

Serirane lezije debelega črevesa in danke

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Molekularni podtipi raka debelega črevesa in danke

Vsaj tri molekularne poti za nastanek RDČD:

- 1) kromosomska nestabilnost (»Chromosomal instability – CIN«), 60-70% sporadičnih
- 2) okvare v MMR genih, t.j. genih za popravljanje DNA (»MisMatch Repair«), 15-20% sporadičnih & Lynch syndrom
- 3) hipermetilacija CpG regij (»CpG island hypermethylation phenotype – CIMP»), 20-30%.

Serirana pot

Značilnost tumorjev, ki nastanejo po drugi ali tretji molekularni poti je mikrosatelitska nestabilnost (MSI).

- pri 20% kolorektalnih karcinomov je prekurzor serirana sprememba
- karcinomi, ki vzniknejo preko serirane molekularne poti so molekularno heterogeni
- prognoza je različna

Serirani (nazobčani) polipi

The classification of serrated colorectal lesions according to 2019 WHO classification

Histological type

Subtype

Hyperplastic polyp (HP)

Microvescicular type (MVHP)

Goblet cell-rich type (GCHP)

Sessile serrated lesion (SSL)

SSL with dysplasia (SSLD)

Traditional serrated adenoma (TSA)

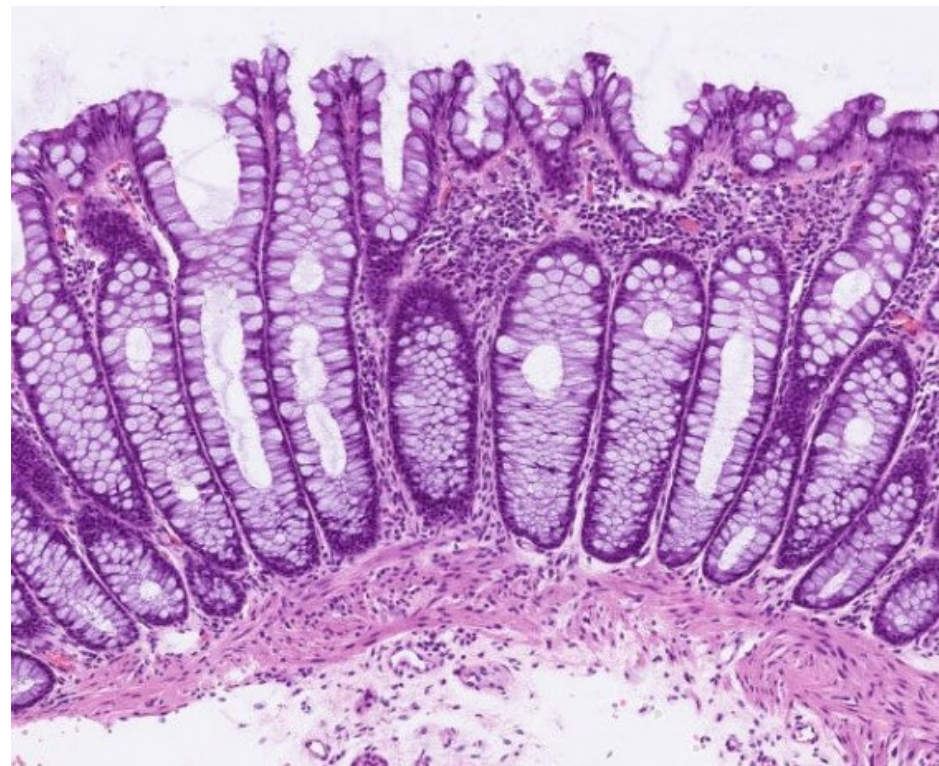
Serrated adenoma, unclassified

WHO World Health Organization

Hiperplastični polip

- ✓ 75% vseh nazobčanih sprememb
- ✓ prevalenca 20-30%
- ✓ levi kolon, pogosto multipli
- ✓ < 5 mm

- ✓ brez rizika napredovanja v RDČ
- ✓ BRAF mutacije



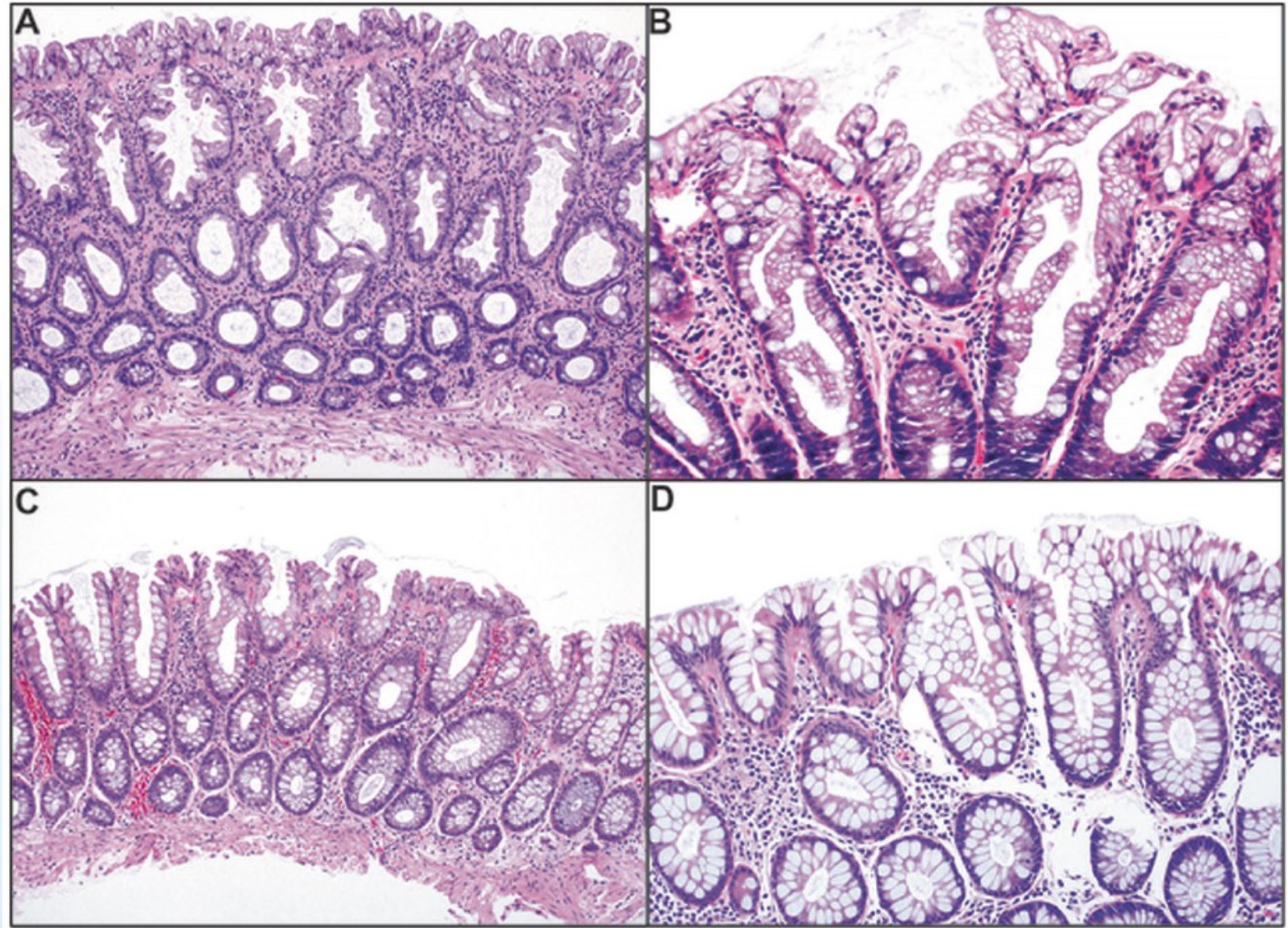
- ✓ proliferacijska cona v bazi kript
- ✓ kripte vzporedne, urejene
- ✓ nazobčanost zgornje 2/3 kript
- ✓ Endoskopsko Kudo II

Mikrovezikularni HP

- prekurzor SSL
- 40-50% seriranih polipov
- 10% v transverznem in D kolonu
- BRAF 80%, KRAS 0%, CIMP-H

S čašastimi celicami bogat HP

- 20-30% seriranih polipov
- Rektosigma
- Prekurzor TSA
- BRAF 0%, KRAS 50%, CIMP-L



Ločevanje v klinični praksi ni pomembno.

Sesilna serirana lezija

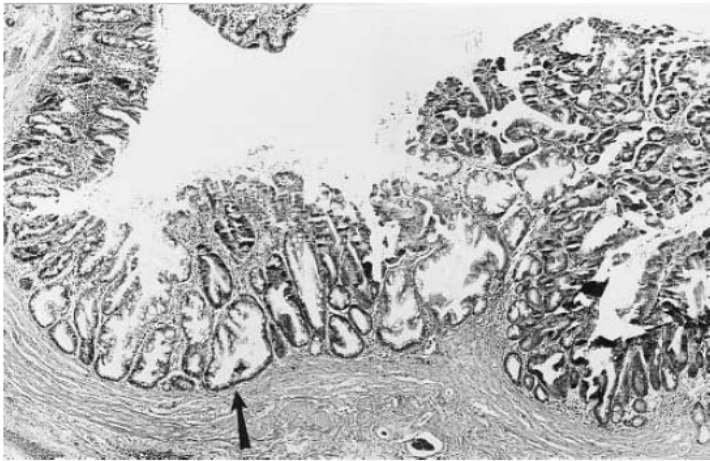
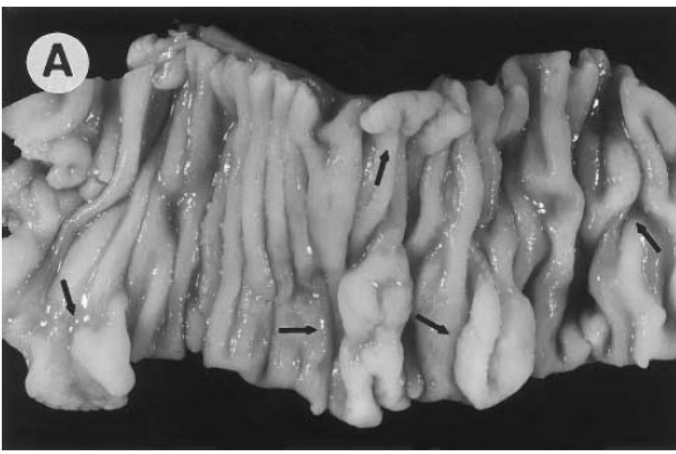
Serrated Adenomatous Polyposis in Humans

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

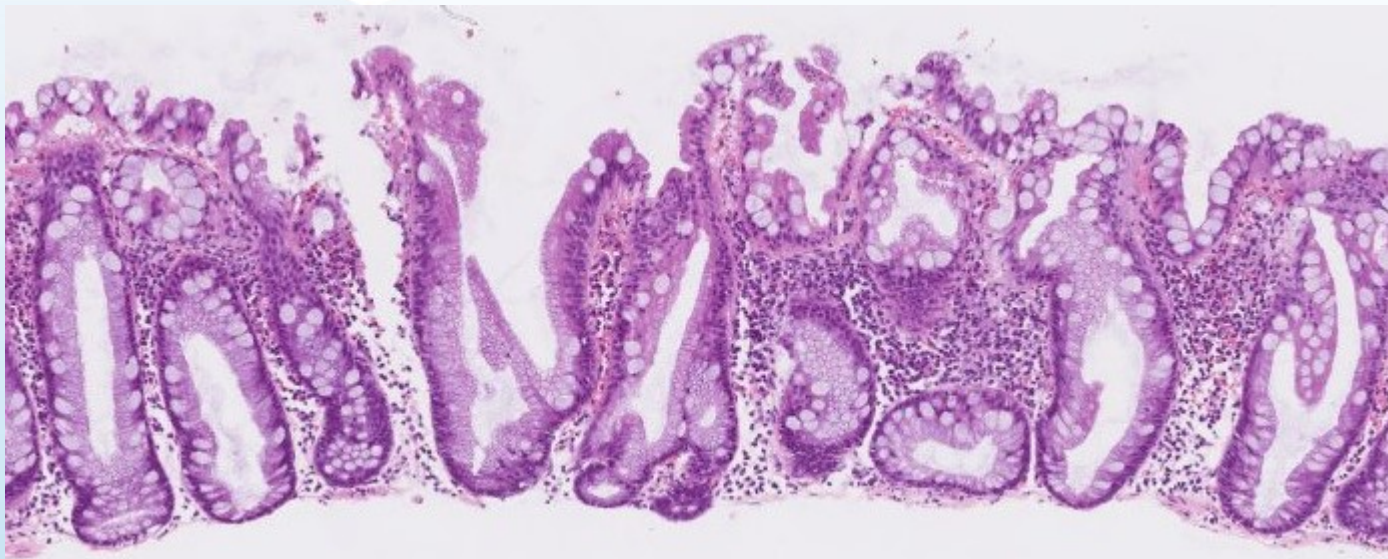
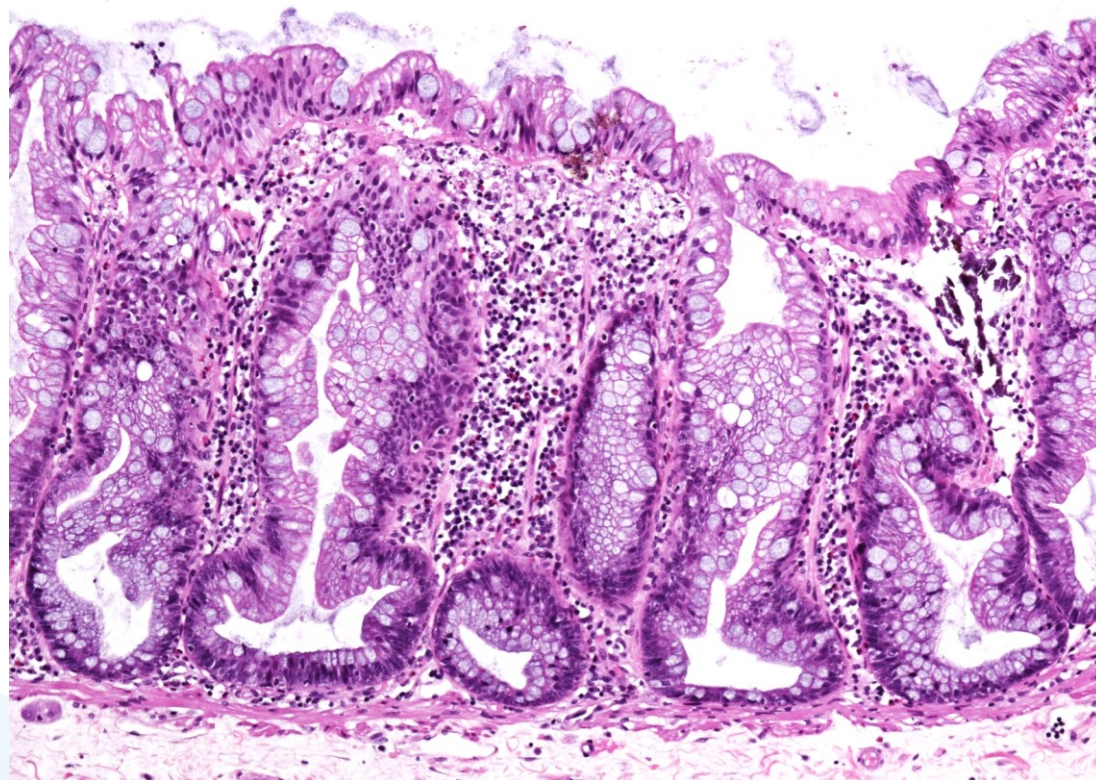
Patient	Sex/age (yr)	Polyps				Cancer	
		No.	Size (cm)	Shape	Distribution	Present	Synchronous versus metachronous
1	M/53	Numerous	0.5–1.5	S	Left colon	Yes	Synchronous
2	M/43	Numerous	0.5–2.0	S	Diffuse	Yes	Synchronous
3	F/85	>50	0.3–1.5	S > P	Diffuse	Yes	Synchronous
4	M/39	>50	0.5–4.0	S > P	Left colon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



