA	At least two of basal crypt dilation, basal crypt serration, crypt branching, and horizontal crypt growth
	Borderline SSA	Only one of the above criteria, or equivocal evidence of two of the above criteria
	MVHP	None of the above criteria, or one equivocal criterion
WHO 2010	SSA	At least two adjacent crypts or three individual crypts with features of SSA
	MVHP	Not meeting the above criteria
Aust *et al.*	SSA	Two of basal crypt serration, horizontal crypt growth, inverted crypts, and basal crypt dilation
		The above features in at least two crypts
	MVHP	Not meeting the above criteria

Bettington, 2013

Lesioni serrate distribuzione e rischio

- HPs account for 70–95% **of all serrated** lesions and are predominantly left-sided
- SSA/Ps comprise 5–25% **of serrated lesions** and are predominately right sided
- TSAs **are much less common** than SSA/Ps. Distal colon (left)

In clinical studies the prevalence of SSA/Ps is generally less than 2%



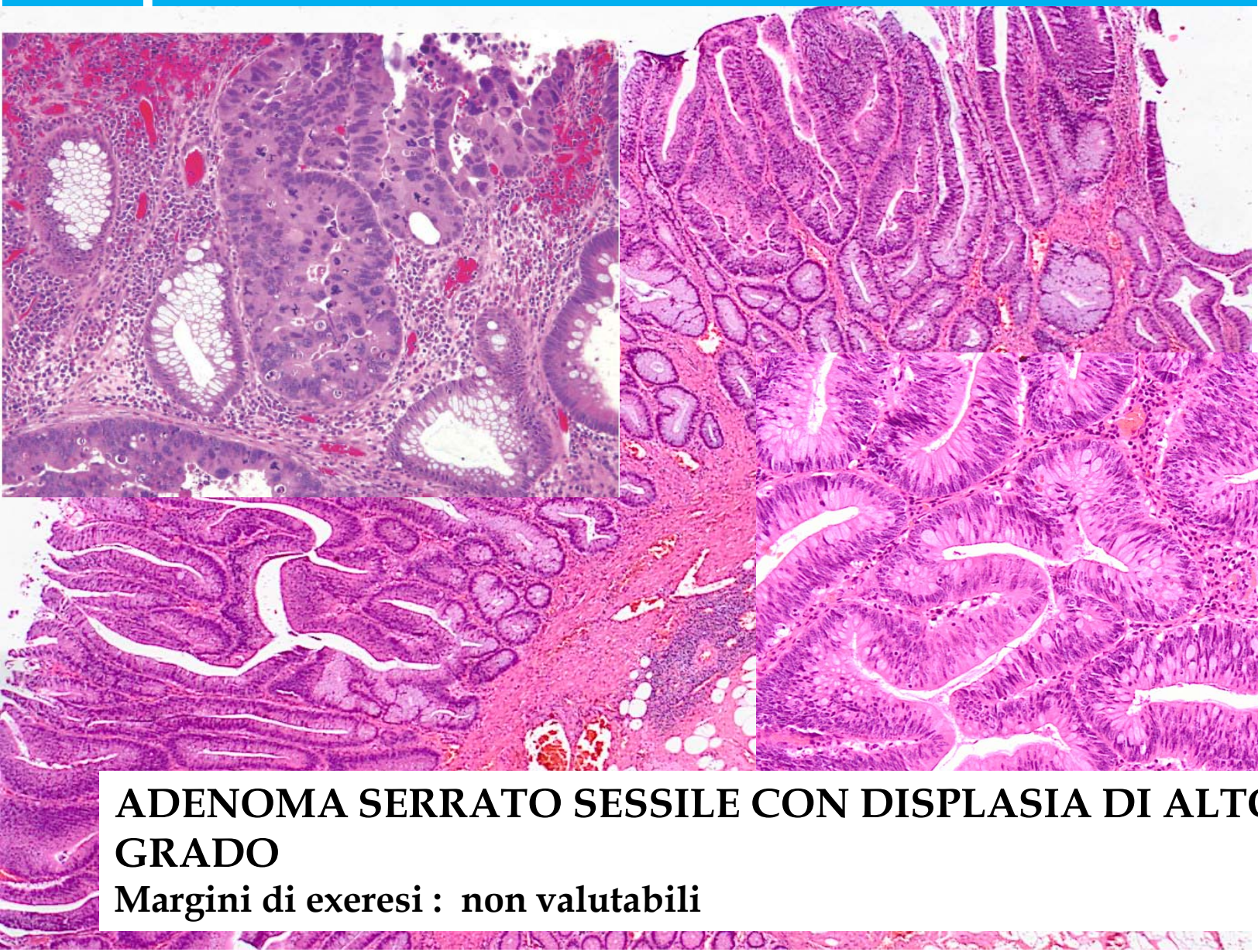
[Rex et al, 2012]

