2014 12 27

SPC

解剖病理科
蕭正祥主任

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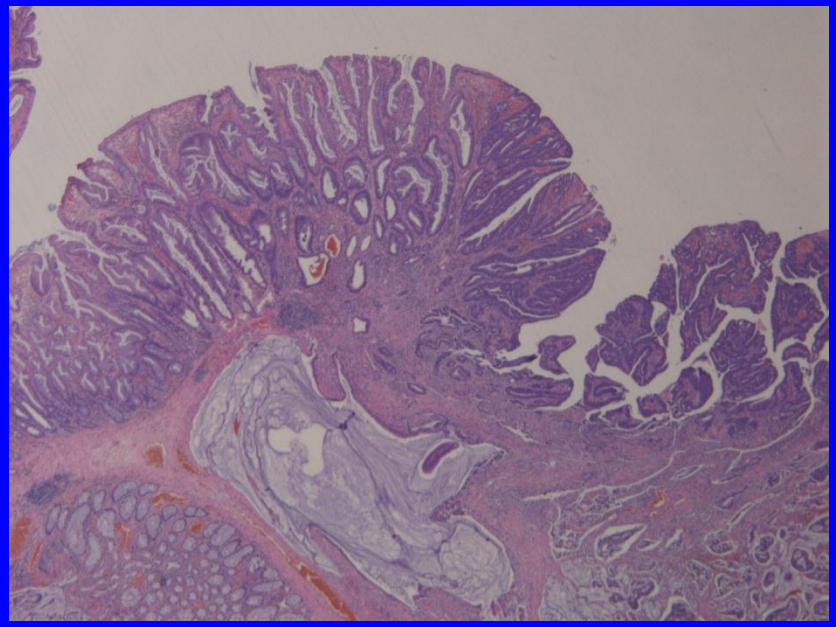
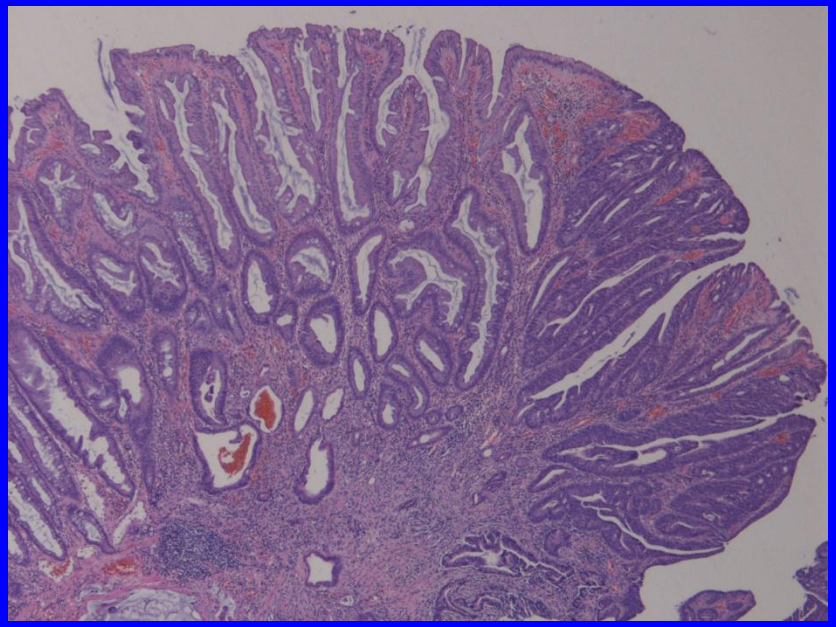
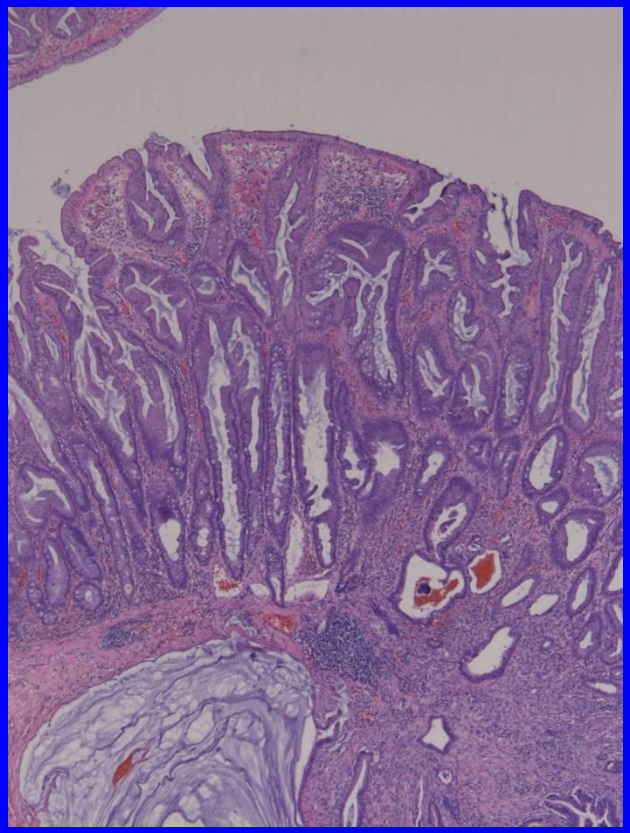
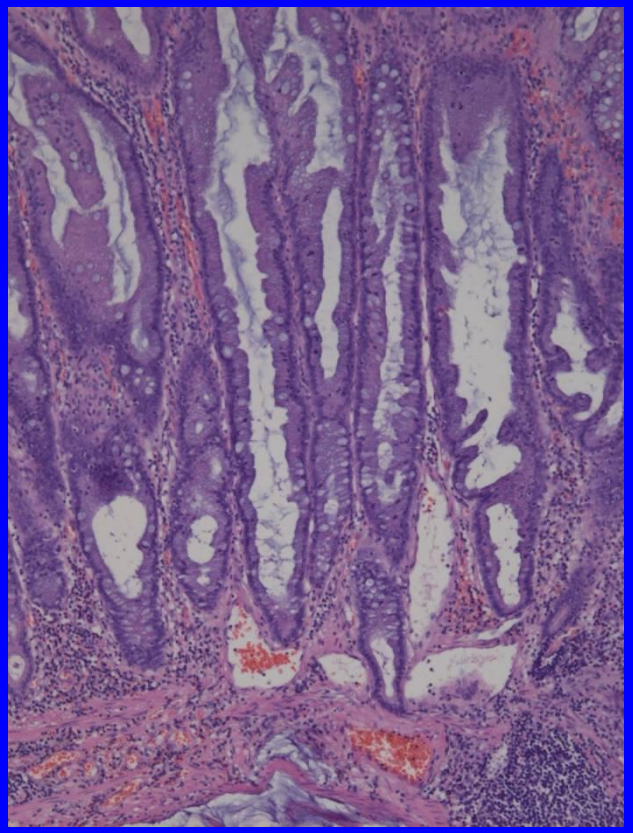
58/M