Sesilna serirana lezija

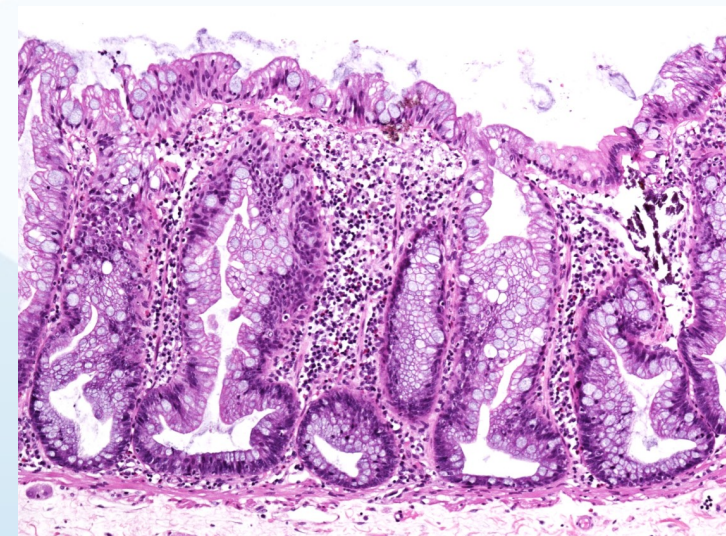
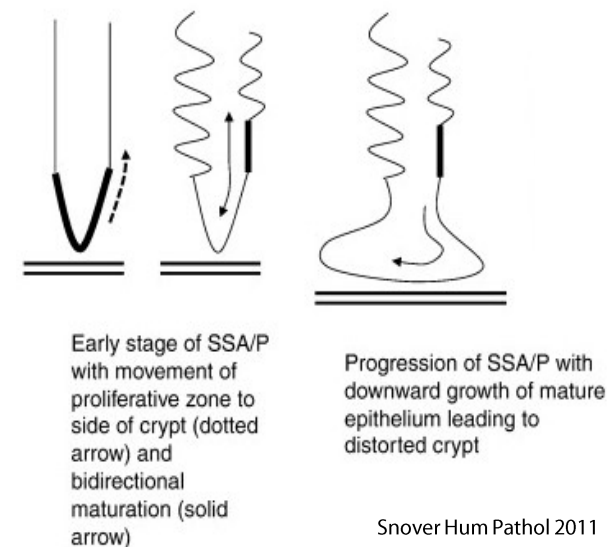
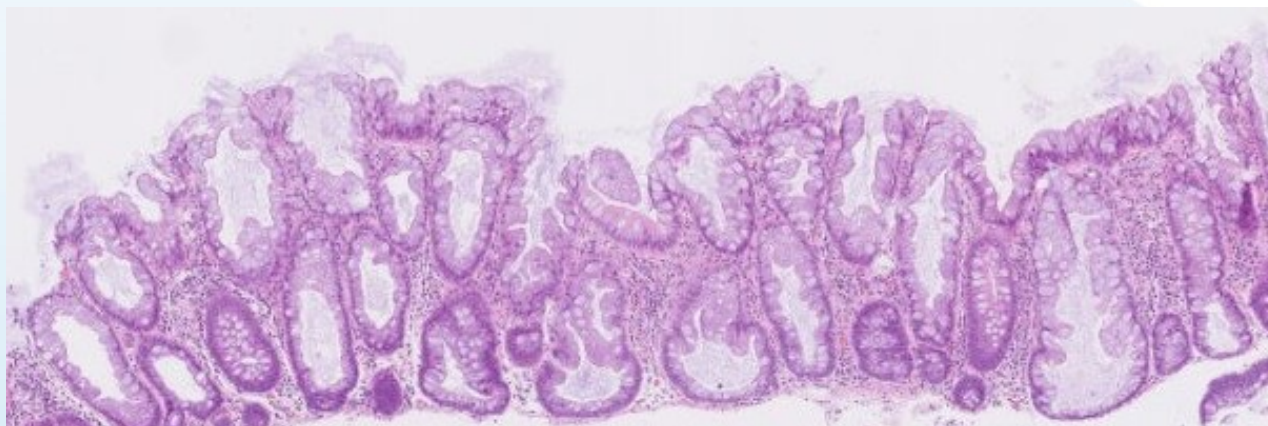
- ✓ prekurzor CRC, prevalenca 5-10%
- ✓ 25 % seriranih polipov
- ✓ povsod, predvsem desni kolon
- ✓ > 10 mm
- ✓ endoskopsko slabše razpoznavne, Kudo II
- ✓ lahko napredujejo v RDČ po „serirani poti“
- ✓ BRAF mutacije (70-90%), KRAS (9%)



Sesilna serirana lezija – histološka slika

Aberantni proliferacijski centri – pomik proliferacijske cone ob baze proti lateralni strani kripte → značilna histološka slika SSL:

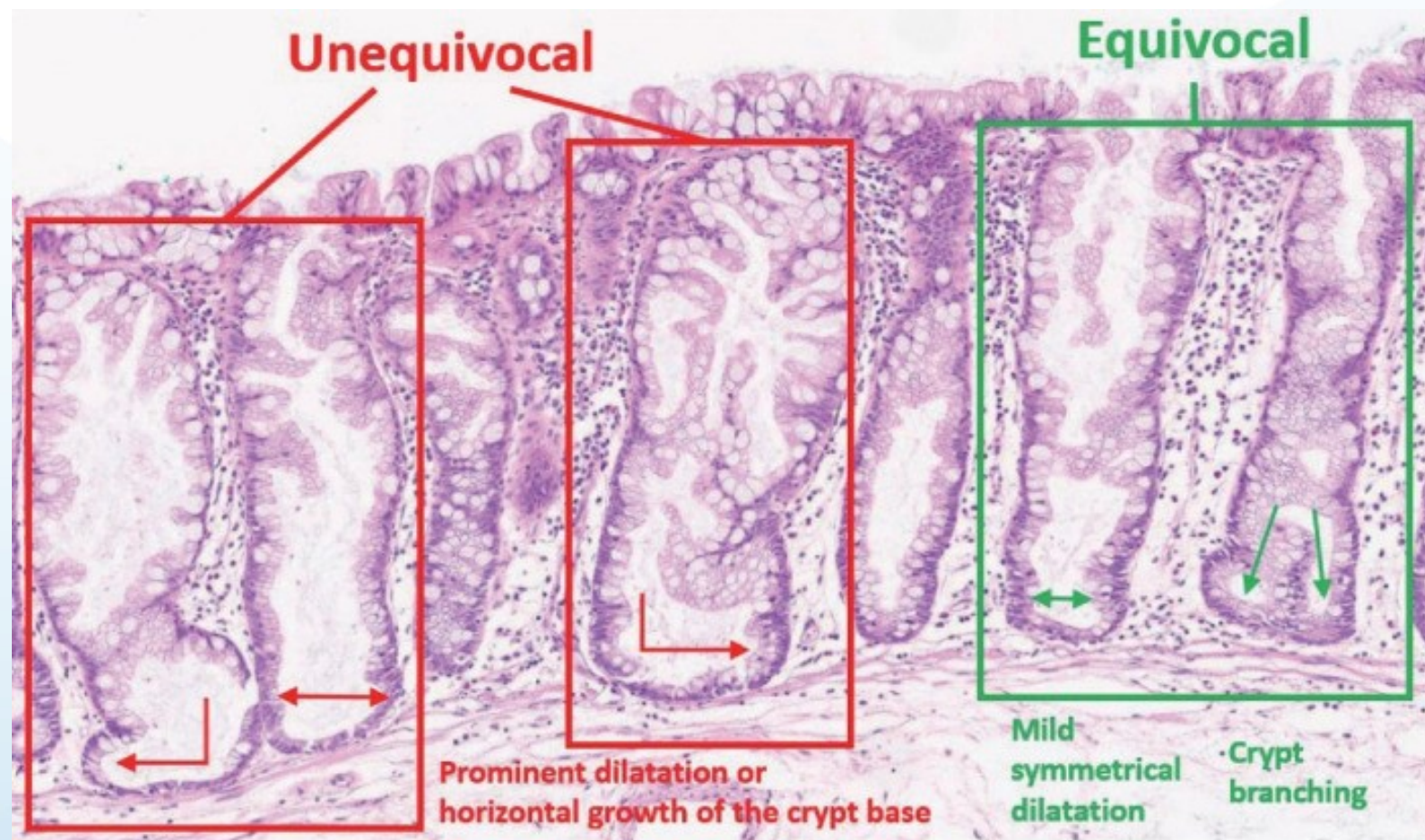
- (1) Horizontalno širjenje kript vzdolž l. muskularis mukoze (dobijo obliko črke L ali obrnjene črke T);
- (2) Razširjene baze kript (spodnja tretjina kript);
- (3) Poudarjena seriranost (nazobčanost), ki se širi proti bazi kript;
- (4) Asimetrična proliferacija



Za diagnozo zadošča nedvomna prisotnost vsaj ene tipične kript!

Sesilna serirana lezija – histološka slika

- ✓ 1 nedvnomno tipična kript
- ✓ Globlje rezine



Journal of Pathology and Translational Medicine 2020; 54: 276-289

Hyperplastic polyp or sessile serrated lesion? The contribution of serial sections to reclassification



Diana R. Jaravaza^{1*}  and Jonathan M. Rigby^{1,2} 

Abstract

Background: The histological discrimination of hyperplastic polyps from sessile serrated lesions can be difficult. Sessile serrated lesions and hyperplastic polyps are types of serrated polyps which confer different malignancy risks, and surveillance intervals, and are sometimes difficult to discriminate. Our aim was to reclassify previously diagnosed hyperplastic polyps as sessile serrated lesions or confirmed hyperplastic polyps, using additional serial sections.

Methods: Clinicopathological data for all colorectal hyperplastic polyps diagnosed in 2016 and 2017 was collected. The slides were reviewed and classified as hyperplastic polyps, sessile serrated lesion, or other, using current World Health Organization criteria. Eight additional serial sections were performed for the confirmed hyperplastic polyp group and reviewed.

Results: Of an initial 147 hyperplastic polyps from 93 patients, 9 (6.1%) were classified as sessile serrated lesions, 103 as hyperplastic polyps, and 35 as other. Of the 103 confirmed hyperplastic polyps, 7 (6.8%) were proximal, and 8 (7.8%) had a largest fragment size of ≥ 5 mm and < 10 mm. After 8 additional serial sections, 11 (10.7%) were reclassified as sessile serrated lesions. They were all less than 5 mm and represented 14.3% of proximal polyps and 10.4% of distal polyps. An average of 3.6 serial sections were required for a change in diagnosis.

