

Colorectal cancer

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Outline

- Case presentation
- Epidemiology of CRC
- Clinical presentation
- Pathways to CRC
- Screening modalities
- Colonoscopic detection
- Issues with screening

CRC 2nd most common cancer in Australia

- Incidence (2009):
 - 14 410 new cases of CRC in Australia
 - Accounting for 12.6% of all new cancers
 - Risk of developing CRC before the age of 85 was 1 in 12
- Mortality (2010)
 - CRC accounts 9.3% of all cancer deaths
 - Risk of dying from CRC before the age of 85 was 1:45
- Survival
 - 5 year relative survival increased from 48% (1982-1987) to 66.2% (2006-2010)

Risk factors that influence screening

- Age (sporadic CRC)
 - US Surveillance Epidemiology and End results Reporting database: CRC is increasing in under the age of 50, and declining in older groups
 - Young age CRC are usually symptomatic at diagnosis
- Hereditary CRC syndromes:
 - FAP: 1% of CRC
 - Lynch syndrome 3% of CRC
- Personal/Fhx of sporadic CRC/polyps
- IBD
- Abdominal radiation: survivors of childhood malignancy
- Other: acromegaly, renal transplant

Clinical presentation

- Patients may present:
 - Suspicious symptoms and or signs: bleeding, pain, anemia, imaging abnormalities (Ct/PET)
 - Emergency: intestinal obstruction, GI bleeding
 - Asymptomatic

Mr AD

- 37 years old man, Academic at ANU
- Phx: nil
- Fhx nil
- HOPC: could not complete the marathon in good time due to fatigue
- Inx: Hb 111, Ferritin 12, T Sat 10%
- Colonoscopy: right colon adeno-carcinoma
T2N1M0

Screening: stool based

- Shown to be effective in randomized controlled trials
- gFOBT is associated with 15-33% reduction in CRC mortality (Lancet, NEJM 1996)
- iFOBT: pooled sensitivity 0.79 (95% CI 0.69-0.86) and specificity 0.94 (CI 0.92-0.95)
- Improved adherence with iFOBT (no need for dietary restriction, better collection method)
- Stool DNA assays (Cologuard): sensitivity for CRC 92%, advanced precancerous lesions 42% (NEJM 2014)

NBCSP data 2011: iFOBT

- Participation rate at 38%
- Overall positivity rate 7.8%
- Men 8.8% vs female 7.0%
- Positivity rate increased: remote areas, disadvantaged socioeconomic status, participants with low physical activity
- Positive FOBT: 74% had screening colonoscopy
- 3.2% of +FOBT had CRC
- 12.7% of +FOBT had one or more polyps >10 mm

Screening: direct vision

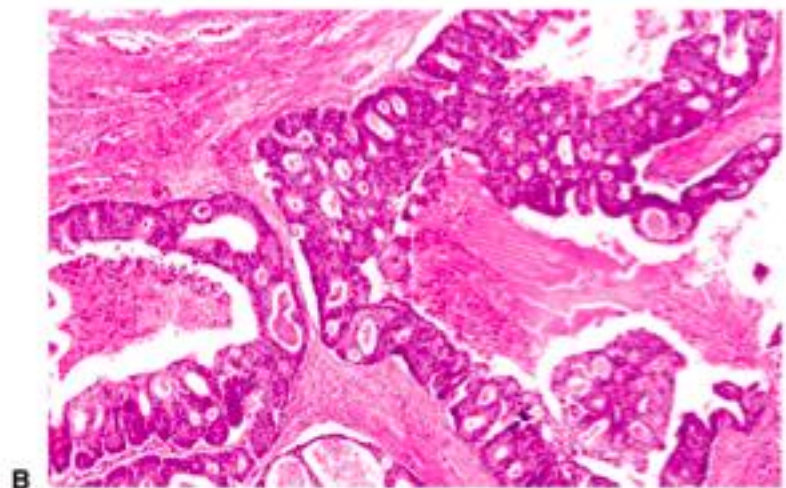
- Flexible sigmoidoscopy:
 - Case control studies: 60% reduction in CRC mortality
- misses right colon lesions
- Can be performed without sedation
- No need for intense bowel prep

Screening colonoscopy

- Effectiveness: long term follow up of NPS: over 70% reduction in CRC incidence after clearing adenomas
- Sensitivity for CRC 95%
- Pooled data miss rate of polyps 22% usually for small polyps (van Rijn Am J Gastroenterol 2006)
- **Technological advances:** high definition colonoscopes, wide angle, NBI, Chromo endoscopy, hood-assisted colonoscopy
- **Audits:** ADR, serrated polyps detection rate, withdrawal time, caecal intubation
- Risks: perforation, bleeding, costs

