Croatia and the EU:
Together
Against Cancer

IMPROVEMENT OF QUALITY OF THE NATIONAL CANCER SCREENING PROGRAMMES IMPLEMENTATION (CRO SCREENING)

MINISTRY OF HEALTH OF THE REPUBLIC OF LITHUANIA

NCI

LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

CPVA

NIJZ
Nacionalni institut za javno zdravje

Ministry of Health

HZJZ

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Croatia and the EU: Together Against Cancer

Quality indicators for colonoscopy and colonoscopist

Mirjana Kalauz

Clinical Hospital Center Zagreb

Why is quality monitoring important in CRC screening programme?

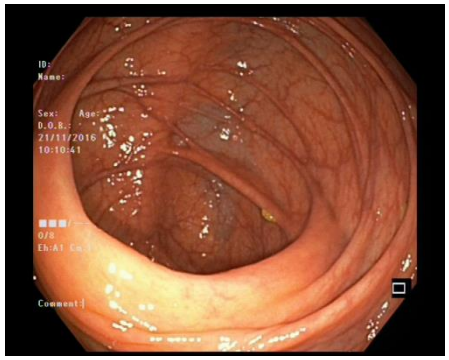
- Quality adjustment in all endoscopic centers
- Better outcomes measures of programme (decreased incidence of CRC, decreased mortality from CRC)
- Quality standards implementation and monitoring is important for accreditation process
- Improving quality in endoscopy in symptomatic patients

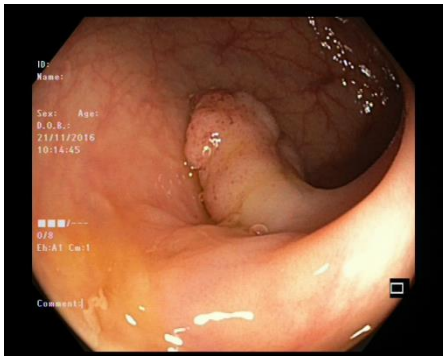
OBJECTIVES

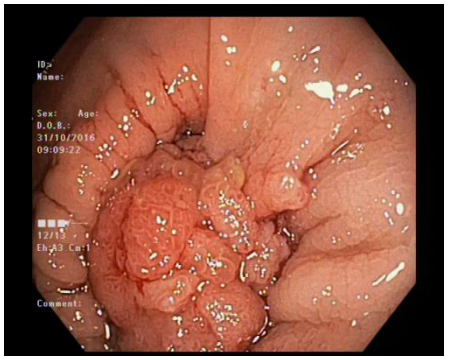
- Review protective effect of colonoscopy against CRC
- Review factors associated with interval cancers
- Discuss colonoscopy quality measures
- Propose quality indicators parameters in screening programe in Croatia (and to be included in new guidelineses)

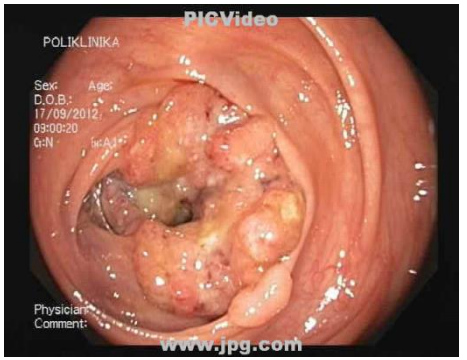
Colonoscopy is the best test for polyp & adenoma detection

- The gold standard for colorectal cancer screening/surveillance
- Outperforms CT and MR colonography

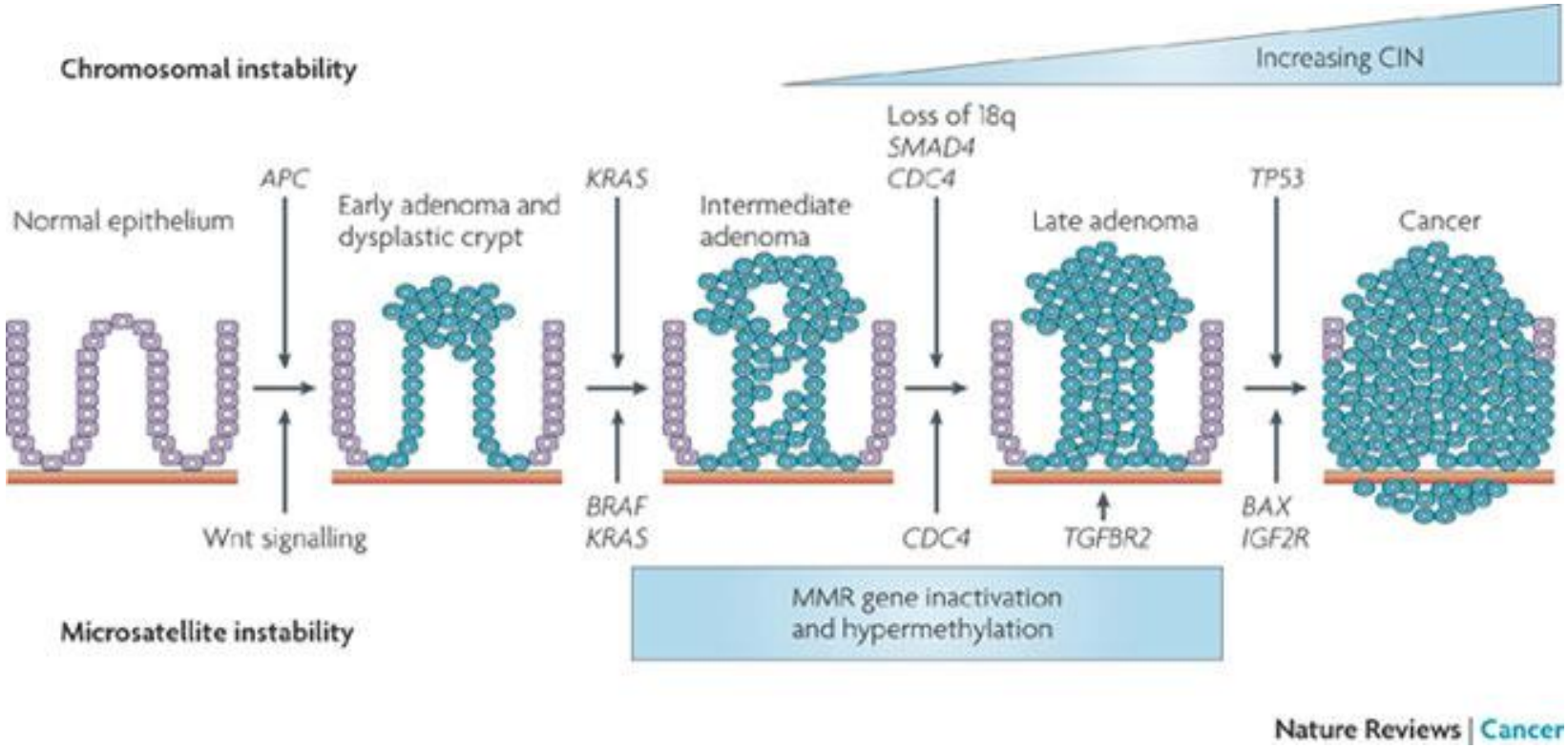








Normal mucosa Early adenoma Late adenoma Cancer

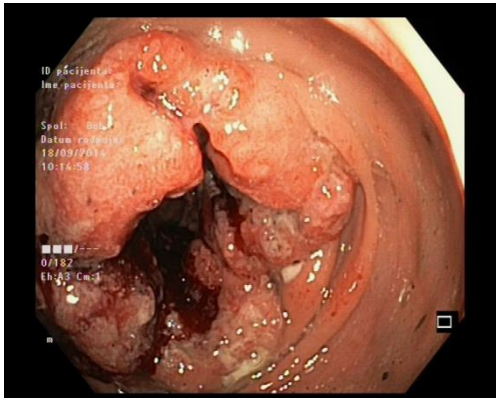


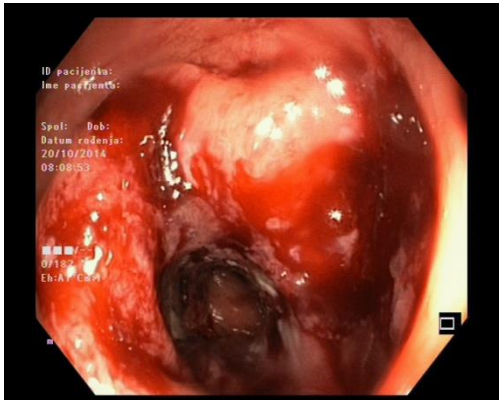
Colonoscopy prevents CRC and CRC mortality

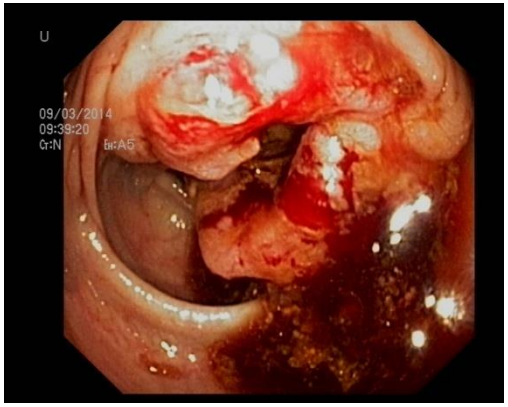
Author year	Country	Design	Primary endopoint	Residual risk
Kahl 2009	U.S.	Cohort	Incidence	0,33
Baxter 2009	Canada	Case-control	Mortality	0,63
Mulder 2010	Netherlands	Case-control	Incidence	0,56
Singh 2010	Canada	Cohort	Mortality	0,71
Brenner 2011	Germany	Case-control	Incidence	0,23
Baxter 2012	U.S.	Case-control	Mortality	0,40

Interval colon cancer occur

- Reduction of mortality to far from zero
- Diagnosed after colonoscopy, within interval until next colonoscopy (PCCRC)
- N=727 (0,27%)
  - Corley NEJM 2010







Interval CRC

- 3.4% to 9% of all CRC cases
- primarily in the right colon
- Endoscopist-related variables are the most important risk factor for interval CRC
- 71% to 86% attributable to missed or incompletely resected polyps

Bressler et al. Gastroenterology 2007; 132:96-102
Singh et al. Am J Gastroenterol 2010; 105: 2588-96
Farrar et al. CGH 2006: 4:1259-64
Cooper et al. Cancer 2012; 118: 3044-52
Robertson et al. Gut 2014; 63: 949-56
Pohl et al. CGH 2010; 8: 858-64.