Conclusion: Histopathological distinction between hyperplastic polyps and sessile serrated lesions remains a challenge. This study has uncovered a potential role for the use of additional serial sections in the morphological reappraisal of small hyperplastic polyps, especially when proximally located.

Keywords: Sessile serrated lesion, Sessile serrated adenoma/polyp, Hyperplastic polyp, Levels, Serial sections

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. Ijspeert¹, Koos de Wit¹, Manon van der Vlugt^{1,2}, Barbara A. J. Bastiaansen^{1,2}, Paul Fockens^{1,2}, Evelien Dekker^{1,2}

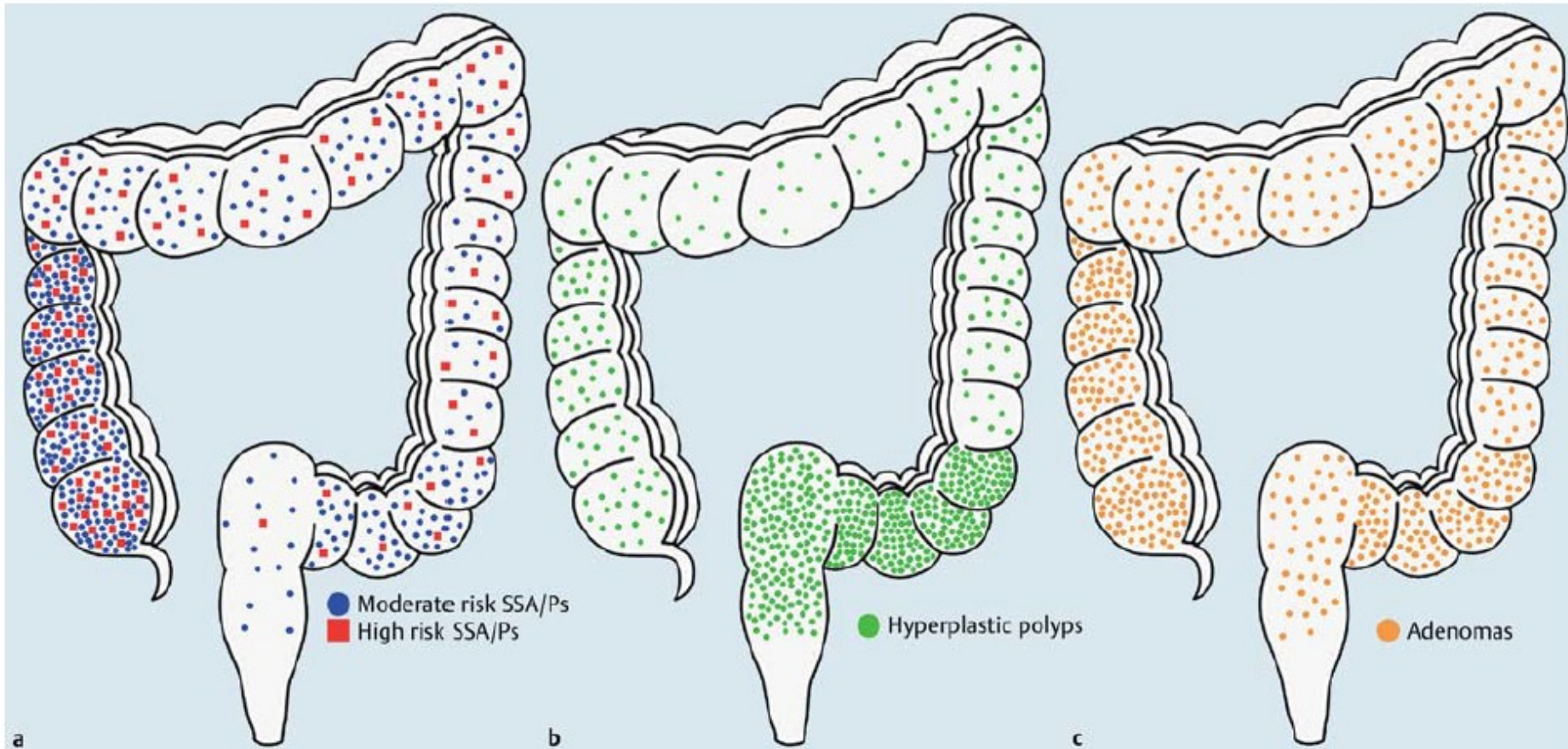


Fig. 2 Colonic distribution of polyps: **a** distribution of moderate risk and high risk sessile serrated adenomas/polyps (SSA/Ps); **b** distribution of hyperplastic polyps; **c** distribution of adenomas.

Tradicionalni nazobčani adenom

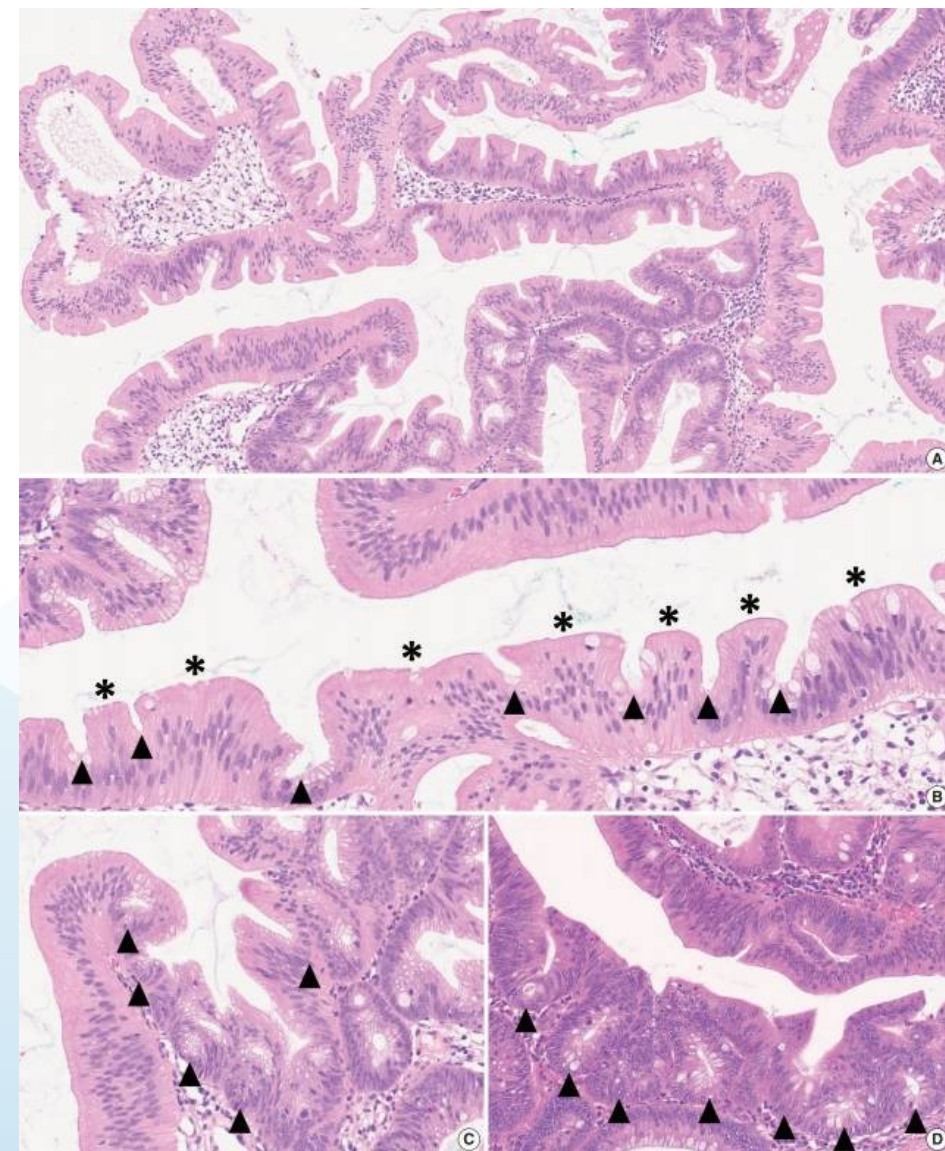
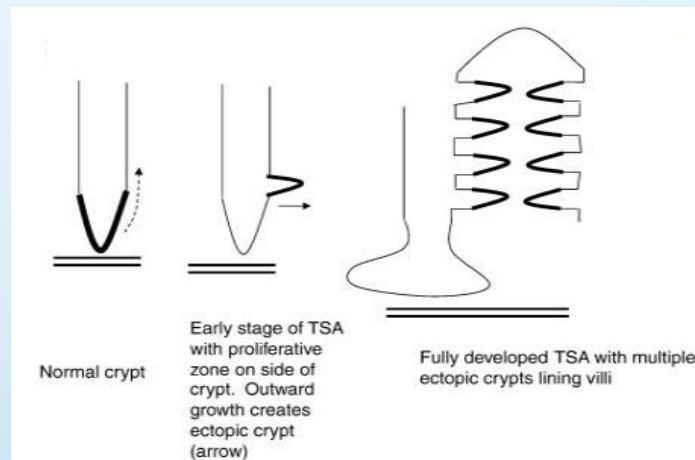
Histološke značilnosti:

Vsaj 2/3 lastnosti & vsaj 1 v > 50% površine

(Bettington et al. Am J Surg Pathol 2014 / Mod Pathol 2014)

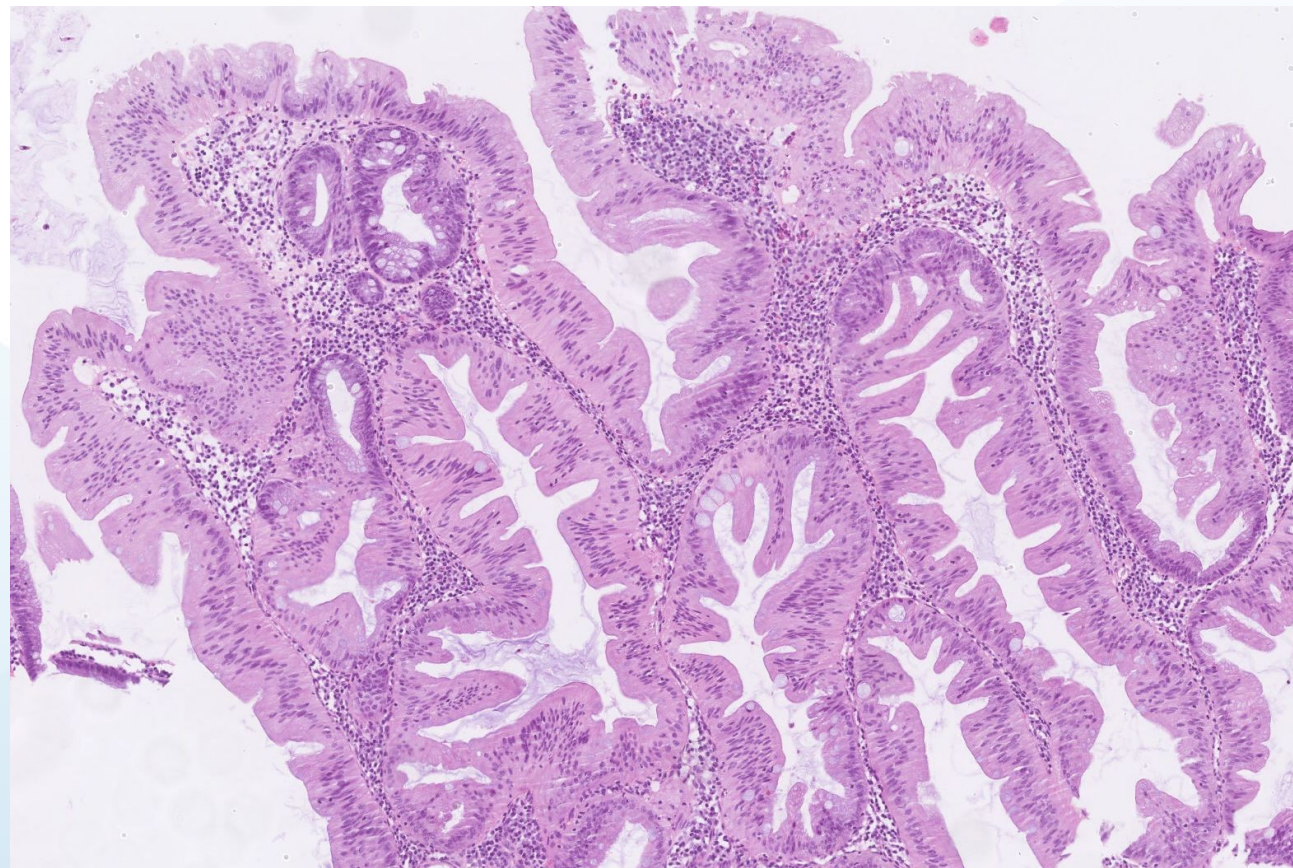
1. **Citološke značilnosti:** eozinofilna citoplazma, unimorfna podolgovata jetra
2. **Nazobčanost** z špranjastimi vrezninami
3. **Ektopične kripte** (pri sesilnih lahko niso prisotne) brez povezave z muskularis mukoze

Nobena od naštetih značilnosti ni specifična!