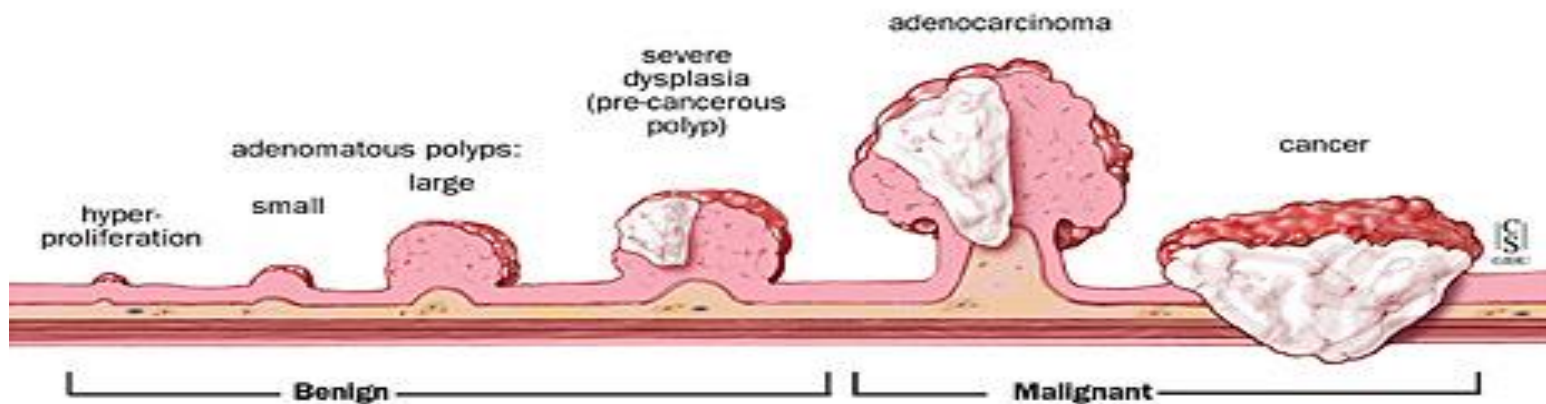
Most CRCs are adenocarcinomas

- Polypoid and ulcerating, or infiltrative lesion
- Arise from precursor lesion
- WHO classification subtypes
 - Mucinous
 - Signet ring cell, etc...
- Grading in a 4- or 2-tiered system (\geq / $<$ 50% glands)
- Staging
 - Depth of invasion
 - Lymph node metastasis



Why performing polypectomy?

Adenoma-carcinoma sequence



Who to screen:

- Cancer council of Australia
- Organized (NBCSP) vs opportunistic screening
- Asymptomatic individuals
- Start at the age of 50 (low risk)
- FOBT every second year
- +FOBT: follow up with colonoscopy