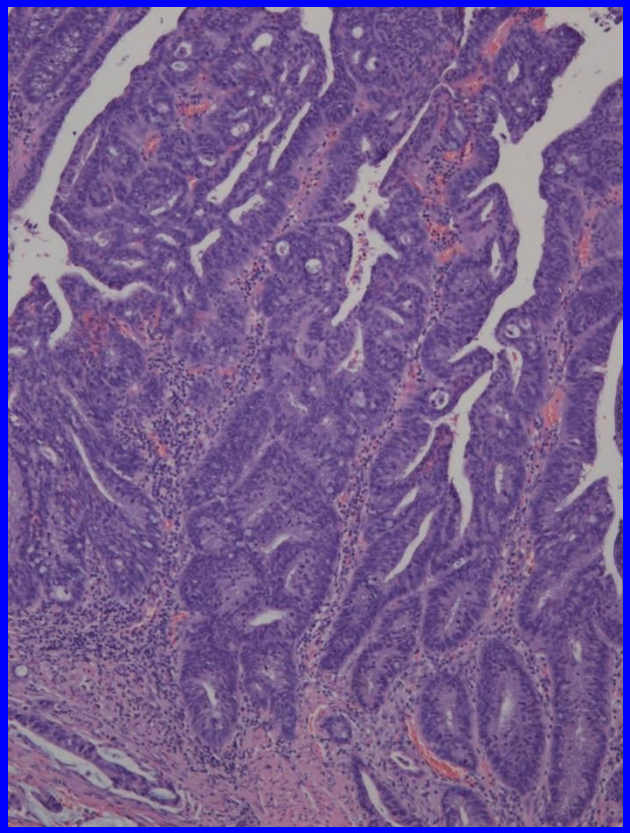
103-15126
Sigmoid Colon

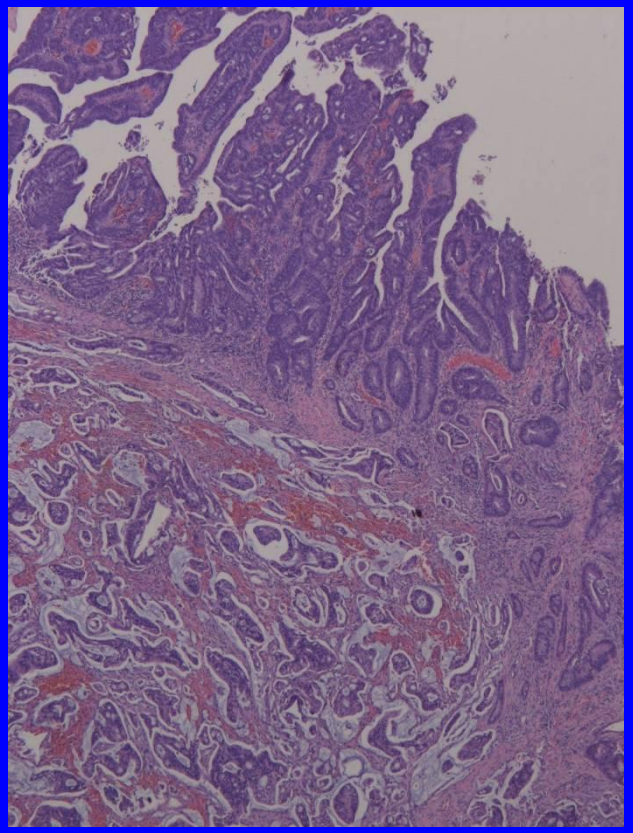


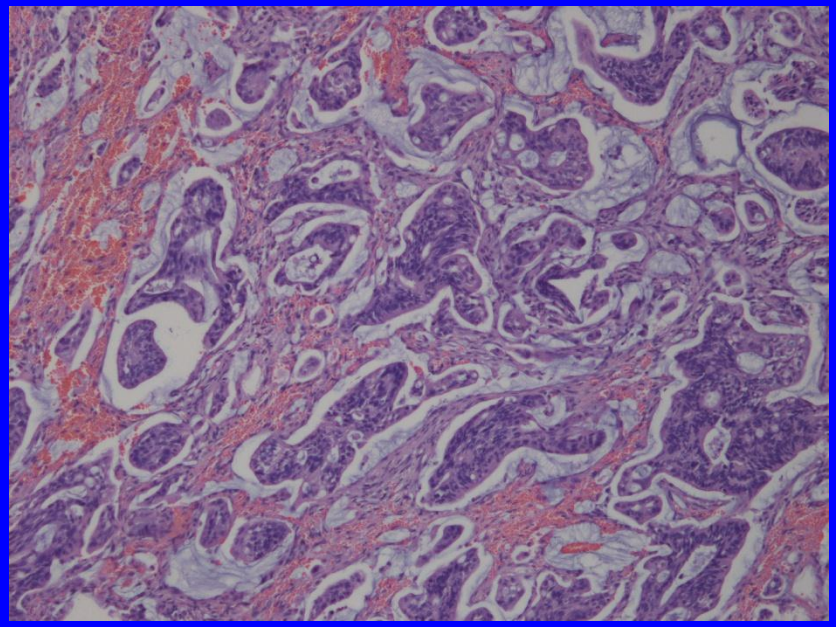


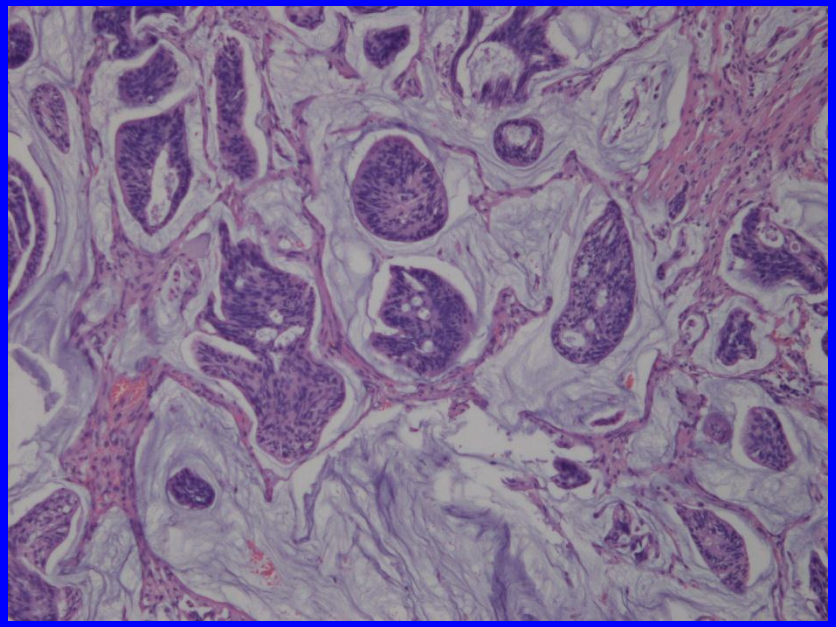












Diag: Sessile serrated adenoma with invasive adenocarcinoma

Serrated Polyps

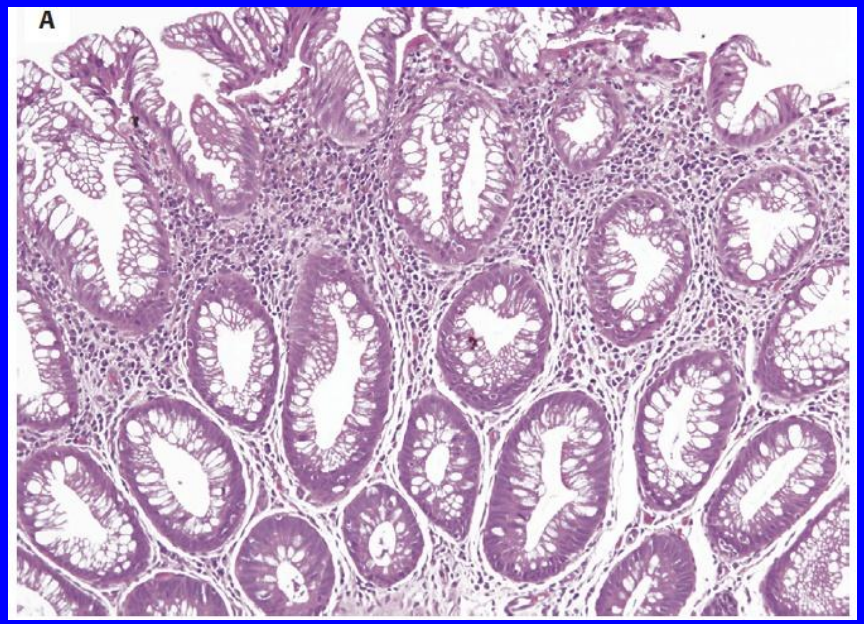
Serrated Polyp

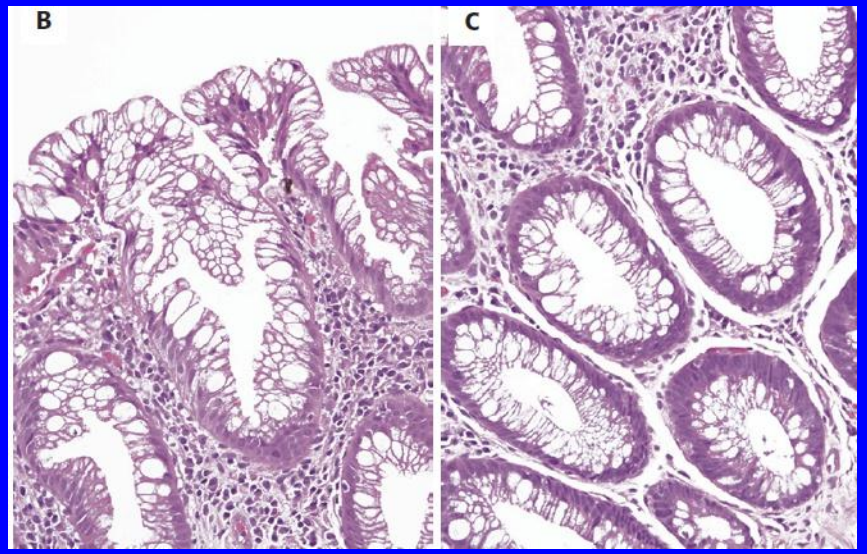
- Definition:
  - A heterogeneous group of lesions characterized morphologically by a serrated (sawtooth or stellate) architecture of the epithelial compartment.
  - The lesions include:
    - Hyperplastic polyps (HP)
    - Sessile serrated adenoma/polyps (SSA/P)
    - Traditional serrated adenomas (TSA)

Hyperplastic polyp (HP)

- Clinical features:
  - Most common serrated lesions (> ¾)
  - Distal colon (rectosigmoid)
  - Sessile lesions of 1-5 mm in size
- Histological features
  1. Microvesicular type (MVHP) – most common
  2. Goblet-cell rich (GCHP)
  3. Mucin-poor type (MPHP)
  - Straight crypts with narrow base and lined with undifferentiated cells
  - Proliferation in the lower third of the crypts
  - Serration in the luminal aspects

Hyperplastic polyp





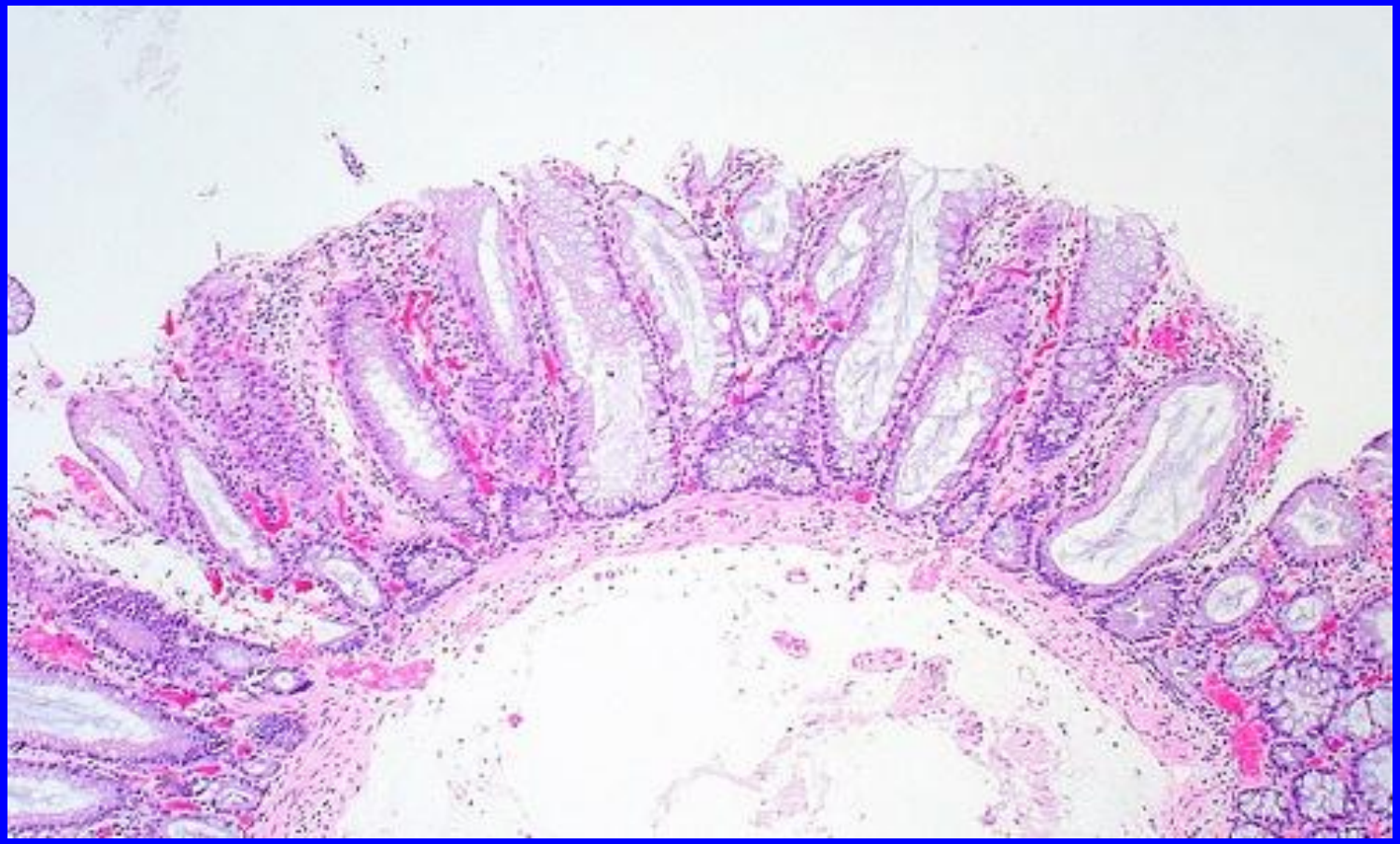
Sessile serrated adenoma/polyps (SSA/P)