Tradicionalni nazobčani adenom

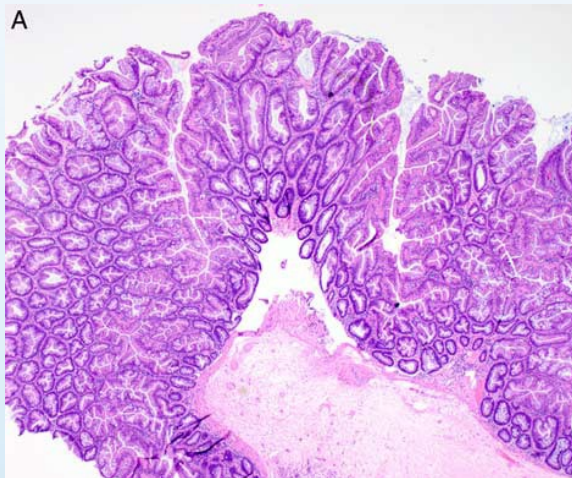
- ✓ redki prevalenca manj kot 1%
- ✓ levi kolon
- ✓ polipoidni, redkeje ploščati
- ✓ vilozni/ tubulovilozni; vilusi z zaobljeno kapico
- ✓ SSL je lahko prekurzor (viden v robu TSA)
- ✓ napredujejo v displazijo – intestinalni in nazobčani tip
- ✓ displazijo omenjamo v izvidu samo če je visoke stopnje
- ✓ verjetnost in hitrost napredovanja v RDČ ni znana
- ✓ heterogen molekularni profil



TSA – genetsko heterogeni

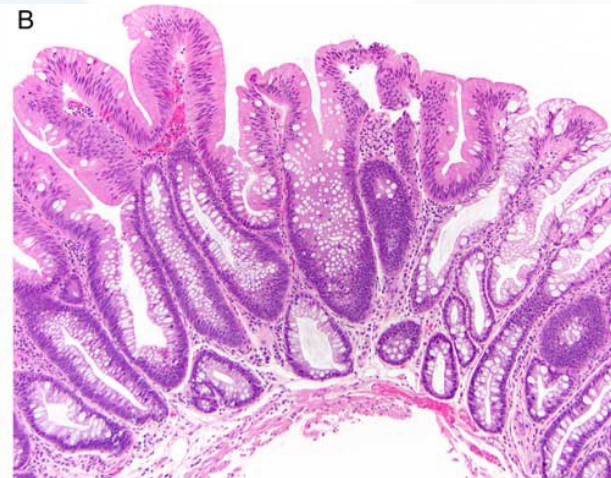
BRAF mutirani (>50%)

Proksimalni, ploščati
V robu mvHP ali SSL
CIMP-H, ohranjena ekspresija MLH1
P53 mutacije
RNF43 mutacije



KRAS mutirani (~30%)

Distalno, egzofitični
V robu imajo ploščat TSA ali goblet cell HP
CIMP-L

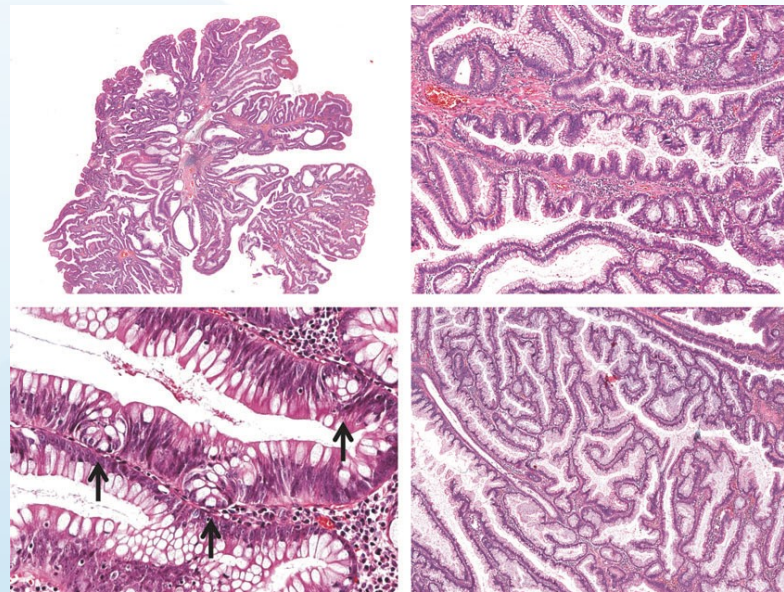
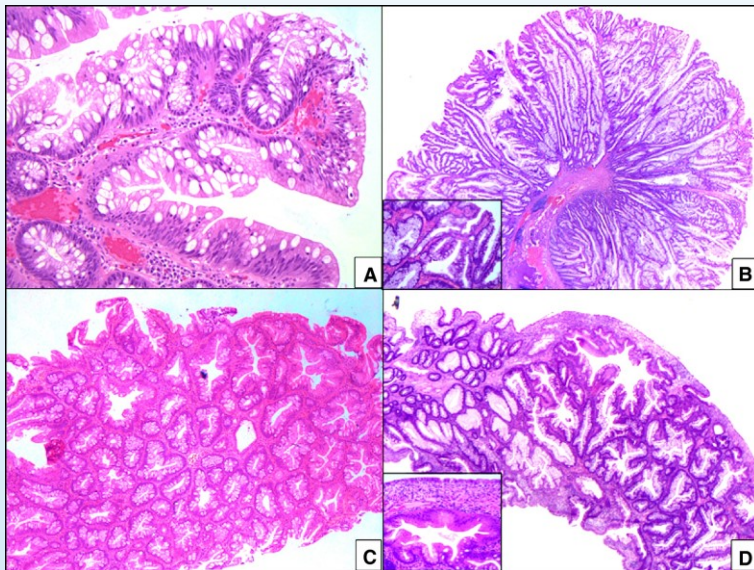


Am J Surg Pathol 2022;46:e64–e70

Tveganje za maligno transformacijo in hitrost napredovanja v karcinom pri TSA nista poznana.

Serrated adenoma, unclassified – introduced in 2019 WHO

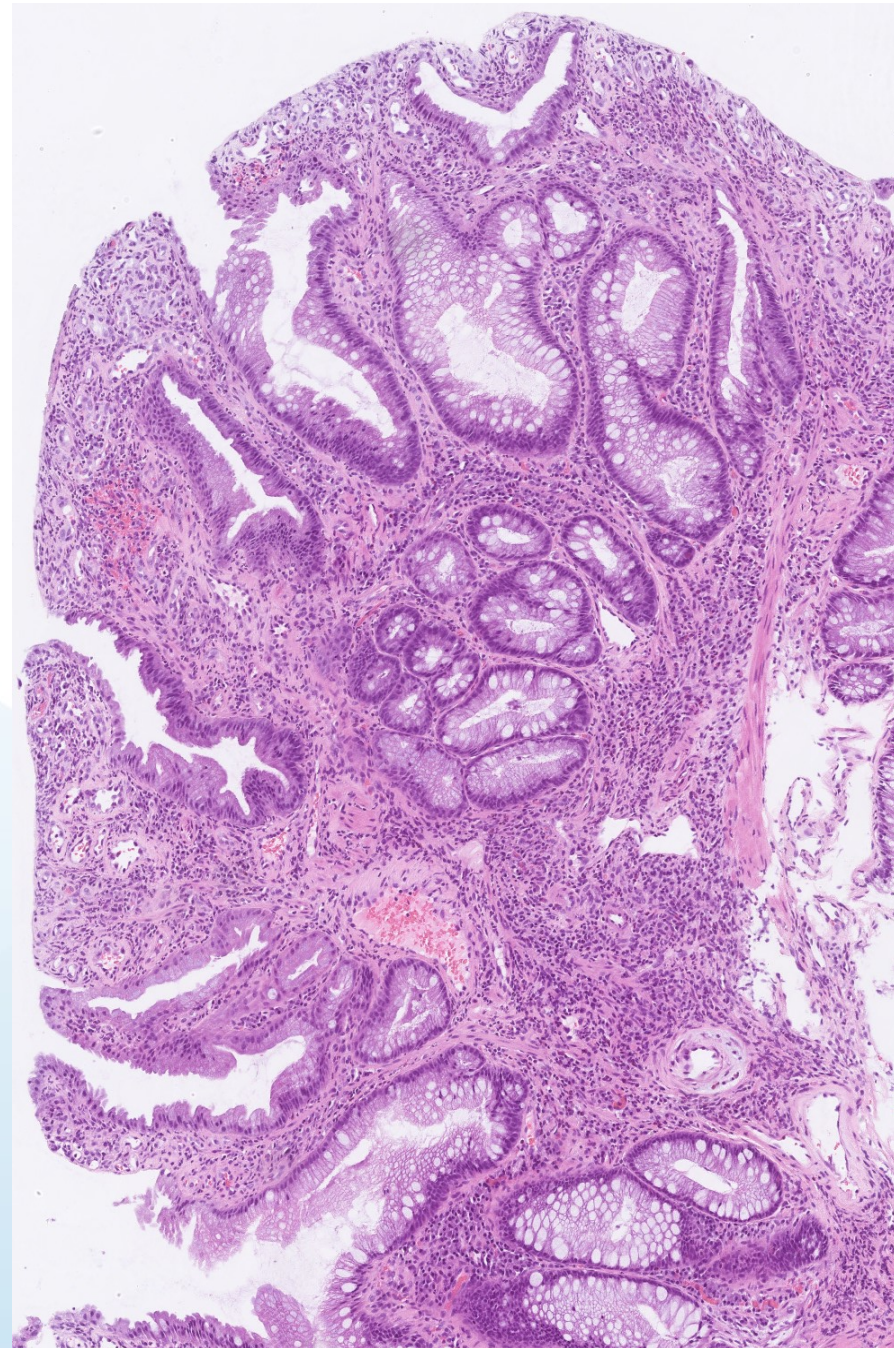
- ✓ Nazobčan polip, ki ga ni možno uvrstiti v nobeno skupino
- ✓ heterogena skupina
- ✓ Naslednja edicija WHO
- ✓ Kandidati : Mucin-rich TSA (Mr-TSA), Serrated TVA (sTVA), superficially serrated adenoma (SuSA)



Posnemovalci

Vnetni polipi & mukozni prolaps

- Lahko eozinofilna citoplazma kot pri TSA
- Nazobčane konture kript kot pri SSL ali TSA
- Bolj poudarjeno vnetje lamine proprije, izrazitejše arhitekturne spremembe



Serirani polipozni sindrom (SPS)

The diagnosis is defined by the WHO 2019 based on any one of the following criteria:

Kriterij 1:

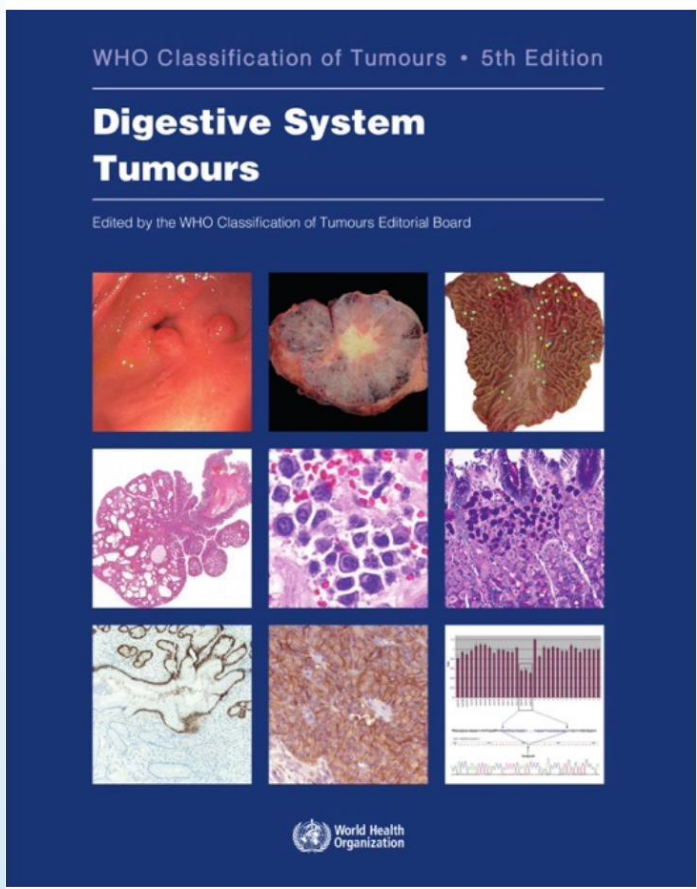
≥5 seriranih lezij/polipov proksimalno od rektuma velikosti ≥5 mm, med katerimi sta vsaj dva velikosti ≥10 mm

ali

Kriterij 2:

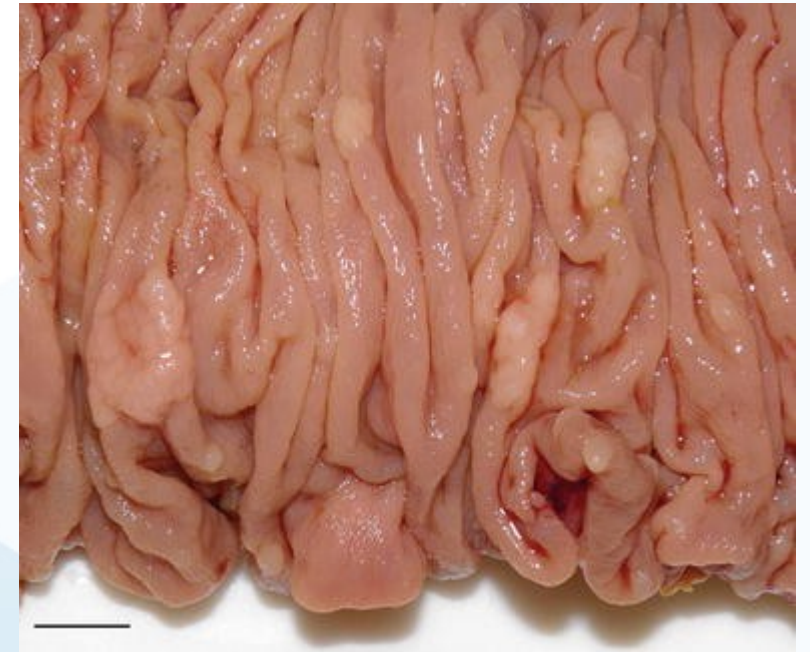
>20 seriranih lezij/polipov katerekoli velikosti, razporejenih skozi kolorektum, od katerih je ≥5 proksimalno od rektuma

Pri oceni kumulativno upoštevajo (seštevajo) lezije, ki so lahko odkrite pri večjem številu opravljenih kolonoskopij.