Lower Protection in the Right Colon

Author, year	Outcome	Overall CRC (95% CI)	Left-sided CRC (95% CI)	Right-sided CRC (95% CI)
Baxter, 2009 Ontario, Canada	CRC Mortality (OR)	**0.63 (0.57-0.69)**	**0.33 (0.28-0.39)**	**0.99 (0.86-1.14)**
Singh, 2010 Manitoba, Canada	CRC Mortality (SMR)	**0.71 (0.61-0.82)**	**0.53 (0.42-0.67)**	**0.94 (0.77-1.17)**
Brenner, 2011 Rhine-Neckar, Germany	CRC Incidence (OR)	**0.23 (0.19-0.27)**	**0.16 (0.12- 0.20)**	**0.44 (0.35-0.55)**
Baxter, 2012 SEER-Medicare	CRC Mortality (OR)	**0.40 (0.37-0.43)**	**0.24 (0.21-0.27)**	**0.58 (0.53-0.64)**

Baxter et al. Ann Inter Med 2009; 150: 1-8

Singh et al. Gastroenterology 2010;139:1128–37

Brenner et al. Ann Inter Med 2011;154: 22–30

Baxter et al. J Clin Oncol 2012; 30:2664-9.

Incomplete Resection: CARE study

- 346 polyps 5-20 mm, margins biopsied
- IRR for neoplastic polyps: 10.1%
- more common for:
  - Large vs. small neoplastic polyps

    (17.3% vs 6.8%; *P=0.003)*
  - SSA/P vs other neoplastic polyps

    (31.0% vs 7.2%; *P<0.001)*
- Nearly half (47.6%) of all large (10–20 mm) SSA/P incompletely removed.

Pohl et al. Gastroenterology 2013;144:74–80

Factors affecting right-sided protection

- **REVERSIBLE:**
  Bowel prep (split is now standard of care)
  Operator Dependent
    - Cecal Intubation
    - Withdrawal time and technique
    - Adenoma detection
    - Detection of flat and depressed (non-polypoid) neoplasms
    - Detection of serrated lesions
    - Complete polypectomy
    - Operator specialty

- **IRREVERSIBLE:**
  Tumor Biology

Rex.Gastroenterology 2011; 140: 19-21
Rex et al. Am J Gastro 2015; 110: 72-90

Colonoscopy quality measures
Preprocedure

Preprocedure

1. Frequency with which colonoscopy is performed for an indication that is included in a published standard list of appropriate indications, and the indication is documented	Process	>80%
2. Frequency with which informed consent is obtained, including specific discussions of risks associated with colonoscopy, and fully documented	Process	>98%
3. Frequency with which colonoscopies follow recommended post-polypectomy and post-cancer resection surveillance intervals and 10-year intervals between screening colonoscopies in average-risk patients who have negative examination results and adequate bowel cleansing (priority indicator)	Process	≥90%
4. Frequency with which ulcerative colitis and Crohn's colitis surveillance is recommended within proper intervals	Process	≥90%

Colonoscopy quality measure Intraprocedure

Intraprocedure

5. Frequency with which the procedure note documents the quality of preparation	Process	>98%
6. Frequency with which bowel preparation is adequate to allow the use of recommended surveillance or screening intervals	Process	≥85% of outpatient exams
7. Frequency with which visualization of the cecum by notation of landmarks and photodocumentation of landmarks is documented in every procedure (priority indicator)	Process	
Cecal intubation rate with photography (all examinations)		≥90%
Cecal intubation rate with photography (screening)		≥95%
8. Frequency with which adenomas are detected in asymptomatic average-risk individuals (screening) (priority indicator)	Outcome	
Adenoma detection rate for male/female population		≥25%
Adenoma detection rate for male patients		≥30%
Adenoma detection rate for female patients		≥20%
9a. Frequency with which withdrawal time is measured	Process	>98%
9b. Average withdrawal time in negative-result screening colonoscopies	Process	≥6 min
10. Frequency with which biopsy specimens are obtained when colonoscopy is performed for an indication of chronic diarrhea	Process	>98%
11. Frequency of recommended tissue sampling when colonoscopy is performed for surveillance in ulcerative colitis and Crohn's colitis	Process	>98%
12. Frequency with which endoscopic removal of pedunculated polyps and sessile polyps <2 cm is attempted before surgical referral	Outcome	>98%

Colonoscopy quality measures Postprocedure

Postprocedure

13. Incidence of perforation by procedure type (all indications vs colorectal cancer screening/polyp surveillance) and post-polypectomy bleeding	Outcome	
Incidence of perforation—all examinations		<1:500
Incidence of perforation—screening		<1:1000
Incidence of post-polypectomy bleeding		<1%
14. Frequency with which post-polypectomy bleeding is managed without surgery	Outcome	≥90
15. Frequency with which appropriate recommendation for timing of repeat colonoscopy is documented and provided to the patient after histologic findings are reviewed.	Process	≥90

Review of selected colonoscopy quality measures

- Cecal Intubation Rate
- Withdrawal Time
- Adenoma Detection Rate

Cecal Intubation Rate

- Fundamental step to assess colonoscopy completeness and quality
- Effective endoscopists should be able to achieve rates of ≥ 90% in all cases, and ≥ 95% in screening colonoscopies
- Risk of interval CRC decreased if CIR ≥ 95% compared to < 80%

Baxter et al. Gastroenterology 2011; 140: 65-72.

Withdrawal Time

- Detection of lesions is increased when average withdrawal time is ≥ 6 minutes

- UK study with > 31,000 colonoscopies:

  - Colonoscopists with WT < 7 min had ADR 42.5%, versus WT > 11 min had ADR 47.1% (p< 0.001)

  - No incremental yield beyond WT of 10 min

Lee et al. Endoscopy 2013; 45: 20-6

Withdrawal Time

- Study from Minnesota,
  - 77,000 screening colonoscopies by 51 MDs
  - Longer mean WT associated with higher ADR (3.6% per minute)
  - Interval CRC: Compared with WT ≥6 min, the adjusted incidence rate ratio for WT <6 minutes was 2.3 (95% CI: 1.5−3.4; *P* < .0001).

Shaukat et al. Gastroenterology 2015

Withdrawal Time

- Longer withdrawal time implies careful, more thorough colon mucosa inspection
- Better technique almost invariably requires more time: Cleansing, distention, examination of proximal side of folds
- Despite increased detection of polyps with longer WT, WT still secondary to ADR, especially for high-level detectors
- WT may be most relevant to correct the performance of physicians with low ADR.

Rex et al. Am J Gastro 2015; 110: 72-90.