Alternative pathway to CRC

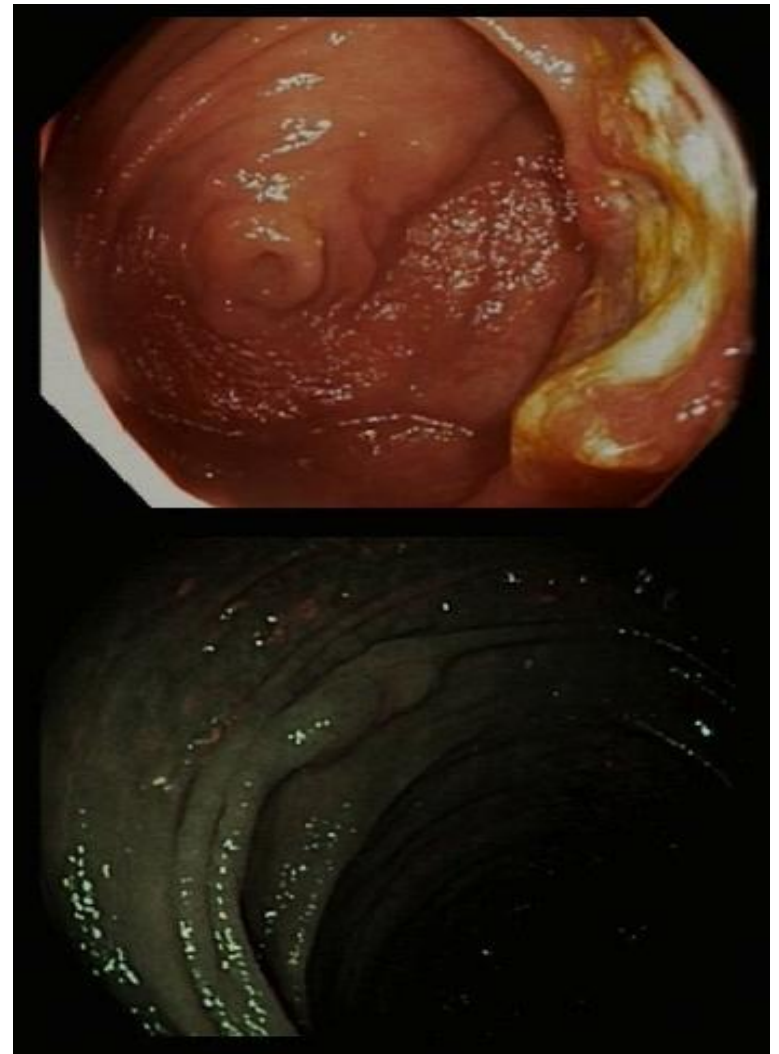
- CRC is a heterogeneous condition
- How to explain 35% of remaining CRC (CIMP+)?
 - Outside sporadic adenomas MSI-H is rarely found.
 - MSI-H CRC rarely harbor *KRAS* mutation and rare alteration of *Wnt* pathway.
- Novel genetic signatures in MSI-H CRC:
 - Extensive promoter region DNA methylation and *BRAF* mutation
- Those alterations are often found in proximal serrated polyps
- Demonstration of serrated polyp-dysplasia-carcinoma transition (*caught in act*)

Mrs JB

- 70 years old retired woman
- Phx:
 - HT
 - Ex-cigarette smoker
 - obesity
- No Fhx of CRC or other extra colonic cancers
- May 2012:
 - 6/12 hx: altered bowel pattern and one episode of large volume rectal bleeding

Index colonoscopy

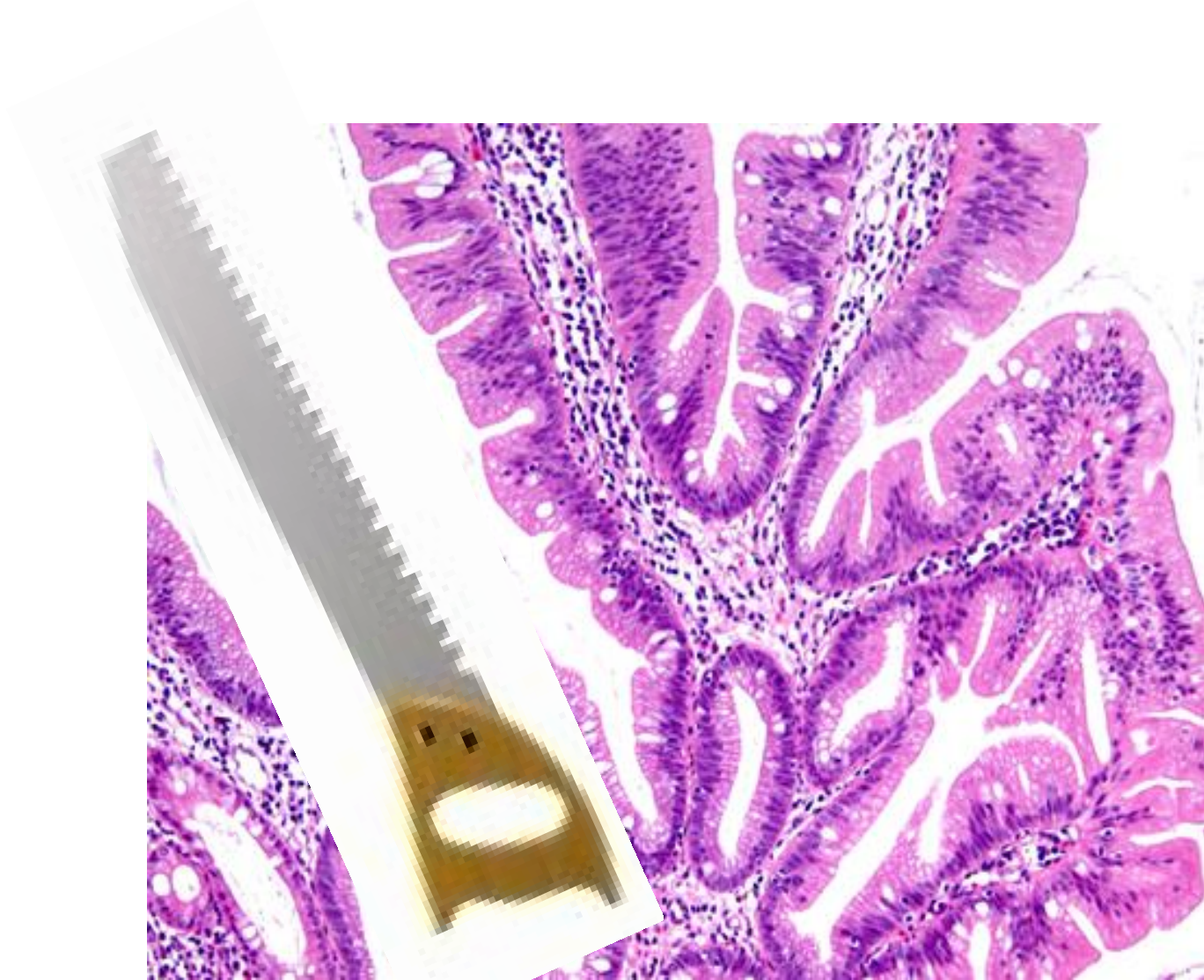
- Colonoscopy revealed
 - Right colon carcinoma and
 - multiple polyps ranging 10 mm.
- Underwent Lap assisted right hemi-colectomy
- Histology T3, N0, M0
- MSI-H and non-staining for MLH1