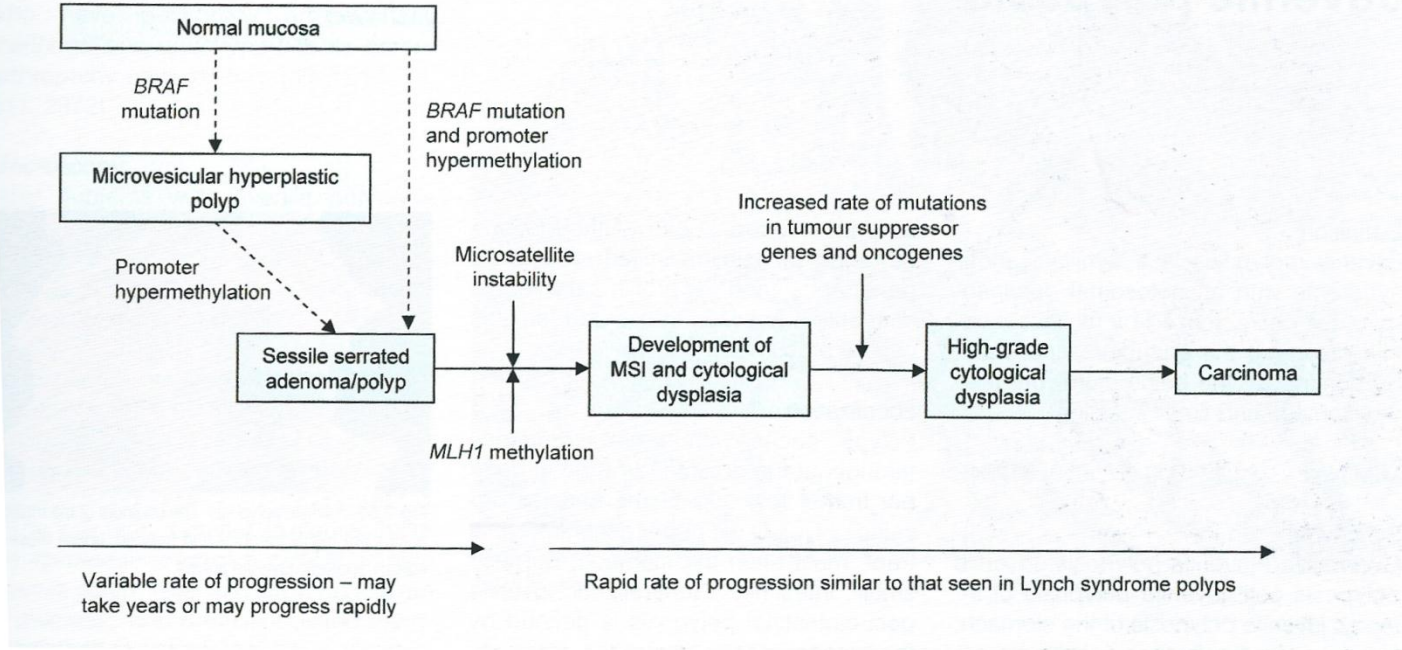
Clinical features:

- More likely in the proximal colon
- Larger than HP (1/2 > 5 mm)
- Flat to sessile with a smooth surface
- Covered with mucus, giving them a yellow appearance
- 15-25% of serrated polyps

SSA/P

- Histological features:
  - Dilated crypts with abnormal shapes including L-shaped and inverted T-shaped
  - Serration at the base of the crypts
  - Mitosis at the side of the crypts
  - Complicated SSA/P : with dysplasia or carcinoma
- Molecular pathology:
  - Precursor of sporadic carcinomas with microsatellite instability (MSI)
  - *MLH1* methylation in complicated SSA/P





g. 8.49 Schematic representation of the development of sporadic colorectal carcinoma with microsatellite instability (MSI) via methylation of the *MLH1* gene. The earliest steps in progression from normal mucosa to sessile serrated adenoma/polyp (SSA/P) are currently under debate (dotted lines).