Adenoma Detection Rate

- ADR = Surrogate measure for CRC incidence and interval CRC incidence
- originally based on large variability in adenoma detection between endoscopists
- Proportion of screening colonoscopies where at least one adenoma is detected
- **Targets:**

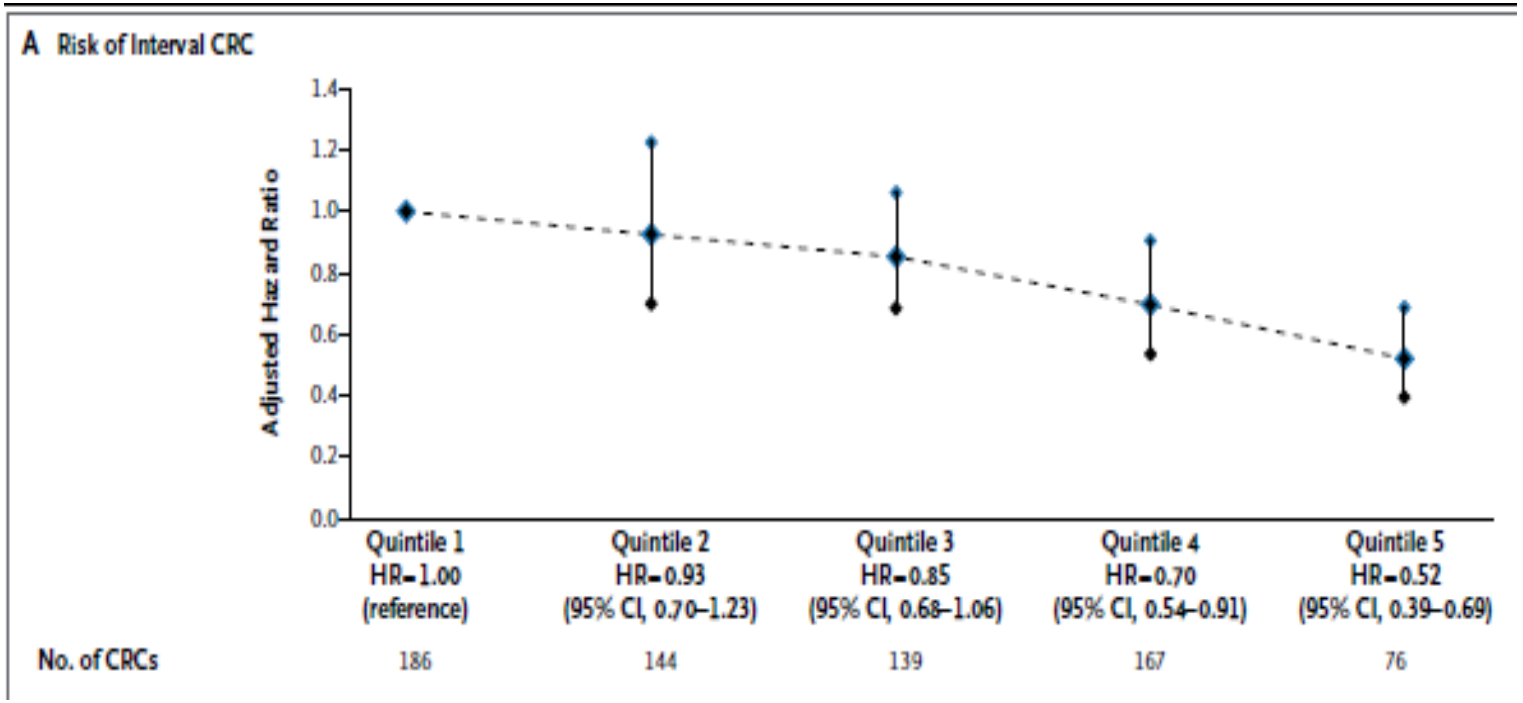
  Men: ≥ 30%

  Women: ≥ 20%

  Mixed male/female population: ≥ 25%

Rex et al. Am J Gastro 2015; 110: 72-90.

We should care if adenomas are missed!!!
Risk of CRC is reduced with higher ADR



Corley et al. NEJM 2014, Kaminsky et.al NEJM 2010

Polyp Detection Rate

- PDR = Surrogate measure for ADR
- Advantage: No need for manual pathology entry, collected automatically with procedure reports/billing
- Correlates well with ADR

William et al. Gastrointest Endosc 2012; 75: 576-82

Limitations:

- Surrogate of a surrogate
- Even more corruptible than ADR

Fayad and Kahi CGH 2014; 12: 1973-80.

Adenoma Per Colonoscopy (APC) Rate

- Total number of adenomas divided by total number of screening colonoscopies
- Better "global" measure of adenoma detection

  - 42,000 colonoscopies, 316 French endoscopists
  - For MDs with ADR around 35%, APC varied from 0.36 to 0.98

  Denis et al. Dig Liv Dis 2014; 46:176-81

- Overcomes "one and done" issue with standard ADR

Limitations:

- Could increase costs if providers have to submit adenomas in separate bottles
- Additional validation studies needed.

Not just adenomas...

Pathway	Frequency	Genes	MSI	Precursor	Speed
CIN	65% to 70%	APC K-ras p53	No	Adenoma	Slow
Lynch	3%	MLH1 MLH2 MLH6 PMS2	Yes	Adenoma	Fast
CIMP	30% to 35%	BRAF	Sometimes	Serrated	Can be fast

Rex DK, et al.[5]

Molecular basis of colorectal cancer

Basic Molecular Pathways in CRC

- Chromosomal Instability (CIN) Pathway---60%-70%

  - Adenoma-carcinoma sequence

- Mutator Pathway---5%
  - Defective DNA mismatch repair (*hMLH1, hMSH2, hMSH6, hPMS2*)
  - Microsatellite instability (MSI)
  - Example: Lynch syndrome

- Serrated pathway---25%-35%

  - *BRAF* oncogene mutations

  - Epigenetic DNA promoter hypermethylation leading to the CpG island methylator phenotype (CIMP)

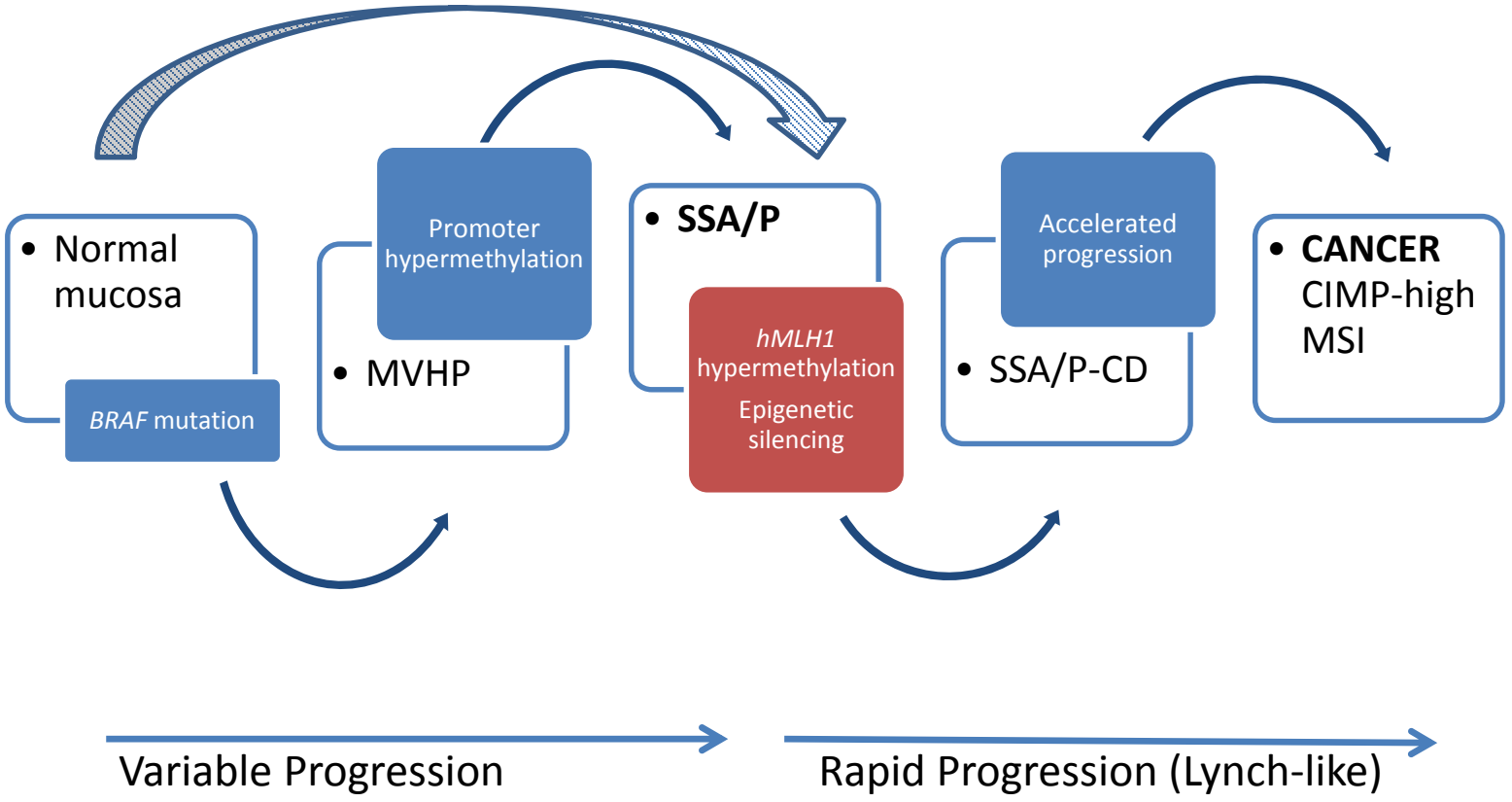
  - MSI +/-

WHO Classification of Serrated Colonic Lesions

- Hyperplastic Polyp
  - Microvesicular HP (MVHP)
  - Goblet-cell rich HP (GCHP)
  - Mucin-poor HP (MPHP)
- Sessile Serrated Adenoma/Polyp (SSA/P)
  - SSA/P without cytological dysplasia
  - SSA/P with cytological dysplasia
- Traditional Serrated Adenoma (TSA)

Snover D, et al. WHO classification of tumours. Pathology and genetics. Tumours of the digestive system. 4th edition. Berlin: Springer-Verlag. 2010.