Mrs JB

- 6/12 repeat colonoscopy:
 - 10 polyps removed (10-15 mm): SSA with HGD, TVA also with HGD
 - multiple other large SSA & adenomas
- Polyp burden managed via colonoscopy
- Developed peritoneal disease

Serrated (*saw-toothed*) polyp



Prevalence: serrated polyps

- Prevalence of serrated polyps in general population in autopsy studies range from 13-40%.
- Prospective population-based colonoscopy studies found 21% of cases had at least one hyperplastic polyp.
- Entity of SSA in the pathology community was established in 2005.
- Prevalence of SSA in patients undergoing colonoscopy is influenced by patient population, endoscopy technique and pathological interpretation

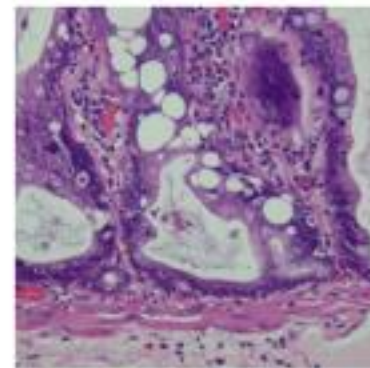
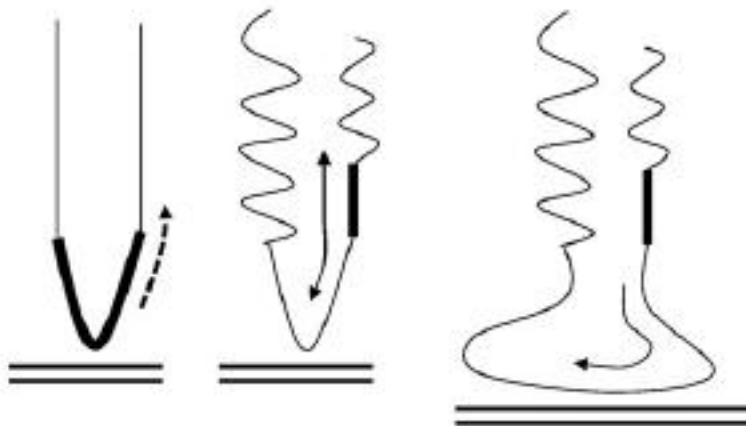
Serrated polyp subtypes

- Hyperplastic polyps
 - Micro-vesicular
 - Goblet cell
 - Mucin-poor
- Sessile serrated adenoma/polyp (SSA)
- Traditional sessile serrated polyp (TSA)
- SSA with cytological dysplasia