Serirani polipozni sindrom (SPS)

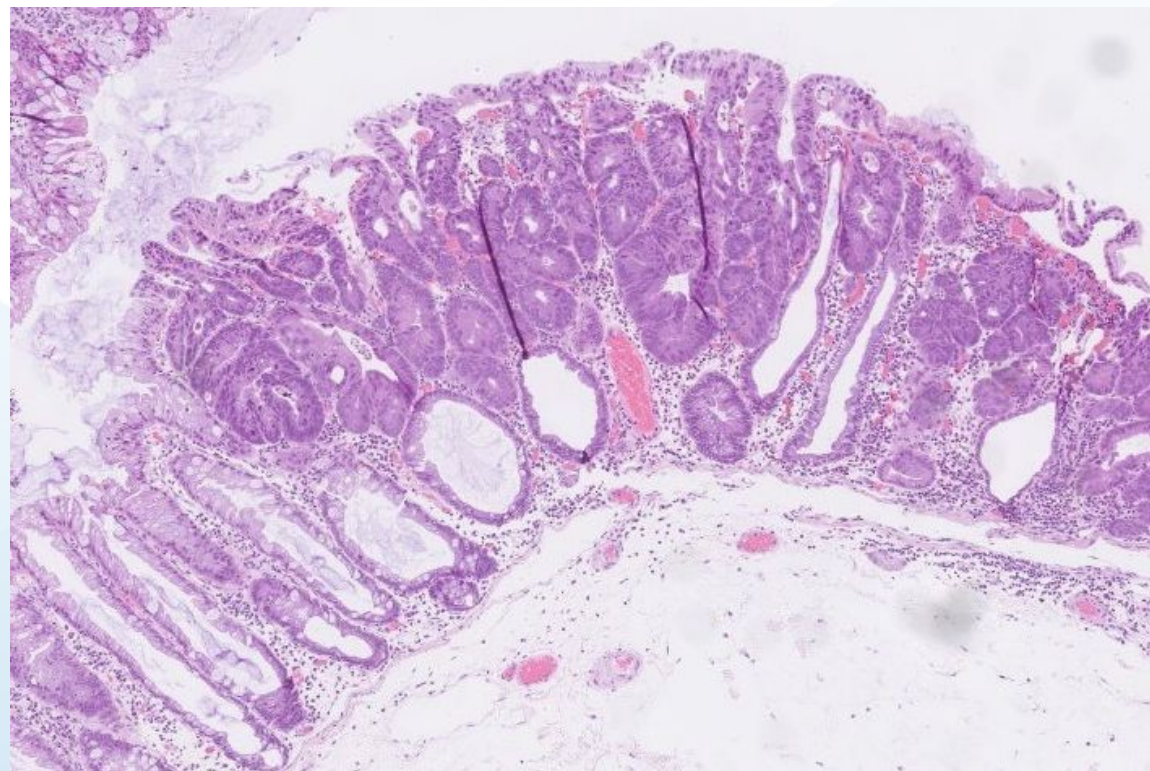
- običajno sporadičen, redek, genetska napaka in način dedovanja niso opredeljeni
- **multipli serirani polipi kolona & povišana incidenca RDČD**
- ni ekstraintestinalnih manifestacij
- 16-35% prizadetih razvije RDČD, večina na prvi kolonoskopiji
- vsi histološki tipi nazobčanih polipov (HP, SSL z ali brez diaplazije, TSA in neopredeljeni serirani polipi)
- sledenje na 1 leto
- izključitev drugih genetskih sindromov povezanih s polipi kolona (MUTYH-associated polyposis, PTEN-hamartoma tumor syndrome)



J Gastroenterol (2013) 48:287–302

SSL z displazijo

- 4-8% of all SSL
- hitra maligna transformacija (tudi pri displaziji nizke stopnje)
- pogostejše v proksimalnem kolonu
- starejši, večje SSL
- lahko tudi v majhnih SSL, <5 mm
- opisani številni histološki tipi displazije (v izvidih ne poročamo)
- ne gradiramo
- če je endoskopsko prepoznan in odstranjen le displastični del lezije je histološka diagnoza adenom



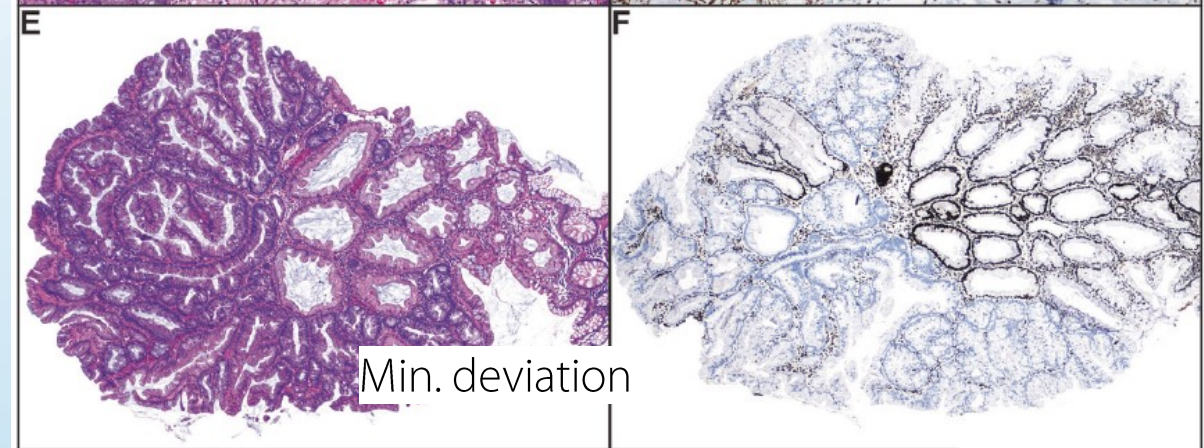
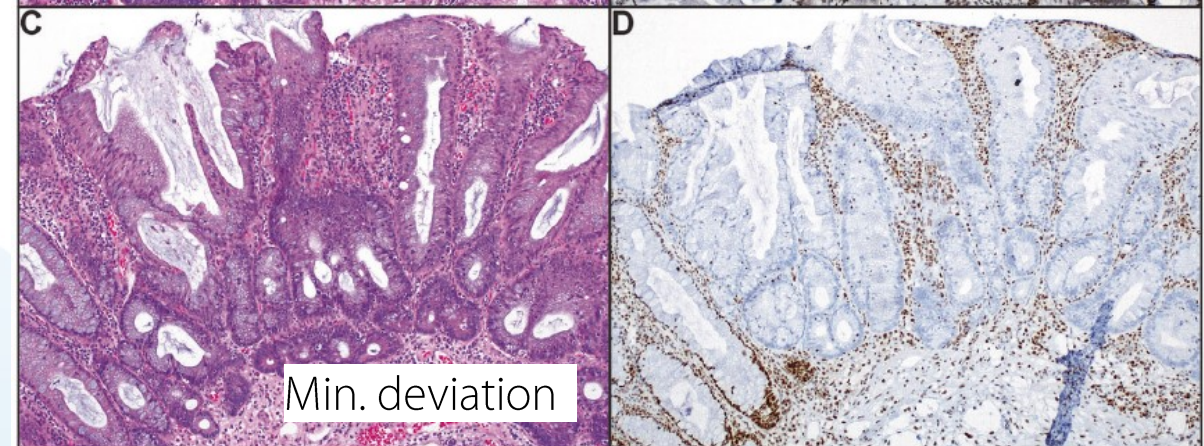
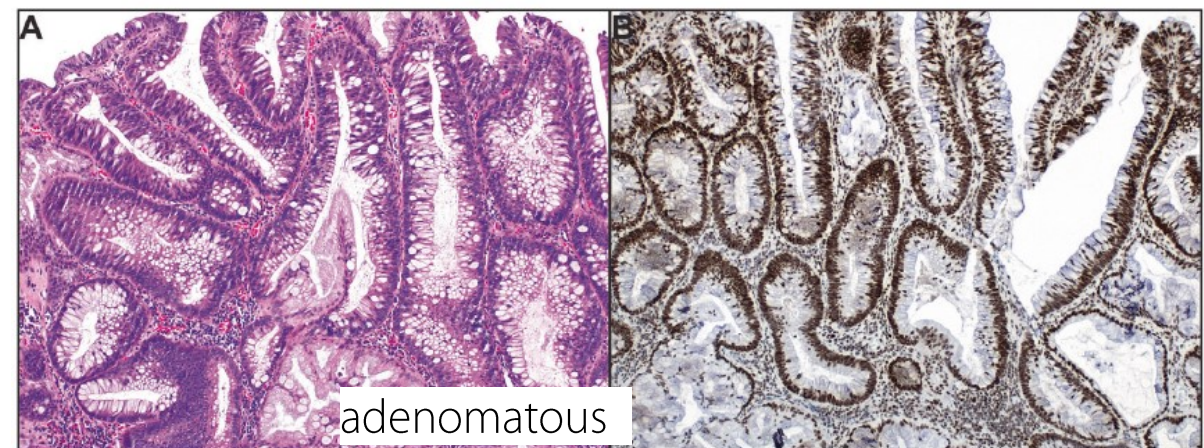
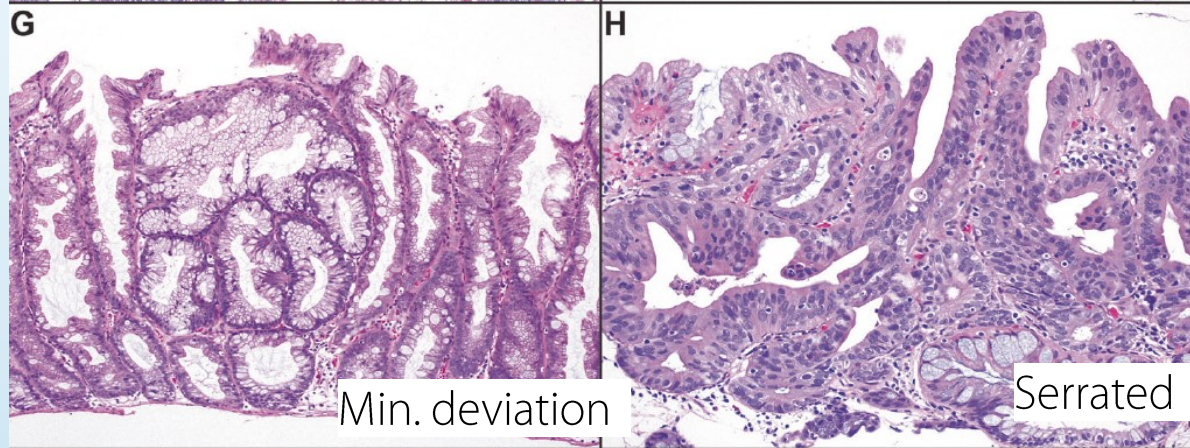
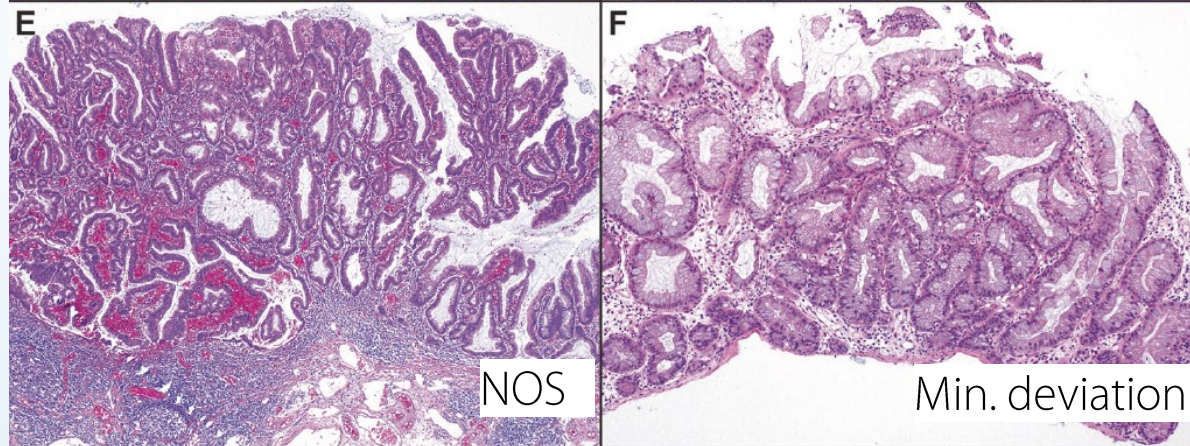
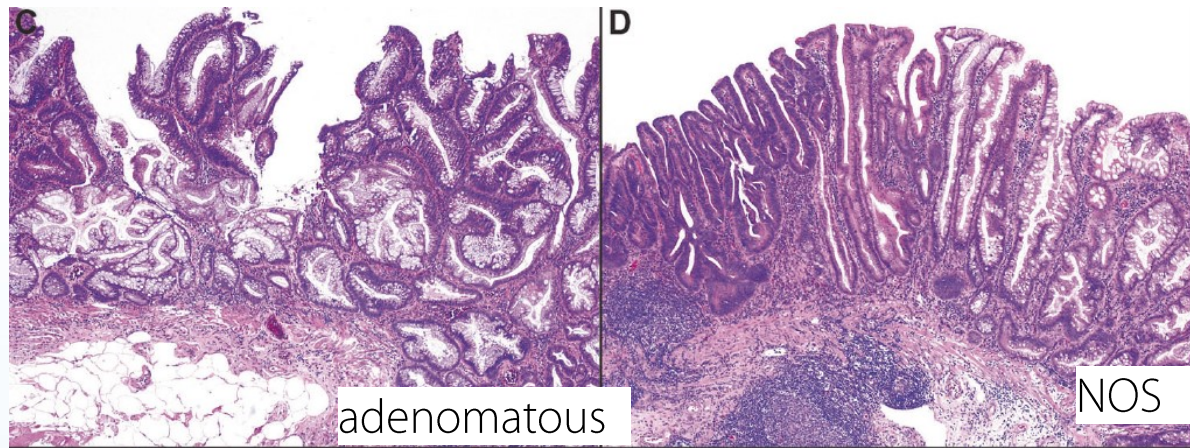
Sessile serrated adenomas with dysplasia: morphological patterns and correlations with MLH1 immunohistochemistry