“Main” Serrated Pathway



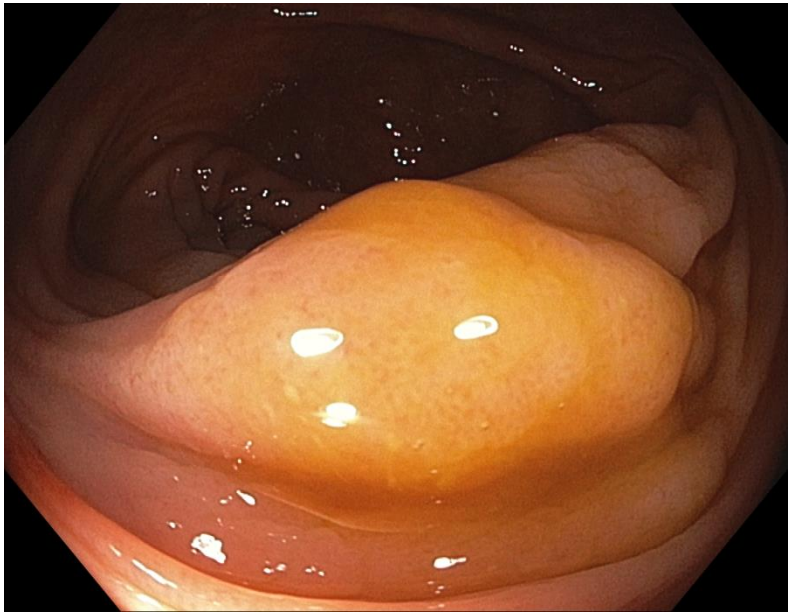
Snover D, et al. WHO classification of tumours. Pathology and genetics. Tumours of the digestive system. 4th edition. Berlin: Springer-Verlag. 2010.

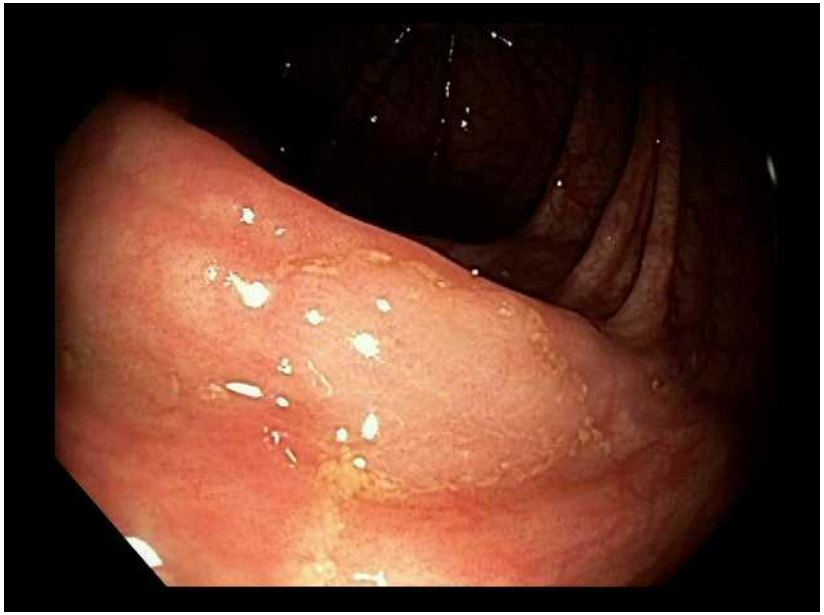
Kahi C. Dig Dis Sci 2015; 60: 773-80.

SSA/P: Most prevalent visual descriptors

- Mucus cap (64%)
- Rim of debris or bubbles (52%)
- Alteration of the contour of a fold (37%)
- Interruption of underlying mucosal vascular pattern (32%)

Tadepalli et al. Gastrointest Endosc 2011; 74: 1360-8





Serrated Pathway and Interval CRC: Overlap of Molecular Signatures

Compared to non-interval CRC, interval CRC more likely to:

- Be located in the proximal colon
- Demonstrate MSI
- Be associated with CIMP

Sawhney et al. Gastroenterology 2006; 131: 1700-5

Arain et al. Am J Gastroenterol 2010; 105: 1189-95

Nishihara et al. NEJM 2013; 369: 1095-1105.

- Nurses' Health Study and the Health Professionals Follow-up Study
  - 88,902 subjects, 22-year follow-up
  - Cancers diagnosed within 5 years of colonoscopy twice more likely to have CIMP and microsatellite instability

Nishihara et al. NEJM 2013; 369: 1095-1105.

Variable detection of proximal serrated lesions

Author (year)	N screening colons	N endoscopists	N polyps	ADR	PSP-DR
Hetzel (2010)	7192	13	4535	**13.5%-36.4%**	**1.4%-7.6%**
Kahi (2011)	6681	15	11,049	**17%-47%**	**1%-18%**
De Wijker-slooth (2013)	1354	5	1635	**24%-40%**	**6%-22%**
Payne (2014)	7215	32 sites	5548	**17.4%-43.5%**	**0%-9.8%**

Hetzel et al. Am J Gastroenterol. 2010; 105: 2656-64
Kahi et al. Clin Gastroenterol Hepatol. 2011; 42-6
De Wijkerslooth et al. Gastrointest Endosc 2013; 77: 617-23
Payne et al. Clin Gastroenterol Hepatol 2014;12:1119–26.

Quality in colonoscopy in Croatia

- Many endoscopic centers
- Overall quality is unknown
- When quality is unknown, we fear large variations
- European guidelines are slowly appearing
- Bowel cancer screening is main quality target in EU

Quality indicators in colonoscopy in screening program in Croatia Proposal I

- Colonoscopists with sufficient number of conducted colonoscopies (85%>200-300)
- Bowel cleansing (>90% BBPS >6)
- Cecal intubation rate (>90%)
- Colonoscopy withdrawal time (>90% 6 min)
- Adenoma detection rate (M>50%; F>30%)

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Quality indicators in colonoscopy in screening program in Croatia Proposal I

- Left and right colon adenoma detection proportion (L:R 65%:35%)
- Sessile serrated lesion right colon detection rate-SSLR (>4%)
- Mean adenoma per positive procedure - MAP+ (no reference standard)?
- Referral to surgery or tertiary endoscopy (<5%)
- Endoscopic complication rate:
  - Probirna kolonoskopija: 0,5%
  - Terapijska kolonoskopija <2,5%
  - Perforacije koje zahtjevaju kirurško terapiju: <1/1000
  - varenja koja zahtjevaju kirurško terapiju:

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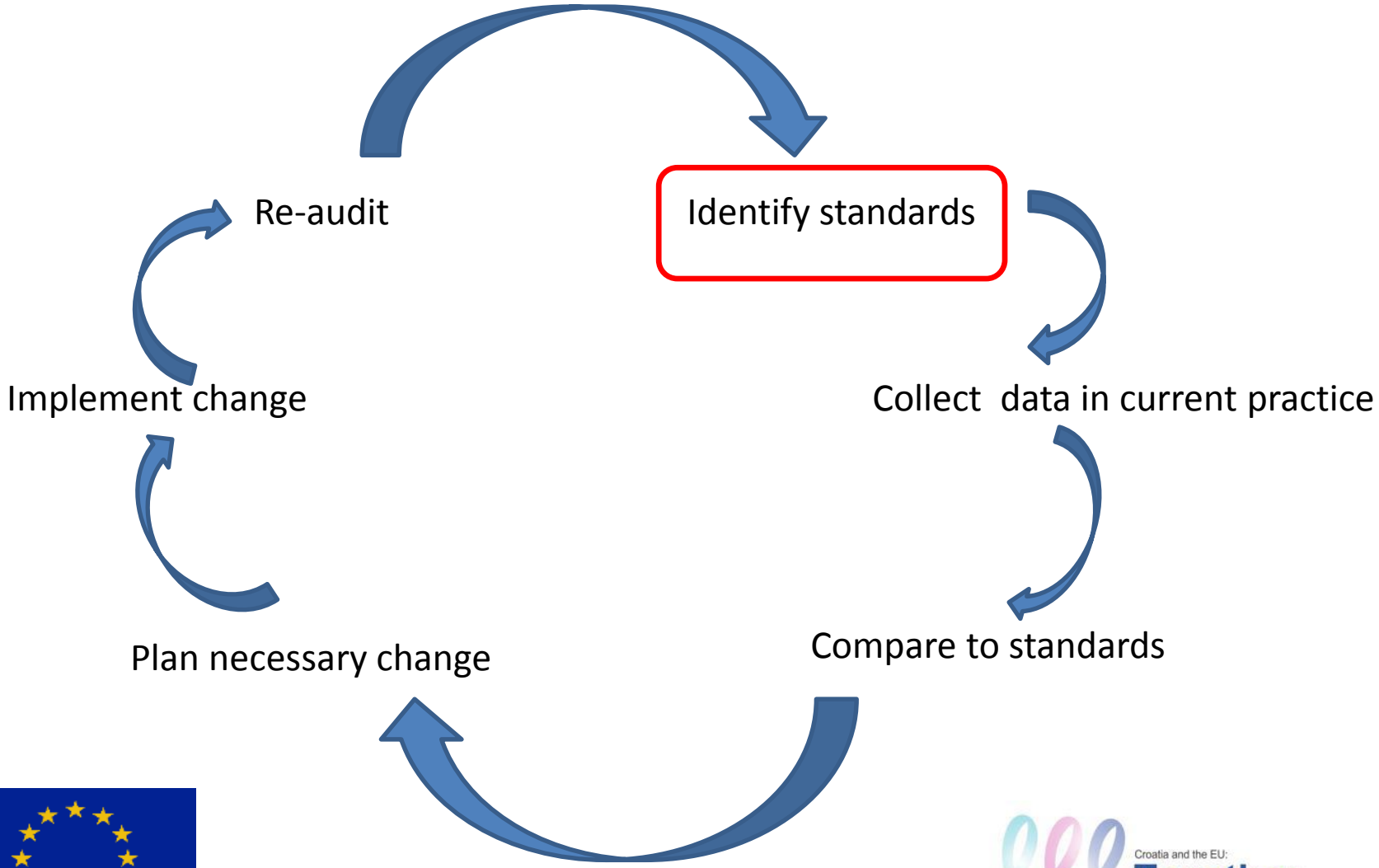