SSA

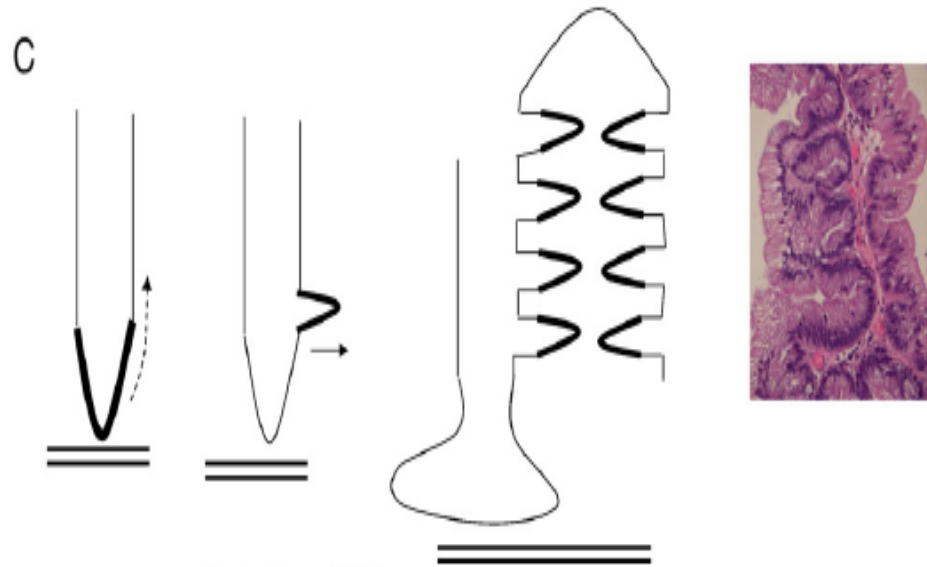
- Architectural crypt distortion and abnormalities in proliferation characteristics
- Proximal colon (usually > 10 mm)
- No cytological dysplasia
- BRAF and DNA methylation
- Continuum with micro-vesicular HP
- Malignant potential high

B



TSA

- Pedunculated lesion
- Distal colorectum
- KRAS mutation
- MSI-L
- Methylation low
- Dysplastic changes
- Ectopic crypt foci
- Malignant potential: high



Hyperplastic (Serrated) Polyposis

- Human model of the serrated pathway of CRC
- Defined as
 - ≥ 5 proximal HPs, 2 of which are > 10 mm
 - or
 - Any number of proximal HPs, with first-degree relative with HPS
 - ≥ 30 HPs of any size throughout the colorectum
- Genetic heterogeneity in CRC from HPS
- Role of MYH?
- Most likely co-dominant mode of inheritance
- Estimated prevalence in UK 1 / 2000

Risk of CRC in Serrated polyposis syndrome

Boparai *et al* 2009: 77 HPS patients (mean follow up 5.6 years):

- 27 (35%) had CRC
 - 22 on first endoscopy
 - 5 interval cancer (median 11 months); 4/5 cancers in diminutive polyps (4-16 mm)
- Cumulative risk of CRC at 5 years under surveillance: 7%

Buchanan *et al* 2010: 126 HPS patients:

- 49 (41%) had CRC; proximal in 24 cases
 - Positive correlation with high polyp burden and males
 - CRC associated adenomas
- * Both studies include retrospective data from familial high risk CRC clinics

Mrs JB (FDR screening)

- Mrs JB fulfills WHO criteria for Serrated polyposis syndrome
- Daughter 39 years old:
 - asymptomatic
 - Eight polyps were removed
 - 10 mm in AC, other polyps descending colon with mucus cap.
 - Histology: hyperplastic polyps and one adenoma with LGD
 - Follow up colonoscopy in 12 months

CRC risk in FDR of patients with HPS?

Boparai et al 2010: total of 347 FDR from 57 pedigrees were analyzed (1970-2006)

- Contributing 11 053 years of follow up:
- During the study period 27 CRC occurred in FDR
- RR of CRC in FDR 5.4 (95% CI 3.7-7.8)