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 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%

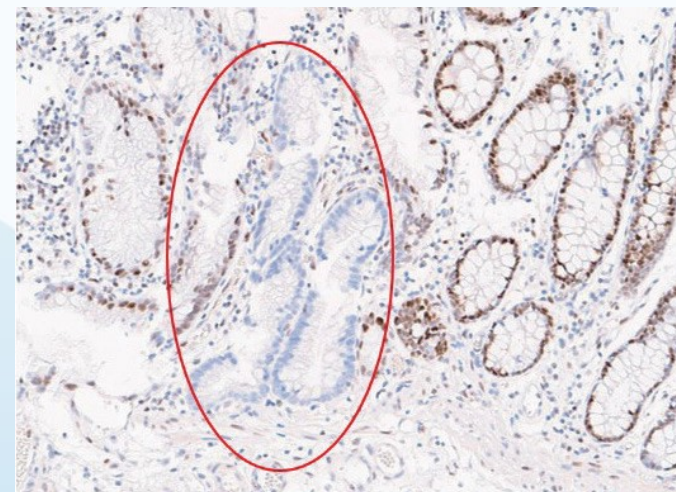
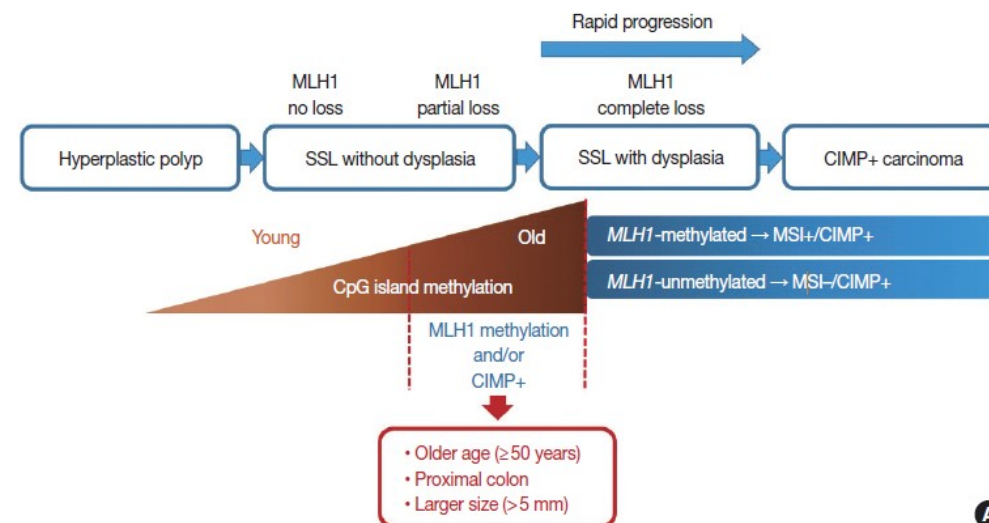
^aFrequency of each pattern from Liu et al. [28] Multiple patterns can be present in a single lesion.



SSL z displazijo – molekularno-genetske značilnosti

BRAF gene mutations, CIMP+
MLH1 izguba (75%) / ohranjen

- MSI-H SSLD: proksimalni veliki SSLs pri starejših
- delna izguba MLH1 v SSL brez displazije – označevalec napredovale lezije?



Kim et al. JPTM 2020

Serirana pot razvoja RDČD

2 veji

1. SSL z BRAF mutacijo razvije displazijo ob hipermetilaciji genoma

1a. Hipermetilacija prizadane promotor gena MLH1 – kopičenje mutacij – RDČD z izgubo ekspresije MLH1 (MSI-H).

1b. Hipermetilacija vodi v inaktivacijo drugih genov (p16 and MGMT) – RDČD z ohranjeno ekspresijo MLH1

2. TSA s KRAS mutacijo vodijo v KRAS mutiran RDČD z ohranjeno ekspresijo MLH1

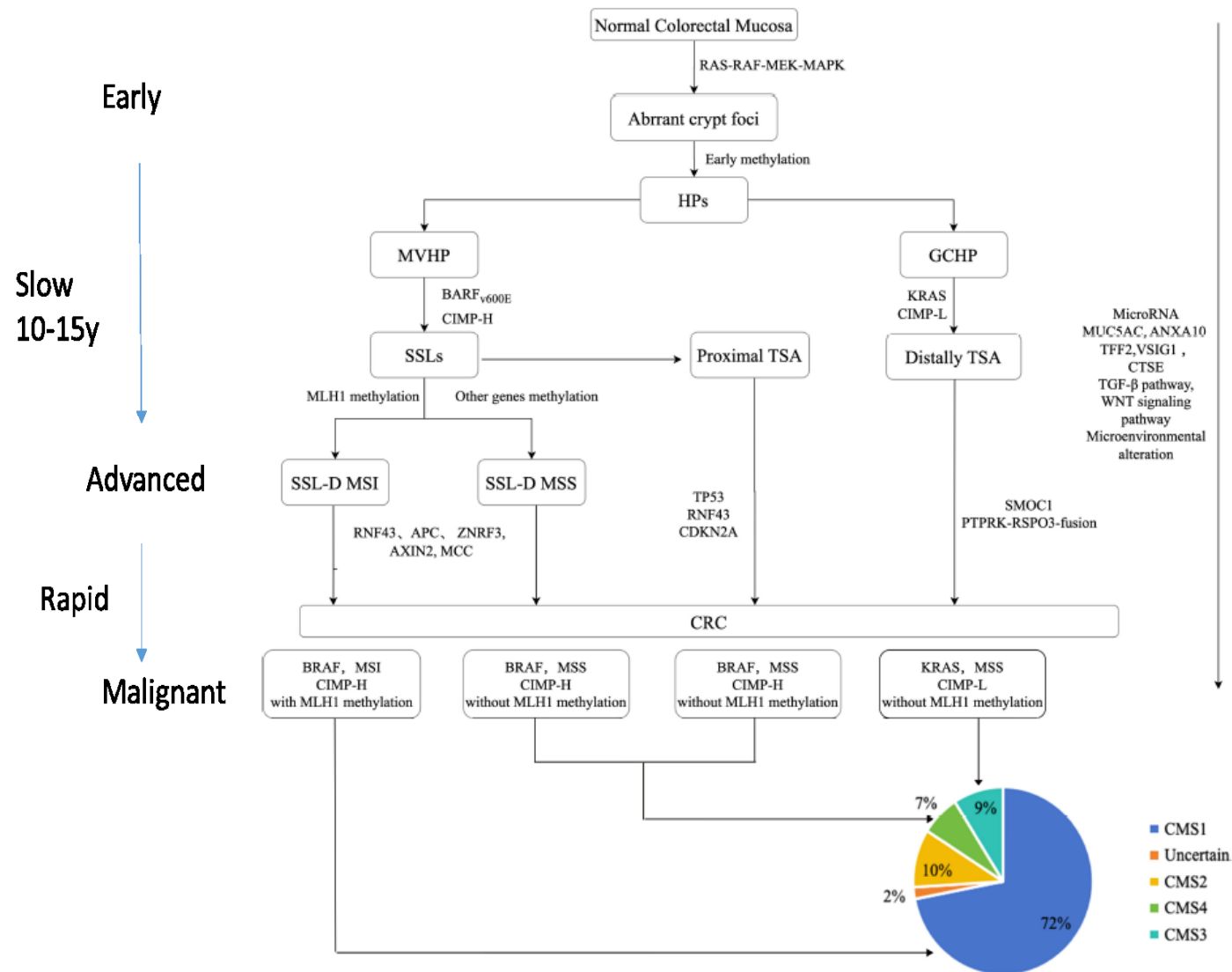
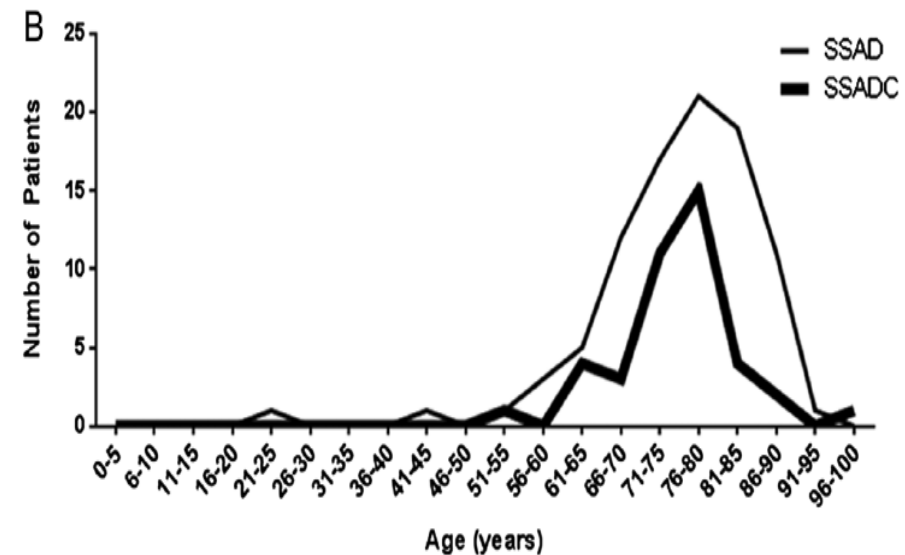


FIGURE 1
The molecular mechanism of serrated pathway.

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

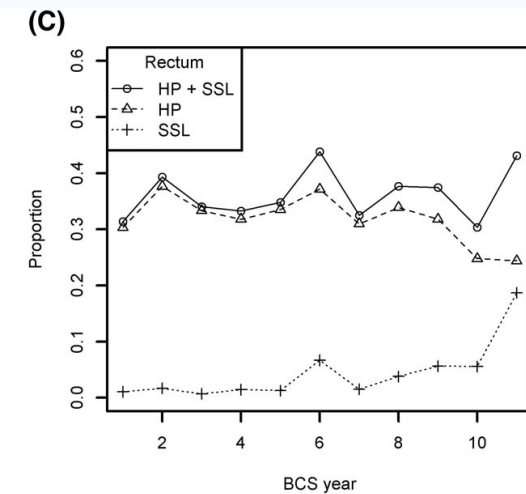
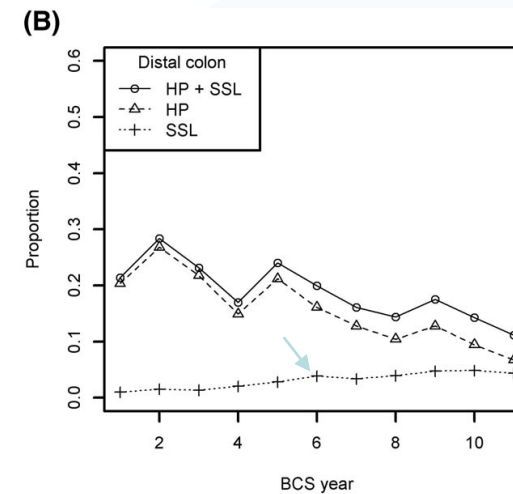
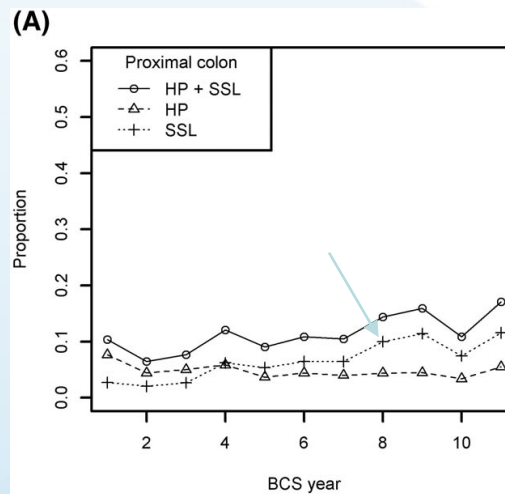
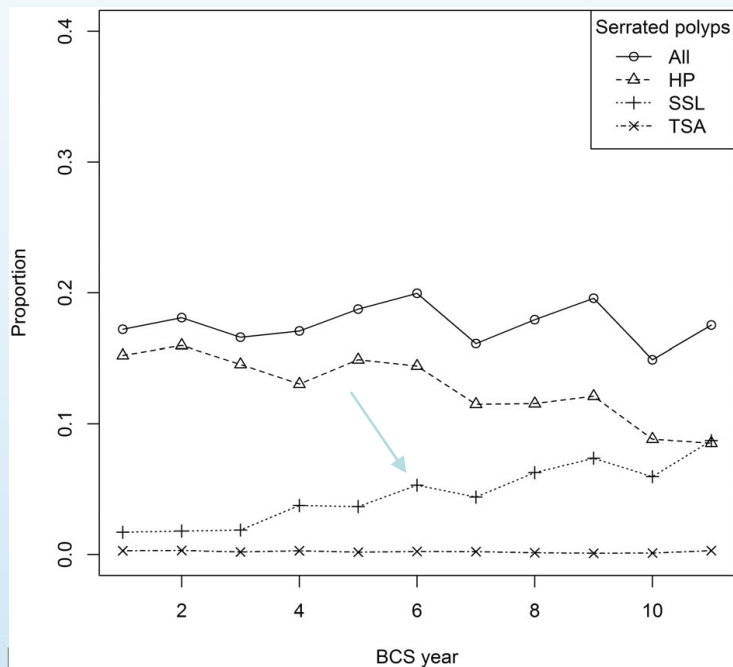
Mark Bettington,^{1,2,3} Neal Walker,^{1,2} Christophe Rosty,^{1,2} Ian Brown,²
Andrew Clouston,^{1,2} Diane McKeone,³ Sally-Ann Pearson,³ Barbara Leggett,^{1,3,4}
Vicki Whitehall^{1,3,5}