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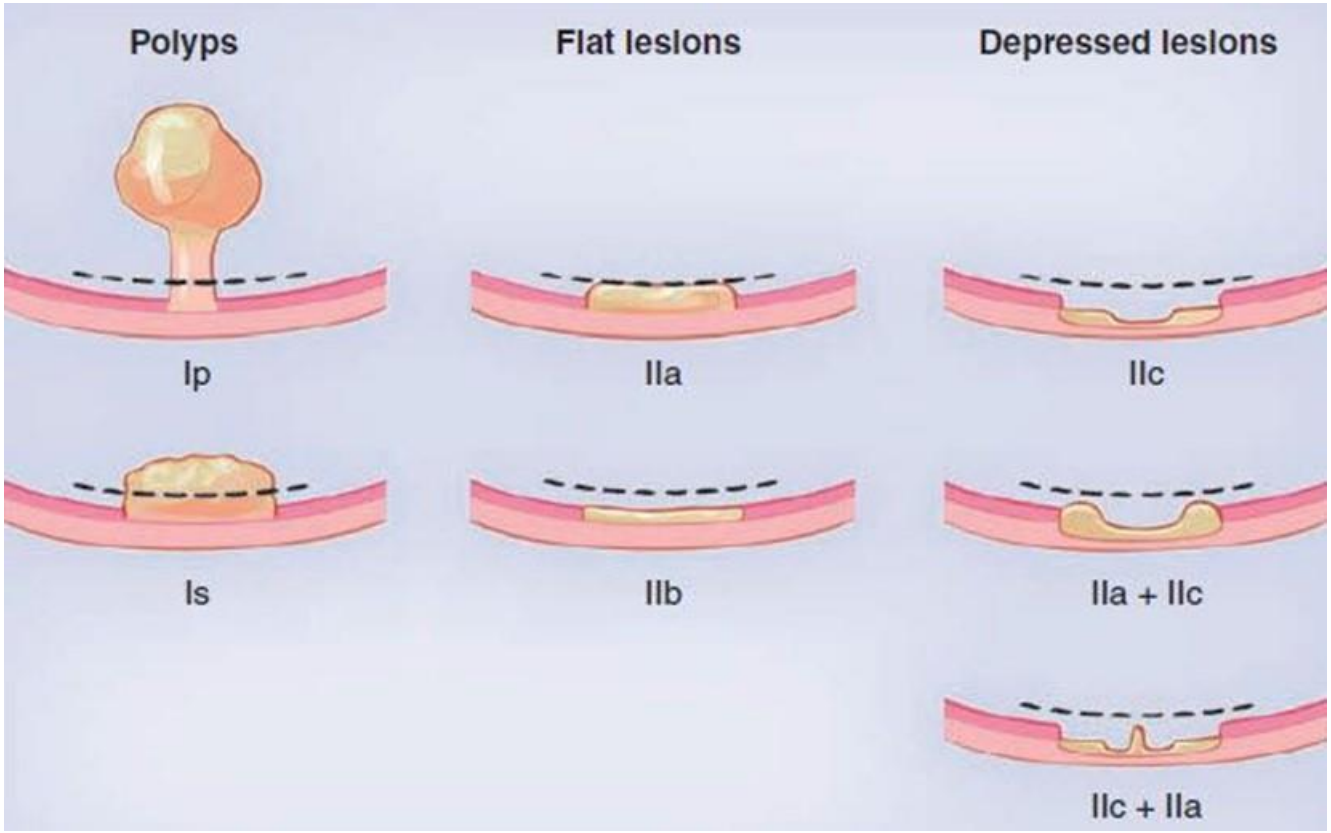
Polyp classification

Mirjana Kalauz
Clinical Hospital Center Zagreb

Polyp classification

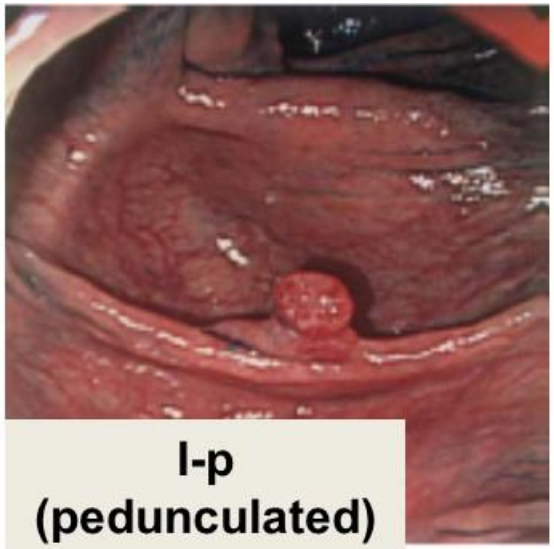
- Paris classification
- Kudo classification
- NICE

Paris classification
Shape of polyp

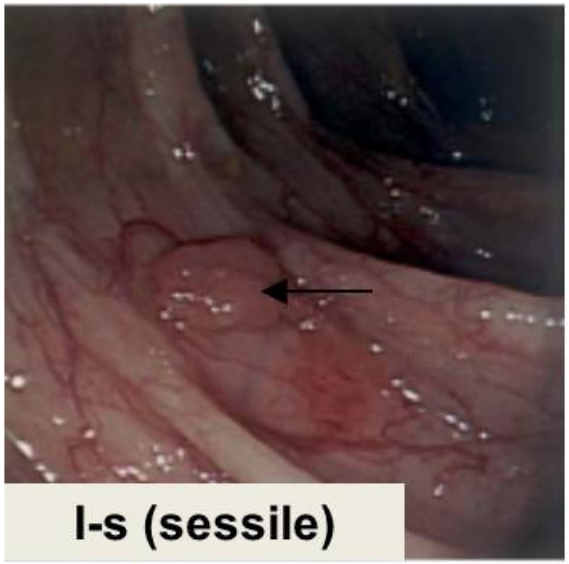


The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. ***Gastrointest. Endosc.*** **58(6 Suppl.), S3–S43 (2003).**

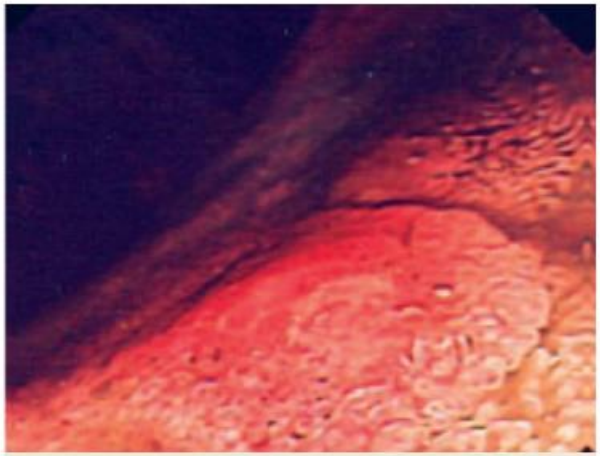
Paris Classification



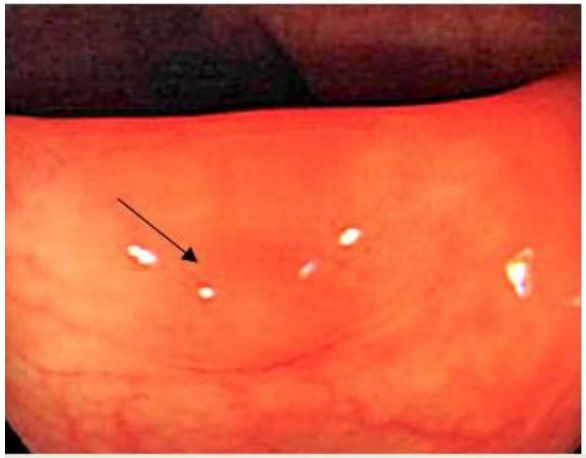
I-p
(pedunculated)



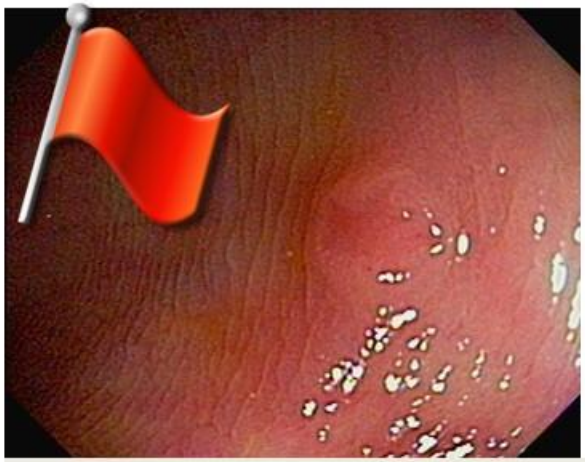
I-s (sessile)