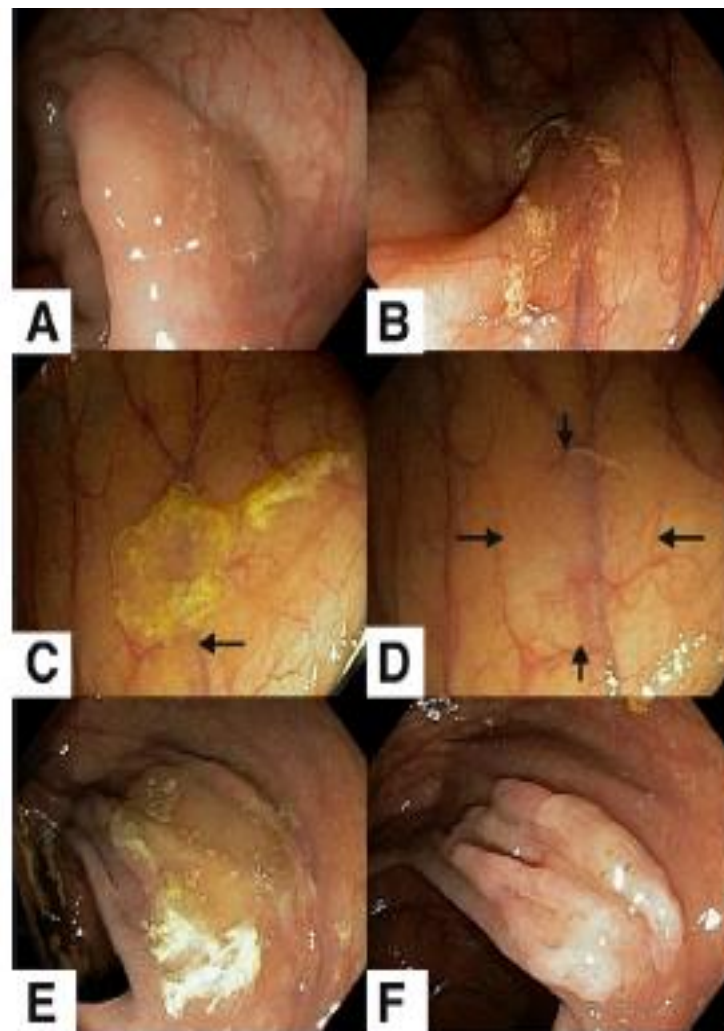
Win et al 2012 cohort of 1639 FDR and SDR of 100 index patients with HPS:

Total of 102 CRC were observed in FDR and SDR

- 54 CRC in FDR SIR 5.16, (95% CI 3.7-7.3)
- 48 CRC in SDR SIR 1.38, (95% CI 1.7-1.19)

Colonoscopic detection

- Common HP in distal colon & rectum:
 - diminutive, sessile,
 - pale and translucent appearance
- SSA: proximal colon,
 - flat, mucus cap,
 - rim of debris,
 - alteration of the contour of the fold,
 - loss of normal vascular pattern
- SSA/P detection is still low
 - prep, poor understanding of SSA
- Interval CRC in SSA:
Proximal, CIMP-H, BRAF mut & MSI-H



Surveillance for serrated polyposis syndrome

- Yearly colonoscopy interval with aim to remove all polyps over 5 mm in size (AJG 2012)
- Biennial colonoscopy (NHMRC guidelines 2011)
- FDR screening colonoscopy at the age of 40 or 10 years younger than index case.

Surveillance for sporadic serrated polyps

Table 5. Consensus opinion surveillance intervals after endoscopic resection of serrated lesions^a

Histology	Size	Number	Location	Interval in years
HP	<10 mm	Any number ^b	Rectosigmoid	10 ^c
HP	≤5 mm	≤3	Proximal to sigmoid	10
HP	Any	≥4	Proximal to sigmoid	5
HP	>5 mm	≥1	Proximal to sigmoid	5
SSA/P or TSA	<10 mm	<3	Any	5
SSA/P or TSA	≥10 mm	1	Any	3
SSA/P or TSA	<10 mm	≥3	Any	3
SSA/P	≥10 mm	≥2	Any	1–3 ^d
SSA/P w/dysplasia	Any	Any		1–3 ^a

AJG 2012 Cleveland consensus

Surgery: serrated polyposis syndrome

- Surgery is indicated when CRC diagnosis or high polyp burden that can't be controlled endoscopically:
 - Extended right hemi-colectomy or subtotal colectomy
 - Yearly screening of remaining colo-rectum
- Post surgery remaining colorectum should be surveyed depending on polyp burden, due to high polyp recurrence (Edelsteine 2012)

Conclusion: serrated polyps

- Serrated polyps are diverse group of polyps with distinct endoscopic, histological and molecular profile
- HPS high risk for CRC and for synchronous CRC
- Increased risk of CRC in FDR
- SSA/P detection rate need to be monitored
- Quality of the colonoscopy must be high,
- Current screening guidelines are based on standard adenoma follow up.

Summary

- CRC is 2nd most common malignancy
- Significant mortality and morbidity
- In most cases is preventable
- Best screening is the one is taken by patient
- No screening tool is perfect
- Patient need to be informed about screening options

Questions