Clinicopathological characters of MSI-H CRC

- Right sided
- Mucinous carcinoma
- Medullary carcinoma with Crohn-like peritumoral lymphocytic infiltration
- Devoid of “dirty” necrosis
- Lower stage
- Better stage-specific prognosis
- Less responsive to 5-FU; more responsive to irinotecan

Surveillance guidelines for SSA/P

- 5-year surveillance for one or two small (< 1 cm) polyps
- 3-year surveillance for any large (> 1 cm) lesion or three or more of any size
- SSA/P with dysplasia: 1-year surveillance after endoscopically removed the lesion then 3-year surveillance

Serrated polyposis

Def.:

1. $\geqq$5 polyps proximal to the sigmoid colon and $\geqq$2 of them > 1 cm.
2. Any number of serrated polyps in an individual who has a first-degree relative with serrated polyposis
3. $\geqq$ 20 serrated polyps of any size distributed throughout the colon

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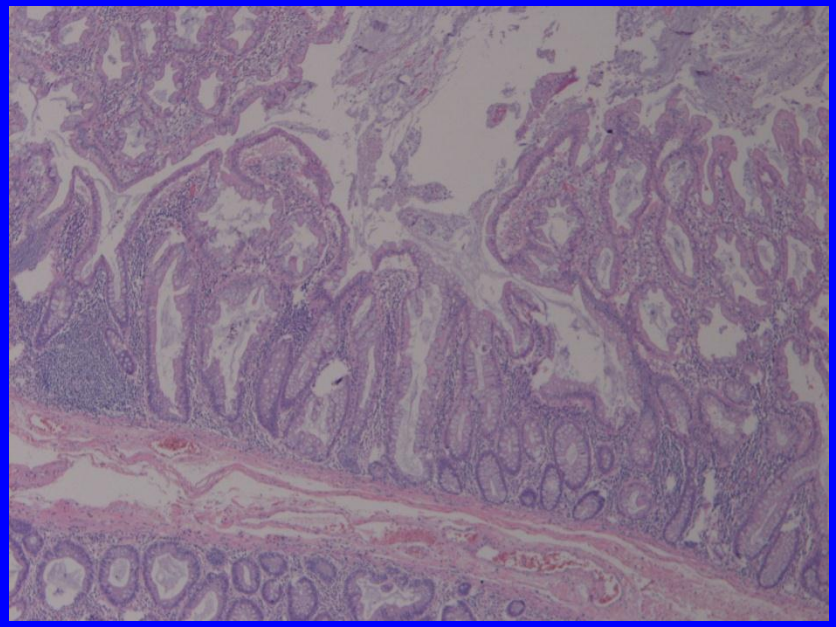
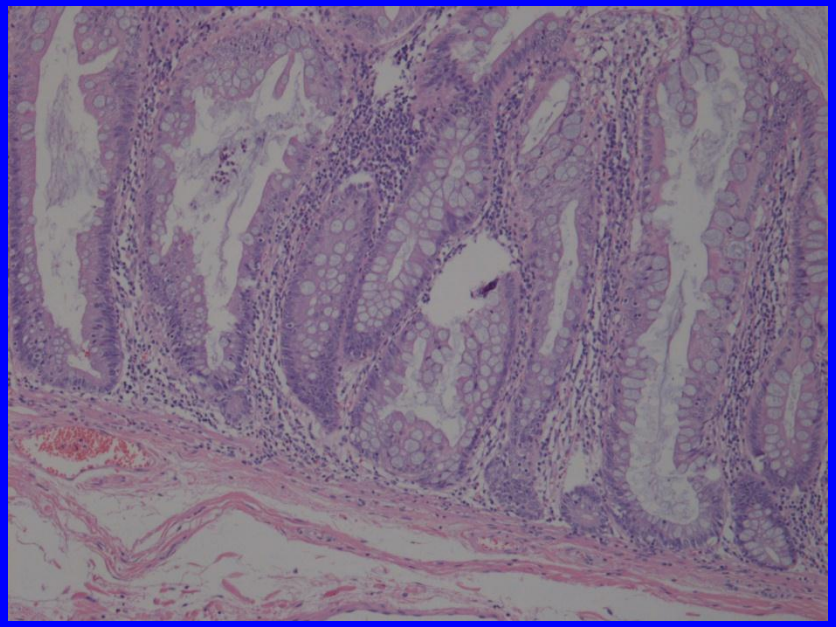
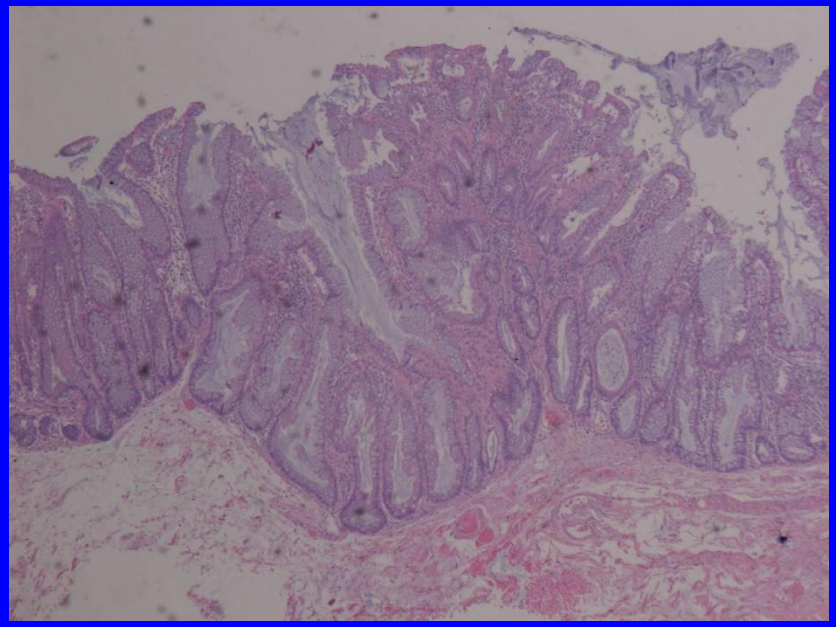
65M