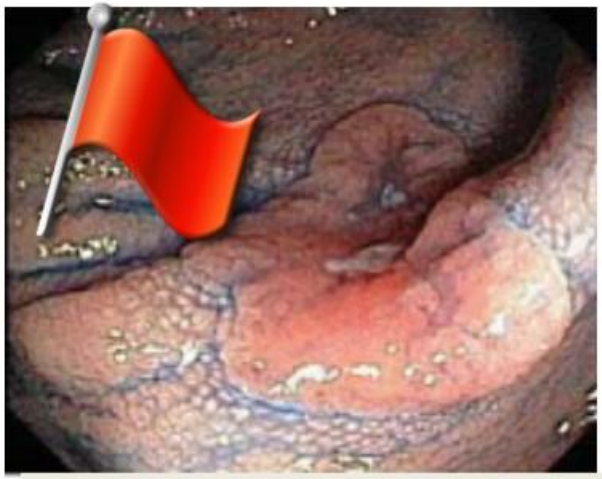
II-a (flat elevated)



II-b (flat flat)



IIc (flat depressed)



III (flat ulcerated)

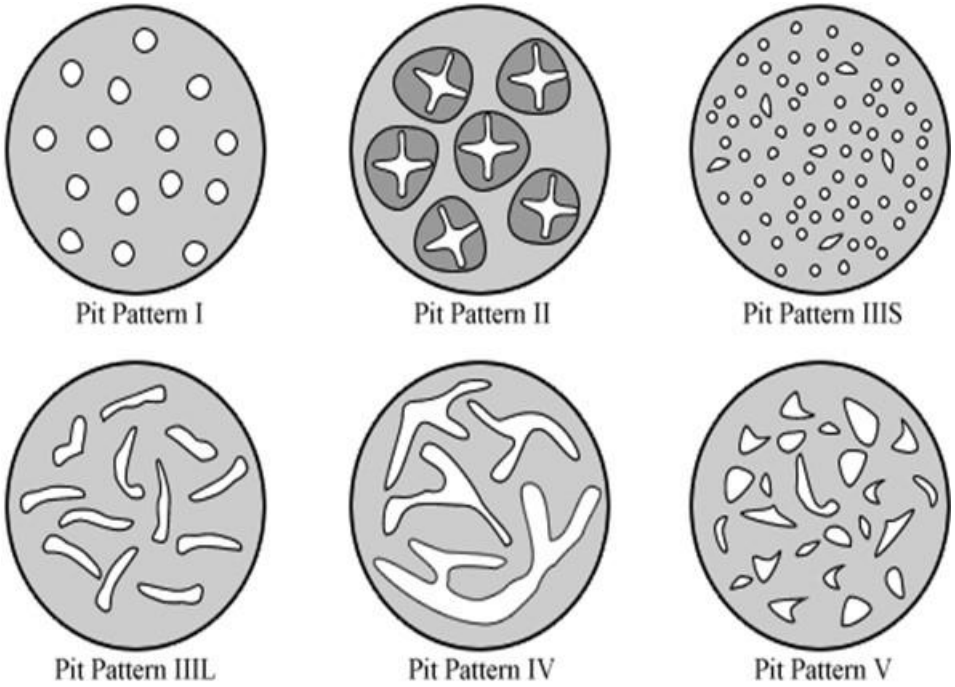
Kudo pit patterns

- Developed for use in chromoendoscopy
  - Indigo carmine remains in depressions (pits)
  - The violet dyes actually stain the mucosa
- Pits = openings of the colonic crypts
- Pit pattern = arrangement of openings on mucosal surface

Kudo pit pattern classification

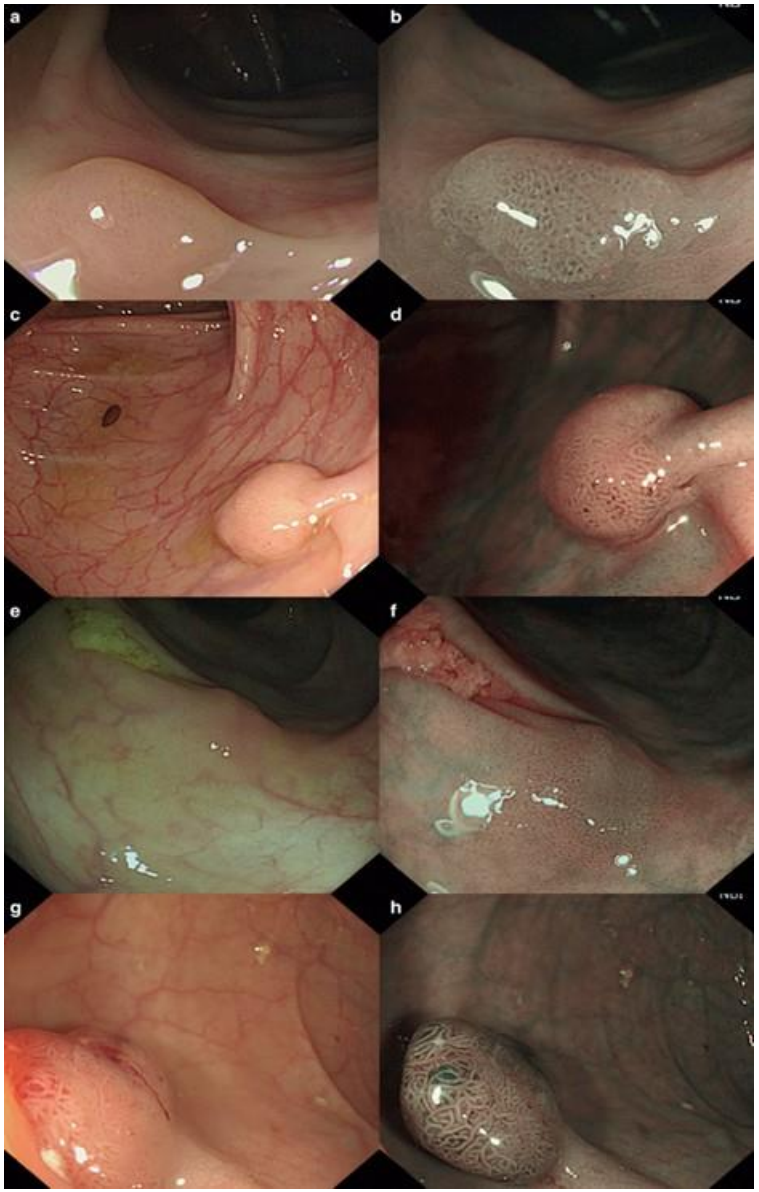
- characteristics of the different pit pattern types

Pit pattern type	Characteristics
I	roundish pits
II	stellar or papillary pits
III S	small roundish or tubular pits (smaller than type I pits)
III L	large roundish or tubular pits (larger than type I pits)
IV	branch-like or gyrus-like pits
V	non-structured pits



Kudo S. Et al. GIE 1996

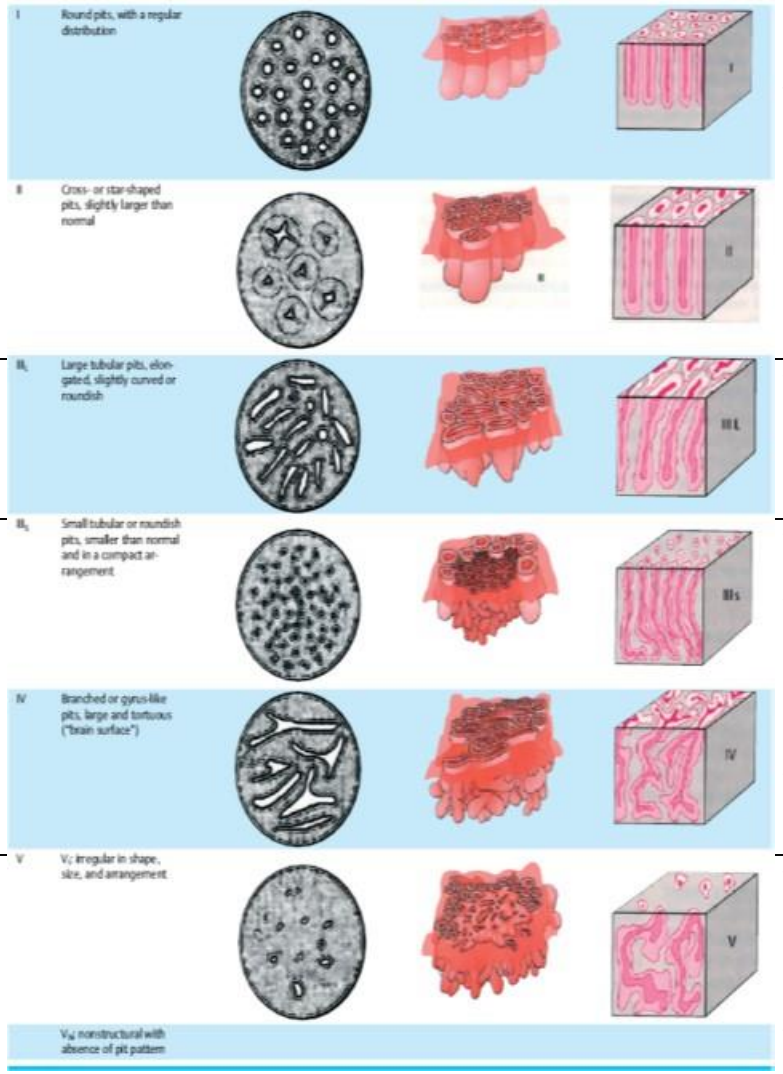
But in real life classification is not really that easy