The 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

Trends in pathology diagnoses during 10 years of a colorectal cancer screening programme

- diagnoses of serrated polyp, of any type, remained relatively constant throughout the study time-frame (14.9%–20.0%)
- a strong downward trend in the proportion of HP diagnosed, and a corresponding increase in the proportion of SSLs diagnosed, predominantly in proximal colon.



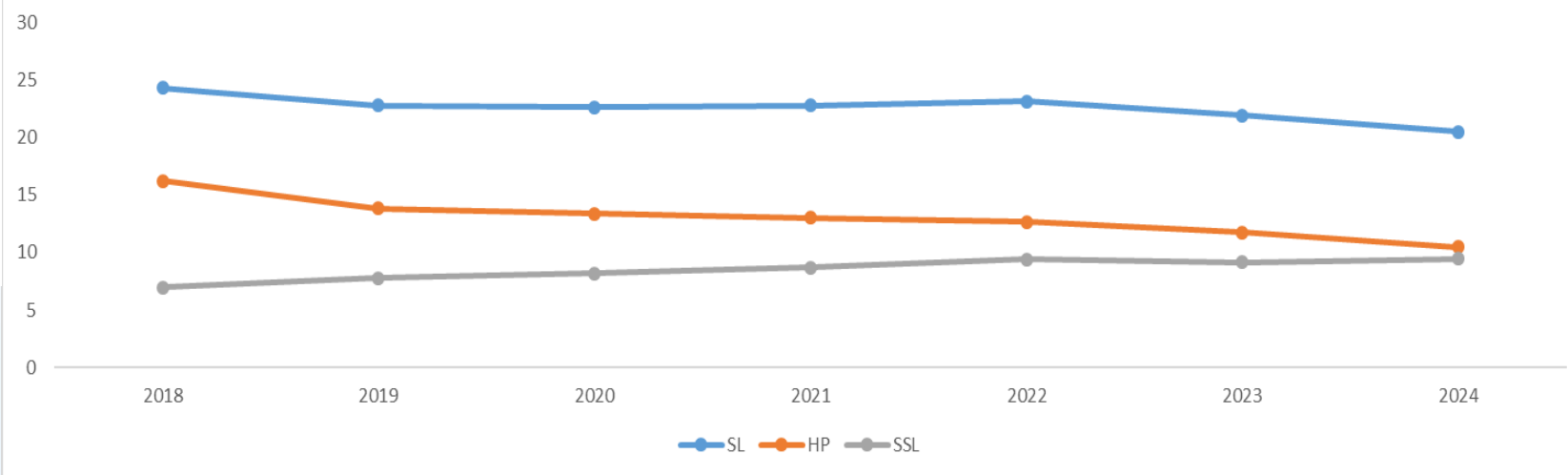
greater detection by endoscopist; increasing awareness by pathologist

Svit

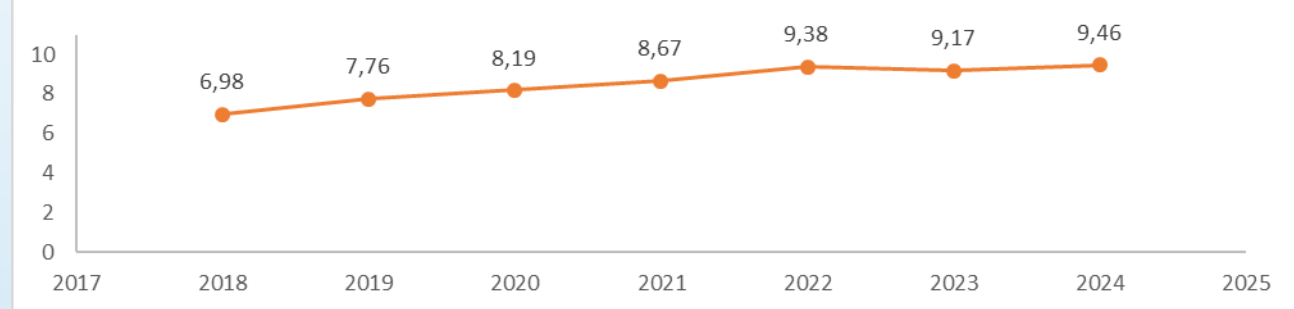


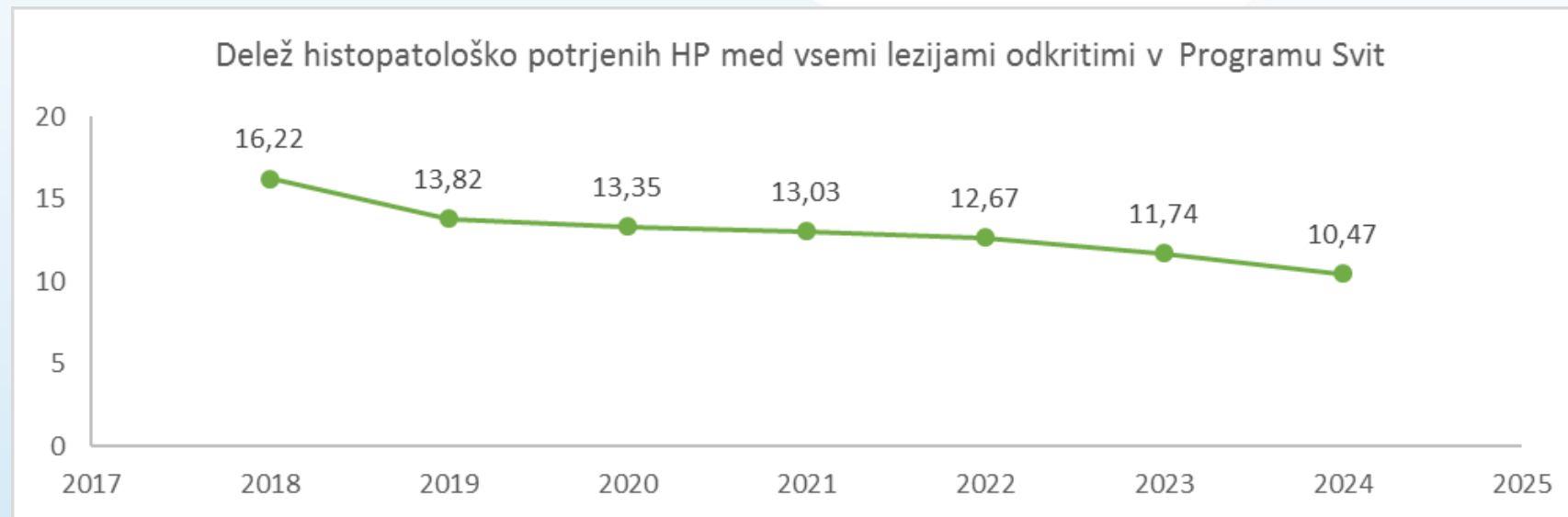
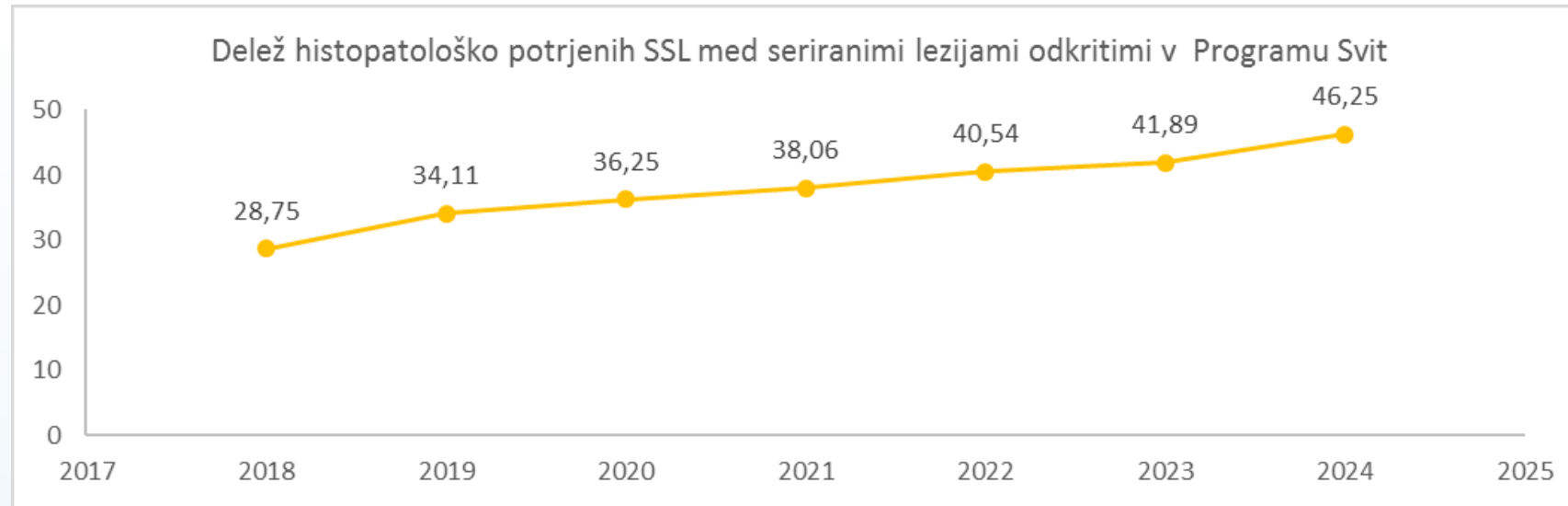
NE BOJTE SE SVETA TAM ZNOTRAJ!