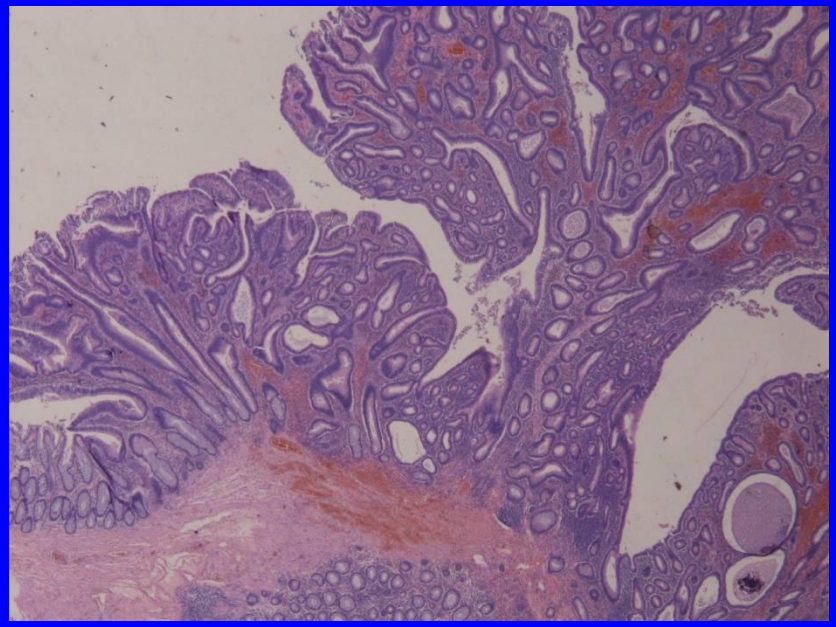
103-3881
ascending to sigmoid colon
60 cm

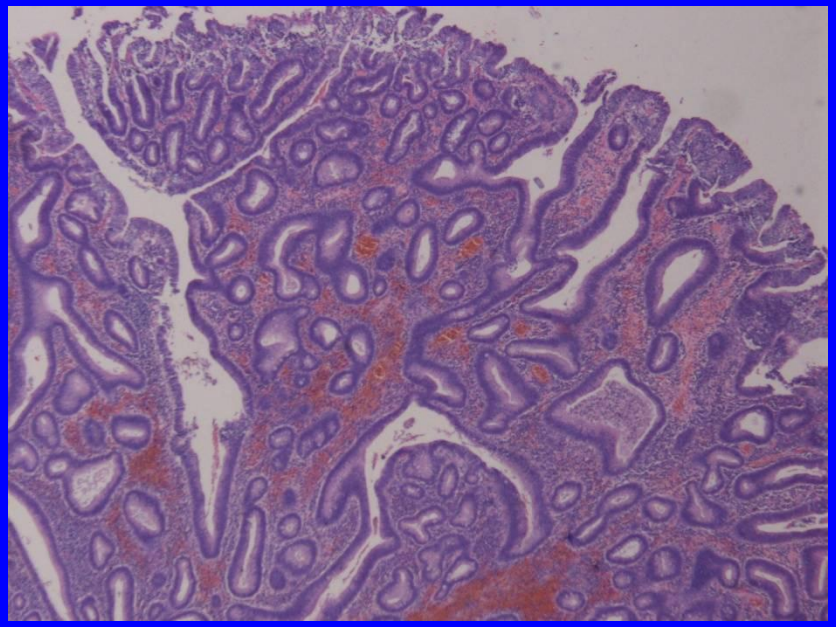
- Gross: 20-30 sessile or pedunculated polyps
- Two largest polyps: 3x2x1 cm and 2.8x1.5x0.5 cm











Two variants of serrated polyposis

- Type 1: multiple SSA/Ps and these polyps are larger and more proximal. High risk for cancer.