Kudo pit patterns

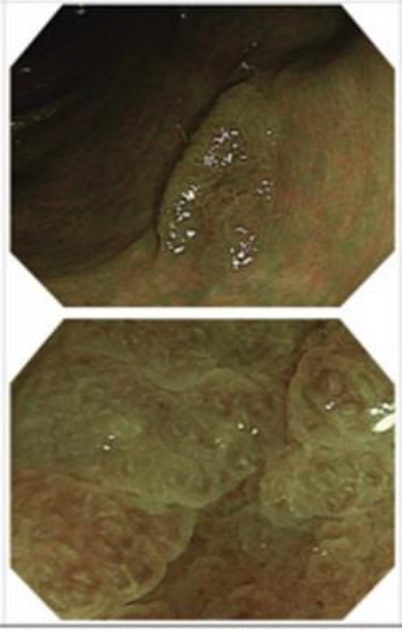
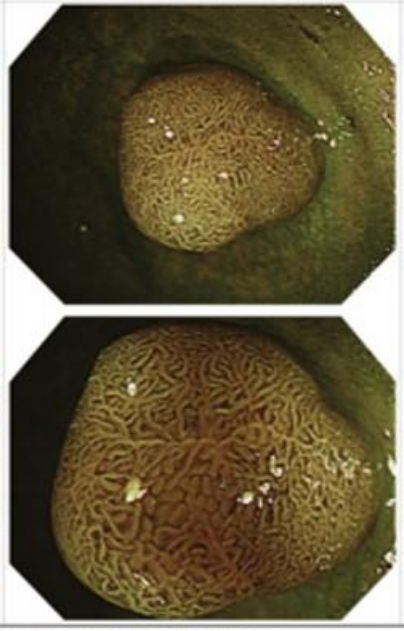
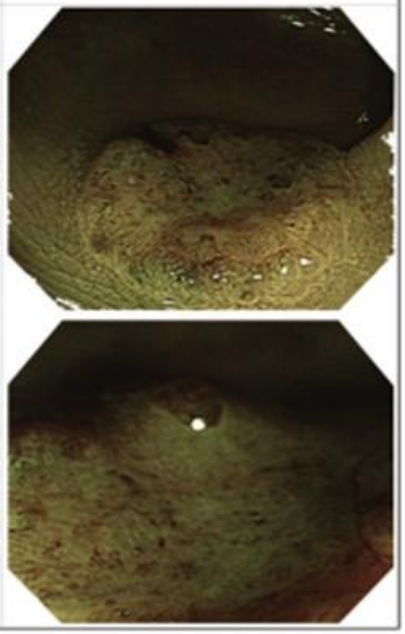
- Technique
  - Feces & mucous must be washed away before staining
  - 2 – 7ml applied to lesion, excess suctioned before observation
    - Spray catheter or syringe injection for indigo carmine
  - Violet dyes require 30 – 60 seconds to stain prior to observation

The Kudo Classification
Pit Patterns



Histology	Management
Hyperplastic	Nothing
Adenoma	Snare polypectomy
High grade adenoma	EMR en bloc or pEMR
Carcinoma	EMR en bloc, ESD, or surgery

NBI International Colorectal Endoscopic (NICE) Classification*

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels 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 structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			

* Can be applied using colonoscopes with or without optical (zoom) magnification

** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.

*** Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Advanced endoscopic imaging: European Society of Gastrointestinal Endoscopy (ESGE) Technology Review

Authors: James E. East[1], Jasper L. Vleugels[2], Philip Roelandt[3], Pradeep Bhandari[4], Raf Bisschops[3], Evelien Dekker[2], Cesare Hassan[5], Gareth Horgan[6], Ralf Kiesslich[7], Gaius Longcroft-Wheaton[4], Ana Wilson[8], Jean-Marc Dumonceau[9]

Institutions: Institutions are listed at end of article.

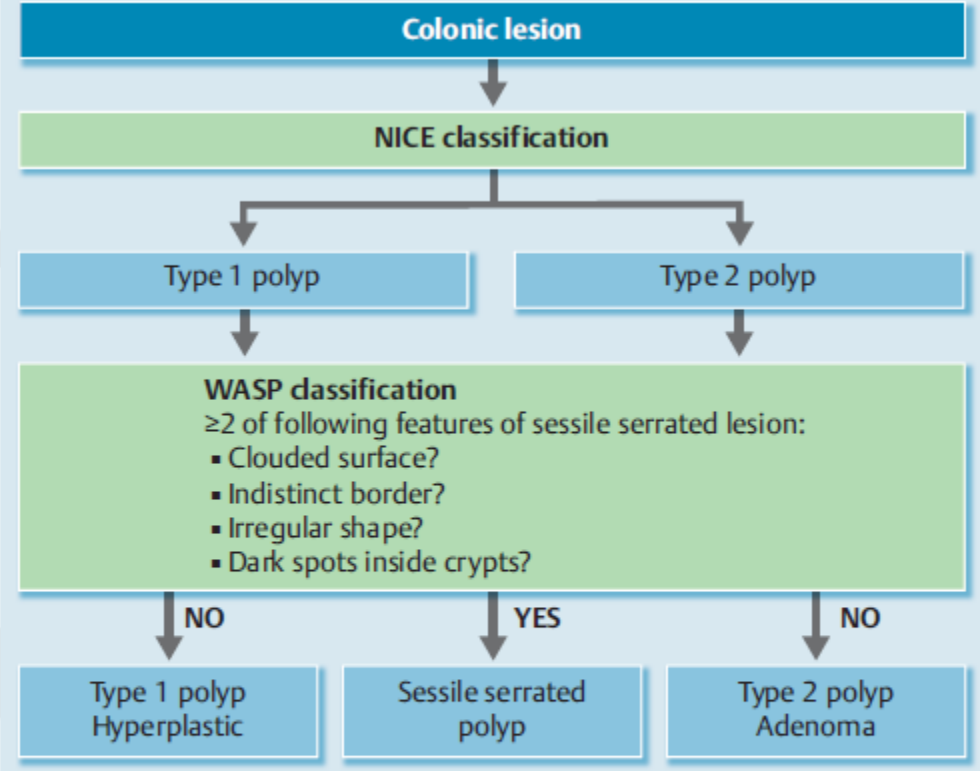


Fig. 4 Workgroup serrAted polypS and Polyposis (WASP) classification for optical diagnosis of hyperplastic polyps, sessile serrated lesions and adenomas, based on the Narrow band imaging International Colorectal Endoscopic (NICE) classification and four sessile serrated lesion-like features.

Post-polypectomy surveillance in colorectal screening programme

Mirjana Kalauz

Clinical Hospital Center Zagreb

Outline

- Background & definitions
- EU/ESGE guidelines
- Case presentations
- Conclusions

Reminder

- Surveillance is the ongoing follow-up of patient at increased risk of the disease

EU/ESGE guiding principals

- Prior adenoma is a risk factor for advanvced neoplasia
- Risk is related to baseline colonoscopy findings: polyp size, number, histological grade

EU/ESGE guiding principals

- Surveillance focus should be highest risk individuals and minimum frequency to provide protection against future cancer

- an indiscriminate use of post-polypectomy surveillance would represent a substantial burden on endoscopy resources

The case for surveillance

- Efficacy of endoscopic surveillance only shown in epidemiological studies
- No RCT
- Patients not in surveillance have 3-4x risk for CRC

BUT:

- Approx 20% endoscopy capacity is colonoscopic surveillance
- Significant volume of unecessary inaccurate surveillance