	Microvesicular HP	Goblet cell HP	TSA
Proportion [19, 21, 37, 99, 116]	40–50 %	20–30 %	2–5 %
Predominant location	Distal	Distal	Distal
Morphology	Normal architecture	Normal architecture	Exophytic polyp
	Upper crypt serration	Subtle surface serration	Complex villous architecture
	Microvesicular mucin	Goblet cell mucin	Ectopic crypt formations
	No dysplasia	No dysplasia	Eosinophilic cells with pencillate nuclei
Predominant molecular alteration	*BRAF*^{V600E} mutation	*KRAS* mutation	*KRAS* mutation *BRAF*^{V600E} mutation
Malignant potential	Very low	Low	High

	SSA	SSA with cytological dysplasia
Proportion [19, 21, 37, 99, 116]	15–25 %	2–5 %
Predominant location	Proximal	Proximal
Morphology	Abnormal architecture	SSA features
	Broad crypt base	Superimposed dysplasia of conventional intestinal type
	Dystrophic goblet cells in crypt base	
	No dysplasia	Sharp demarcation of the dysplastic component
Predominant molecular alteration	*BRAF*^{V600E} mutation	*BRAF*^{V600E} mutation
	CIMP	CIMP
		Microsatellite instability or *TP53* alteration
Malignant potential	High	Very high