Delež histopatološko potrjenih SL, HP in SSL med vsemi lezijami odkritimi v Programu Sviti



Delež histopatološko potrjenih SSL med vsemi lezijami odkritimi v Programu Sviti





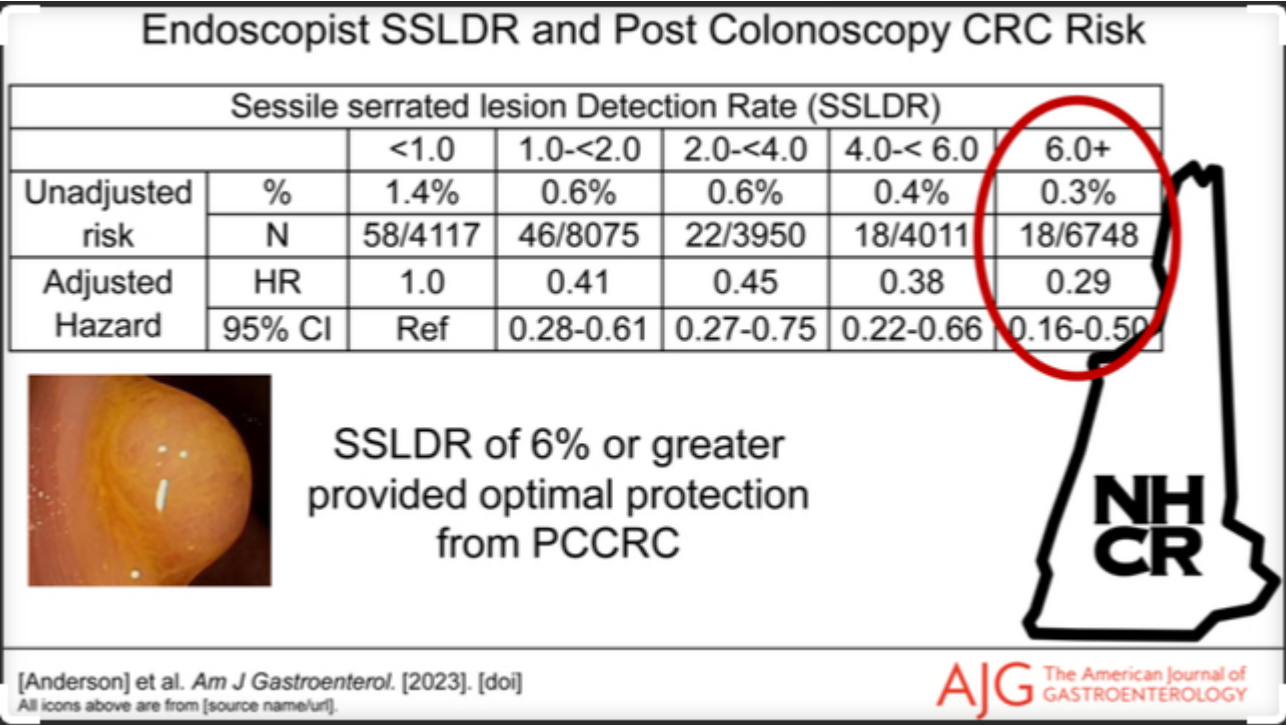
Higher Serrated Polyp Detection Rates are Associated with Lower Risk for Post Colonoscopy Colorectal Cancer: Data From the New Hampshire Colonoscopy Registry

Joseph C Anderson, M.D.^{1,2}, Douglas K Rex⁵, Todd A Mackenzie, PhD¹, William Hisey, M.Sc.^{3,4}, Christina M Robinson, M.S.^{3,4}, Lynn F Butterly, M.D.^{1,3,4,*}

Odkritje „serirane poti“ nastanka RDČD in izboljšana prepoznava SSL v zadnjih desetletjih je prispevala k znižanju incidence RDČD.

Nedavna raziskava več kot 300 000 kolonoskopij je pokazala, da je tveganje za RDČD po kolonoskopiji nižje pri endoskopistih z višjo stopnjo odkrivanja SSL v primerjavi s tistimi z nižjo stopnjo odkrivanja SSL in podobno stopnjo odkrivanja adenomov.

To nakazuje pomembno obratno povezavo med odkrivanjem in odstranitvijo SSL ter pojavnostjo intervalnih kolorektalnih rakov.



Endoskopske korelacije

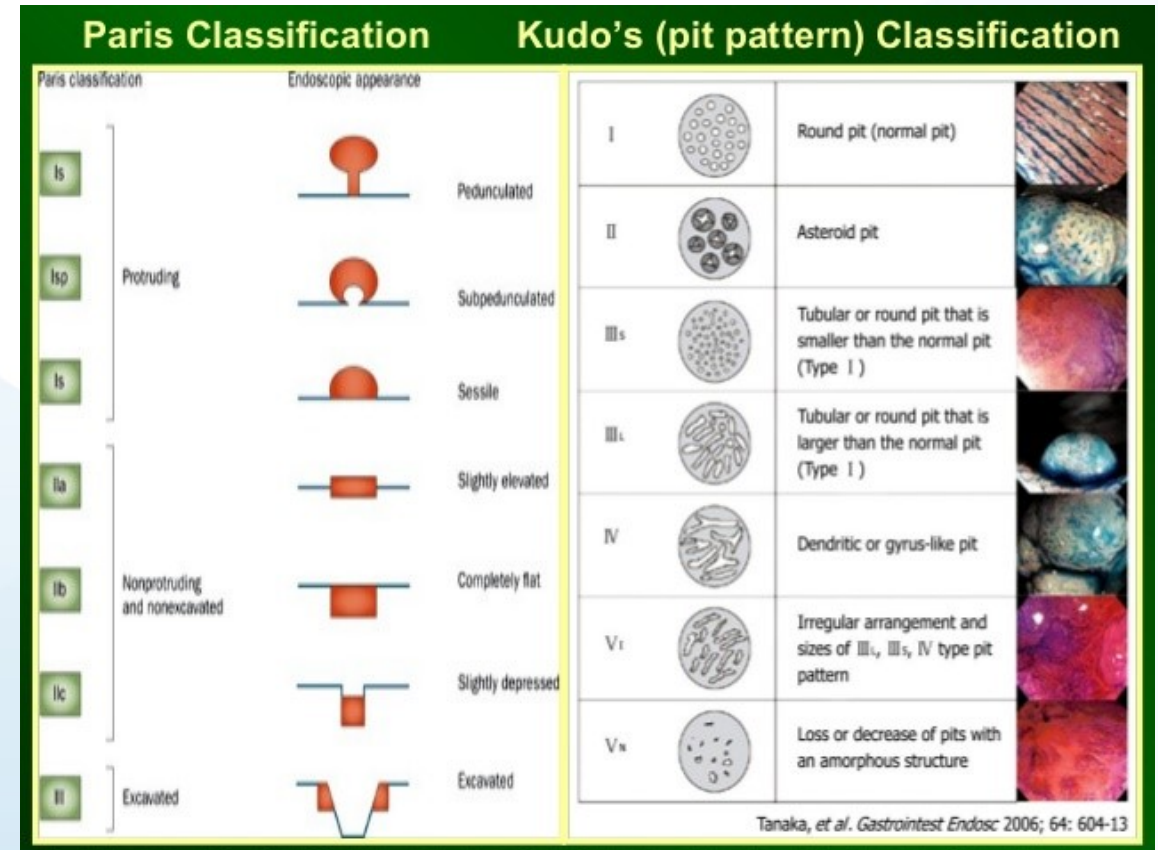
Pravilna prepoznavna sprememb pri endoskopski preiskavi je ključna za obravnavo bolnika in odločitve o načinu zdravljenja

Endoskopski sistemi klasifikacije polipov:

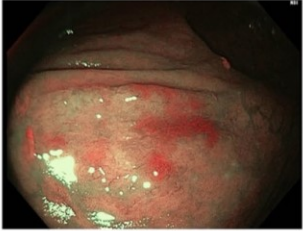
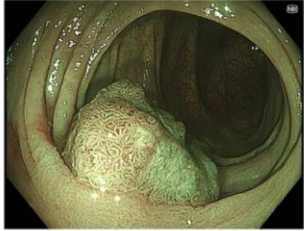
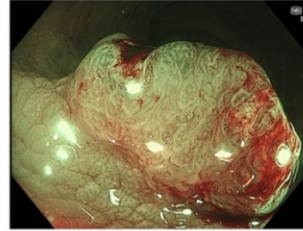
- ✓ Paris classification (modest agreement)
- ✓ Kudo pit pattern classification
- ✓ virtual chromoendoscopy (NBI) – NICE & JNET classification

Table 2. Kudos Pit pattern classification

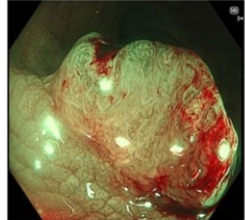
Kudo pit pattern	Description	Associated histology
I	round and normal	Normal
II	stellate	Serrated or inflammatory polyps
III _S	round, tubular, and smaller than type I	Tubular adenoma
III _L	round, tubular, and larger than type I	Tubular adenoma
IV	dendritic or gyrus-like	Villous adenoma
V _N	nonstructured or amorphous	Invasive neoplasm
V _I	irregular arrangement	Invasive neoplasm



Endoscopic correlations

NICE	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures	Has area(s) of disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structures surrounded by brown vessels	Amorphous or absent surface pattern
Most likely pathology	<u>Hyperplastic/sessile serrated polyp</u>	<u>Adenoma (LGD, HGD, superficial submucosal carcinoma)</u>	<u>Deep submucosal invasive cancer</u>
Endoscopic image			

accuracy close to 100%

JNET	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	Invisible	Regular caliber Regular distribution (meshed/spiral pattern)	Variable caliber Irregular distribution	Loose vessel areas Interruption of thick vessels
Surface pattern	Regular dark or white spots Similar to surrounding normal mucosa	Regular (tubular/branched/papillary)	Irregular or obscure	Amorphous areas
Most likely pathology	<u>Hyperplastic/sessile serrated polyp</u>	<u>Low grade adenoma</u>	<u>High grade intramucosal neoplasia/superficial submucosal cancer T1a</u>	<u>Deep submucosal invasive cancer</u>
Endoscopic image				

accuracy for 2a and 2b close to 90%

Sistem NICE natančno razvrsti večji delež lezij, vendar ne omogoča razlikovanja adenomi z displazijo nizke in visoke stopnje.

Klasifikacija JNET se je izkazala za bolj primerno pri odločitvah o ustreznem zdravljenju pri bolnikih z adenomi z nizko- in visoko-stopnjo displazije.

Surveillance after colorectal polyp resection

Sandra Baile-Maxía, Rodrigo Jover*

Bolnike z adenomi premera ≥ 10 mm ali z visoko stopnjo displazije ter bolnike s SSL premera ≥ 10 mm ali z displazijo na splošno obravnavajo kot bolj ogrožene za pojav metakronega RDČD in zato potrebujejo spremljanje.

	ESGE [16]	BSG/ACPGBI/PHE [17]	European Comission [15]	JGES [18]	USMTF [14]
1-2 TA LGD <10mm	Patients not requiring surveillance Routine screening	Low-risk patient (premalignant polyps) Routine screening	Low-risk patients Routine screening	Low-risk patients 3-5 years	1-2 TA <10mm 7-10 years
3-4 TA LGD <10mm					3-4 TA <10 mm 3-5 years
Villous adenoma					Adenoma with villous histology 3 years
TA 10-20mm	Patients requiring surveillance 3 years	High-risk patient (+ ≥ 1 premalignant polyps) 3 years	Intermediate-risk patients 3 years	Intermediate-risk patients 3 years	Adenoma ≥ 10 mm 3 years
Adenoma with HGD					Adenoma with HGD 3 years
5-10 TA <10mm LGD		High-risk patient 3 years			5-10 TA <10 mm 3 years
AT ≥ 20 mm		High-risk patient (+ ≥ 1 premalignant polyps) 3 years			Adenoma ≥ 10 mm 3 years
>10 TA <10mm LGD		High-risk patient 3 years			>10 adenomas 1 year

Table 1

Recommendations on post-polypectomy surveillance intervals after excision of adenomas according to major societies. ESGE: European Society of Gastrointestinal Endoscopy; BSG/ACPGBI/PHE: British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England; JGES: Japanese Gastroenterological Endoscopy Society; USMTF: United States Multi-Society Task Force; TA: tubular adenoma; LGD: low-grade dysplasia; HGD: high-grade dysplasia.

	ESGE [16]	BSG/ACPGBI/PHE [17]	European Comission [15]	JGES [18]	USMTF [14]		
Distal HP 1-5mm*	Patients not requiring surveillance Routine screening	Non-premalignant polyp Routine screening	Low risk Routine screening		≤20 HP in rectum or sigmoid colon <10mm 10 years		
1-5 distal HP 5-10mm*		Low-risk patient (premalignant polyps) Routine screening					
5-20 distal HP 5-10mm*		High-risk patient 3 years					
1-5 proximal HP <10mm**		Low-risk patient (premalignant polyps) Routine screening			≤20 HPs proximal to sigmoid colon <10mm 10 years		
5-20 proximal HP <10mm**		High-risk patient 3 years					
1-2 SP <10 mm		Low-risk patient (premalignant polyps) Routine screening				Any SSP 3-5 years	1-2 SSPs <10 mm 5-10 years
3-4 SP <10 mm							3-4 SSPs <10 mm 3-5 years
5-10 SP <10mm							High-risk patient 3 years
HP ≥10 mm	Patients requiring surveillance 3 years	High-risk patient (+ ≥1 premalignant polyps) 3 years	Intermediate risk 3 years	HP ≥10 mm 3-5 years			
SP ≥10 mm				SSP ≥10 mm 3 years			
SP with dysplasia				SSPs with dysplasia 3 years			
TSA				TSA 3 years			

*Distal: rectum or sigmoid colon. **Proximal: proximal to sigmoid colon

Table 2

Recommendations on post-polypectomy surveillance intervals after polypectomy of serrated lesions according to major societies. ESGE: European Society of Gastrointestinal Endoscopy; BSG/ACPGBI/PHE: British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England; JGES: Japanese Gastroenterological Endoscopy Society; USMTF: United States Multi-Society Task Force; HP: hyperplastic polyp; SP: serrated polyp; SSP: sessile serrated polyp; TSA: traditional serrated adenoma.

Zaključki

1. Serirane lezije vključujejo hiperplastični polip (HP), sesilno serirano lezijo (SSL) in tradicionalni nazobčani adenom (TSA)
2. Histopatološka opredelitev je zahtevna, histološke značilnosti se prekrivajo, v istem polipu lahko vidimo prehode med HP in SSL ali SSL in TSA
3. Serirane lezije napredujejo po dveh molekularnih poteh (BRAF, KRAS mutacije)
4. SSL so prekursor predvsem mikrosatelitno nestabilnih (MSI-H), BRAF mutiranih, desnostranskih karcinomov (dobra prognoza)
5. TSA so prekursor mikrosatelitno stabilnih (MSS), BRAF mutiranih rakov (slaba prognoza)
6. SSL z displazijo je napredovala lezija ne glede na stopnjo displazije
7. Odkrivanje in odstranjevanje seriranih polpov zničuje incidenco RDČD



Hvala !