Radaelli F. DigLiverDis 2012
ESGE Guideline 2013

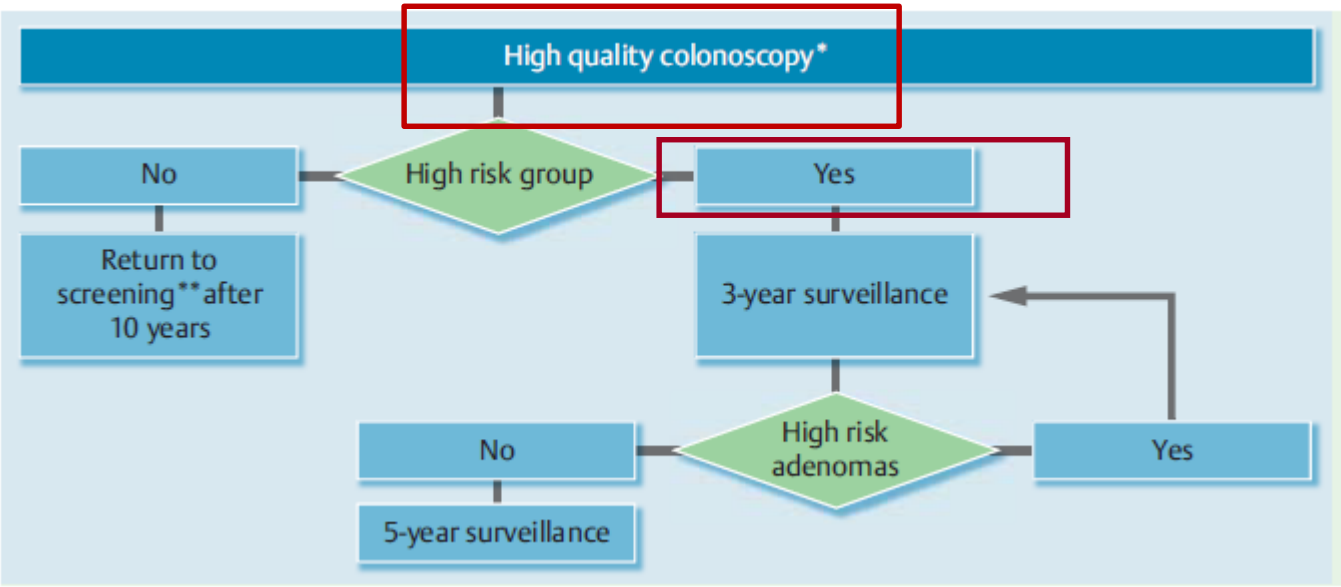
Citat iz guideline str 843 4. pasos

Surveillance Interval

- Studies have shown large proportion of surveillance procedures are inappropriate (40-69%)
- Endoscopist should be responsible
- Histology required so will need mechanism to finalise report
- Adherence to published surveillance should be monitored as a part of QA

Schoen Gastroenterology 2010

Key recommendations



Cesare Hassane et al. Post-polypectomy colonoscopy surveillance: European Society in Gastrointestinal Endoscopy Guideline 2013

ESGE

High quality colonoscopy

- Complete
- Meticulous inspection
- Adequately cleaned
- All neoplastic lesions removed and retrieved
- Endoscopist responsibility for providing written recommendation for surveillance

High Risk

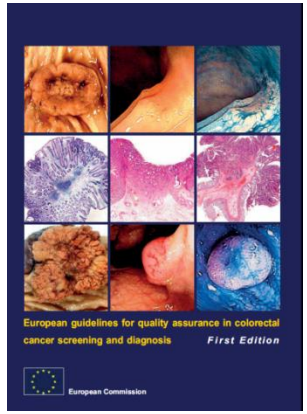
- Repeat at 3 years if:
  - Adenoma with villous histology
  - or high grade dysplasia
  - or ≥10 mm
  - or ≥ 3 adenomas

- Serrated polyps ≥10 mm
  - dysplasia

Low risk

- Repeat at 10 years or return to screening if:
  - 1-2 tubular adenoma
  - or <10 mm
  - or LGD
- Serrated polyps <10 mm, no dysplasia

COLONOSCOPIC SURVEILLANCE FOLLOWING ADENOMA REMOVAL (EU 2010)



Baseline colonoscopy (CS)[1]

Low risk	Intermediate risk	High risk
1-2 adenomas **AND** both small (<10 mm)	3-4 small adenomas **OR** at least 1 ≥10 mm/<20mm	≥ 5 small adenomas **OR** At least one ≥20 mm
AND tubular AND low grade neoplasia[2]	*OR villous OR high grade neoplasia[2]*	
A	**B**	**C**
Routine Screening[3]	**3 years**	**Within 1 year[4]**

Findings at surveillance CS

One negative exam	→ **5 yearly**
Two consecutive negative exams	→ **Routine Screening[3]**
Low or intermediate risk adenomas	→ **B**
High risk adenomas	→ **C**

Findings at surveillance CS

Negative, low or intermediate risk adenomas	→ **3 yearly**
Two consecutive negative exams	→ **5 yearly**
High risk adenomas	→ **C**

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

Smjernice HGD-a

Other key recommendation

- Piecemeal resection >10 mmFU within 6/12 mo
- Inadequate prep-early repeat
- Symptomatic patients prompt repeat

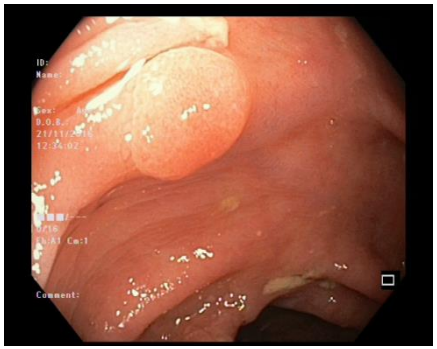
- Stop at ~ 80 years
- FH CRC- no influence
- No evidence for interval FOBT

Zauber Ann Intern Med 2008
Keighley APT 2003
Yag Clinical Endos 2012

Funded by the European Union

Croatia and the EU: Together Against Cancer

Case one



- Female 55
- Rectal bleeding
- Single 8 mm polyp at sygmoid flexure
- Polypectomy performed with cold resection

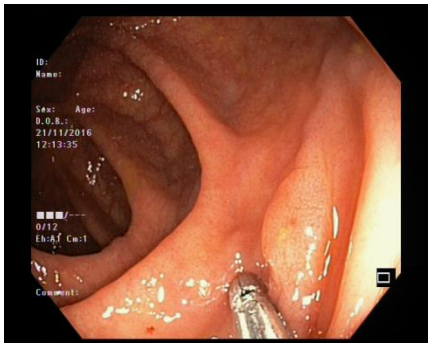
- Histology: 12 mm tubular adenoma, LGD

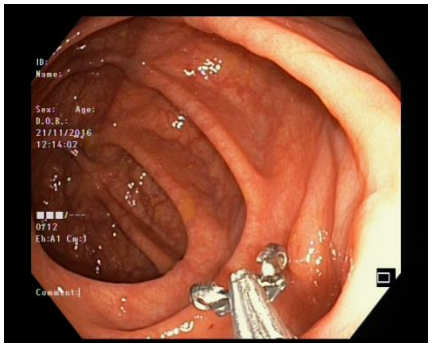
What would be surveillance interval?

- 1 year
- 3 years
- 5 years
- 10 years

Learning points: case one

- Teach precise polyp size measurement to the mm level
- Photograph all lesiones prior to resection
- For lesions in the diminutive size range, consider photography with a closed biopsy forceps
- For lesions 6-15 mm photograph with open snare





Plumb et al. Endoscopy 2016

Case two

- 65 male
- Screening colonoscopy
- Otherwise fit and well
- Single polyp 30 mm
- Piecemeal resection performed
- Histology: villotubular adenoma, LGD

What would be surveillance interval?

- 1 year
- 3 years
- 5 years
- 10 years

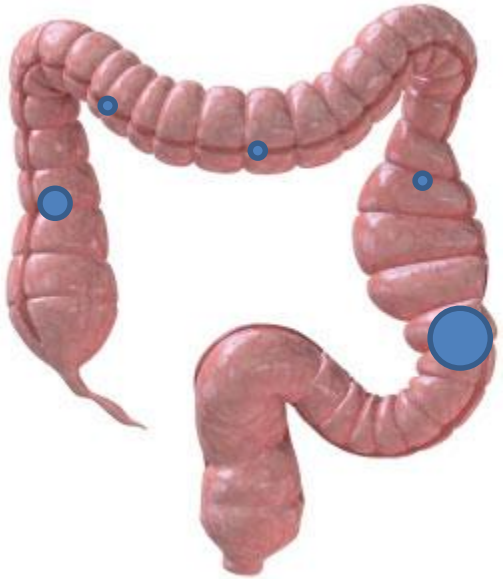
Learning points: case two

- Piecemeal EMR >10 mm
- FU within 6/12 mo before surveillance starts
- Incomplete excision consistently shown to in increase PCCRC

Pohl (CARE study) Gastroenterology 2013

Case three

- 5 polyps (largest in sygmoid colon 25 mm)
- Removed by electroresection
- Histology: tubular and villotubular adenoma (LGD)



What should be screening interval?

- 1 year
- 3 years
- 5 years
- 10 years

= EU guideline

= ESGE guideline

Case four

- 64 male
- Rectal bleeding
- Colonoscopy: 8 mm polyp in rectum. Polypectomy performed with cold biopsy forceps

Case four

- Histology:
- A single fragment measuring 4 mm, tubular adenoma with LGD

- What next?

Learning points: case four

- Careful inspection & accurate description of polyps
- Snare resection of almost all polyps
- Cold forceps only used for biopsy or removal 1-2 mm polyps
- Prompt follow-up
- If malignancy of small lesion suspected,avoid multiple biopsies (may be amenable to ESD)

ADR: Validation (and vindication)

- Polish screening colonoscopy study

  - 45,000 subjects, 186 endoscopists

  - Patients whose endoscopists' ADR was < 20% had at least 10-fold higher risk to be diagnosed with interval CRC, compared to those whose endoscopists had ADR ≥ 20%

  - Interval CRC risk increased as ADR decreased

  Kaminski et al. NEJM 2010; 362: 1795-1803.