Rosty et l, J Gastroenterology 2013

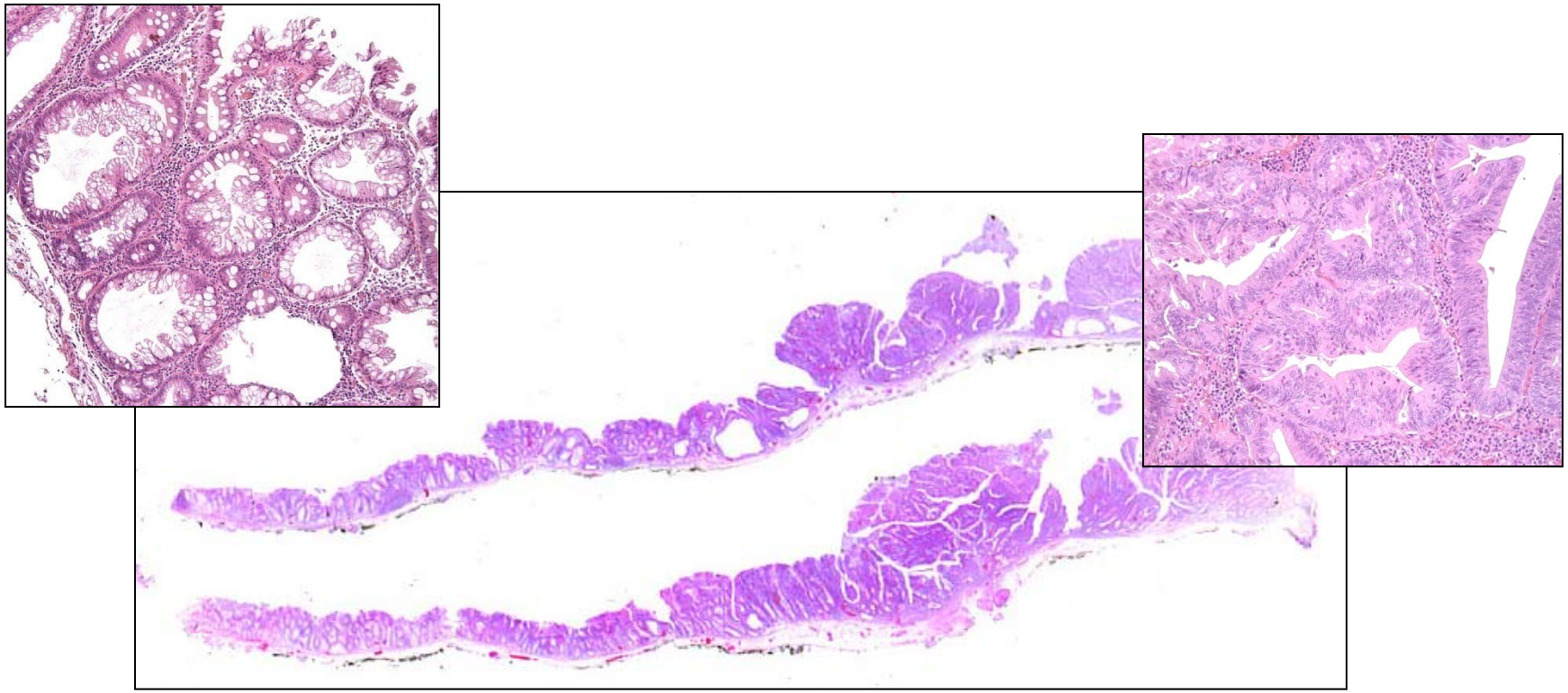
Polipi Serrati: Refertazione



ADENOMA SERRATO SESSILE CON DISPLASIA DI ALTO GRADO

Margini di exeresi : non valutabili

Polipi Serrati: Refertazione



ADENOMA SERRATO SESSILE IN TRANSIZIONE VERSO TSA PIATTO CON DISPLASIA DI ALTO GRADO

Morfologia Serrata in corrispondenza dei margini di exeresi

Polipi serrati: la gestione clinica

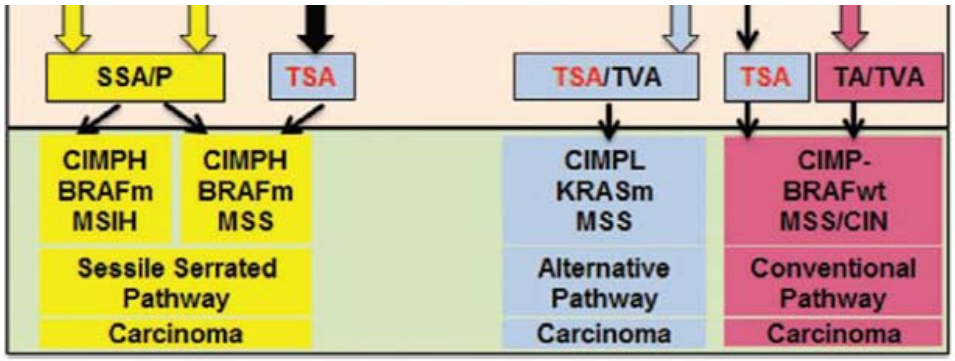
Molecular and Histologic Considerations in the Assessment of Serrated Polyps

Hui-Min Yang, MD; James M. Mitchell, MD; Jorge L. Sepulveda, MD, PhD; Antonia R. Sepulveda, MD, PhD

Table 3. Recommendations for Surveillance Intervals in Patients With Serrated Lesions in the Colon and Rectum, Based on the Review and Recommendations From an Expert Panel[a]

Polyp Type	Size	Number	Location	Interval, y
HP	<10 mm	Any	Rectosigmoid	10
	≤5 mm	≤3	Proximal to sigmoid	10
	Any	>3		5
	>5 mm	≥1		5
SSA/P or TSA	<10 mm	≤2	Any	5
	≥10 mm	1		3
	<10 mm	>2		3
	≥10 mm	≥2		1–3
SSA/P with dysplasia	Any	Any		1–3
SPS[b]				1

Abbreviations: HP, hyperplastic polyp; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma



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MINIREVIEWS

Endoscopic and histologic characteristics of serrated lesions

Driffa Moussata, Gilles Boschetti, Marion Chauvenet, Karine Stroeymeyt, Stéphane Nancey, Fran
Thierry Lecomte, Bernard Flourié

**Table 2 Endoscopic follow-up acc
Society Task Force on Colorec
Society of Gastrointestinal Endosc**

Serrated polyps	Follow-up accordin States multi-so	
HP	5 yr, if > 10 mm o	
SSA without dysplasia	< 3 lesions, < 1 ⩾ 3, > 1 cm	
SSA with dysplasia	3 yr	
TSA	3 yr	
Serrated polyposis	1 yr	1 yr

ESGE: European Society of Gastrointestinal Endoscopy; HP: Hyperplastic polyps; SSA: Sessile serrated adenomas.

CONCLUSION

Under the denomination of serrated polyps, different types of lesions can be encountered, thus requiring a more accurate characterisation. This depends not only on the endoscopists, who must be able to recognise and describe these lesions in order to resect them in one piece, but also on the pathologists, who requires an accurate description and an oriented resected peace. This collaboration is essential in order to improve current knowledge and understanding.