- Type 2: numerous classical hyperplastic polyps throughout the colon. The risk of cancer is modestly increased.

Guidelines of serrated polyposis

- Endoscopic surveillance every 1-3 yrs
  - Polyps of < 3 mm surveillance annually
  - Large tumor should be removed

- Surgery indication:
  - Colonoscopic management is difficult
  - Presence of cytological dysplasia

Effects of *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis

Wendy De Roock, Bart Claes, David Bernasconi, Jef De Schutter, Bart Biesmans, George Fountzilas, Konstantine T Kalogeras, Vassiliki Kotoula, Demetris Papamichael, Pierre Laurent-Puig, Frédérique Penault-Llorca, Philippe Rougier, Bruno Vincenzi, Daniele Santini, Giuseppe Tonini, Federico Cappuzzo, Milo Frattini, Francesca Molinari, Piercarlo Saletti, Sara De Dosso, Miriam Martini, Alberto Bardelli, Salvatore Siena, Andrea Sartore-Bianchi, Josep Tabernero, Teresa Macarulla, Frédéric Di Fiore, Alice Oden Gangloff, Fortunato Ciardiello, Per Pfeiffer, Camilla Qvortrup, Tine Plato Hansen, Eric Van Cutsem, Hubert Piessevaux, Diether Lambrechts, Mauro Delorenzi, Sabine Tejpar

Summary

Background Following the discovery that mutant *KRAS* is associated with resistance to anti-epidermal growth factor receptor (EGFR) antibodies, the tumours of patients with metastatic colorectal cancer are now profiled for seven *KRAS* mutations before receiving cetuximab or panitumumab. However, most patients with *KRAS* wild-type tumours still do not respond. We studied the effect of other downstream mutations on the efficacy of cetuximab in, to our knowledge, the largest cohort to date of patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab plus chemotherapy in the pre-*KRAS* selection era.

Methods 1022 tumour DNA samples (73 from fresh-frozen and 949 from formalin-fixed, paraffin-embedded tissue) from patients treated with cetuximab between 2001 and 2008 were gathered from 11 centres in seven European countries. 773 primary tumour samples had sufficient quality DNA and were included in mutation frequency analyses; mass spectrometry genotyping of tumour samples for *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* was done centrally. We analysed objective response, progression-free survival (PFS), and overall survival in molecularly defined subgroups of the 649 chemotherapy-refractory patients treated with cetuximab plus chemotherapy.

Findings 40·0% (299/747) of the tumours harboured a *KRAS* mutation, 14·5% (108/743) harboured a *PIK3CA* mutation (of which 68·5% [74/108] were located in exon 9 and 20·4% [22/108] in exon 20), 4·7% (36/761) harboured a *BRAF* mutation, and 2·6% (17/644) harboured an *NRAS* mutation. *KRAS* mutants did not derive benefit compared with wild types, with a response rate of 6·7% (17/253) versus 35·8% (126/352; odds ratio [OR] 0·13, 95% CI 0·07–0·22; p<0·0001), a median PFS of 12 weeks versus 24 weeks (hazard ratio [HR] 1·98, 1·66–2·36; p<0·0001), and a median overall survival of 32 weeks versus 50 weeks (1·75, 1·47–2·09; p<0·0001). In *KRAS* wild types, carriers of *BRAF* and *NRAS* mutations had a significantly lower response rate than did *BRAF* and *NRAS* wild types, with a response rate of 8·3% (2/24) in carriers of *BRAF* mutations versus 38·0% in *BRAF* wild types (124/326; OR 0·15, 95% CI 0·02–0·51; p=0·0012); and 7·7% (1/13) in carriers of *NRAS* mutations versus 38·1% in *NRAS* wild types (110/289; OR 0·14, 0·007–0·70; p=0·013). *PIK3CA* exon 9 mutations had no effect, whereas exon 20 mutations were associated with a worse outcome compared with wild types, with a response rate of 0·0% (0/9) versus 36·8% (121/329; OR 0·00, 0·00–0·39; p=0·029), a median PFS of 11·3 weeks versus 24 weeks (HR 2·52, 1·33–4·78; p=0·013), and a median overall survival of 34 weeks versus 51 weeks (3·29, 1·60–6·74; p=0·0057). Multivariate analysis and conditional inference trees confirmed that, if *KRAS* is not mutated, assessing *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations (in that order) gives additional information about outcome. Objective response rates in our series were 24·4% in the unselected population, 36·3% in the *KRAS* wild-type selected population, and 41·2% in the *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* exon 20 wild-type population.

Interpretation While confirming the negative effect of *KRAS* mutations on outcome after cetuximab, we show that *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations are significantly associated with a low response rate. Objective response rates could be improved by additional genotyping of *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations in a *KRAS* wild-type population.

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See **Reflection and Reaction** page 706

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