Workshop FORPATH 28/01/2017
COLON DYSPLASIA

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Subjects

• Colorectal cancer: the clinical problem
• Colorectal cancer: not a single disease
• Conventional adenomas
• Epithelial misplacement in adenomas
• The malignant polyp
• Serrated polyps
• Dysplasia in IBD
• Lynch syndrome
• Polyposis syndromes
Colorectal cancer
the clinical problem
Colorectal cancer: current status

- 3rd most common cancer in ♂, 2nd in ♀
- 2008: 1.2 E6 cases, 608700 deaths
- New chemotherapy regimens, biologicals
- Further improving outcome depends on screening and surveillance protocols

Table 1. Colorectal Cancer Screening Recommendations in Asymptomatic Adults at Average Risk

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screening test and interval</th>
<th>Patient age</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Preventive Services Task Force*7</td>
<td>The following options are equally acceptable</td>
<td>Start at 50 years; individualize after 75 years</td>
</tr>
<tr>
<td></td>
<td>High-sensitivity FOBT annually</td>
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<tr>
<td></td>
<td>Flexible sigmoidoscopy every 5 years with high-sensitivity</td>
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<td></td>
<td>FOBT every 3 years</td>
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<tr>
<td></td>
<td>Colonoscopy every 10 years</td>
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</tbody>
</table>
Colorectal cancer screening based on risk factors

Table 2. Colonoscopy Screening Recommendations Based on Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Age to initiate screening</th>
<th>Interval if normal (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single first-degree relative with colorectal cancer or an advanced adenoma diagnosed at ≥ 60 years of age</td>
<td>50 years (may start at 45 years in blacks)</td>
<td>10</td>
</tr>
<tr>
<td>Single first-degree relative with colorectal cancer or an advanced adenoma diagnosed at &lt; 60 years of age</td>
<td>40 years or 10 years younger than affected relative’s age when diagnosed, whichever is earlier</td>
<td>5</td>
</tr>
<tr>
<td>Two first-degree relatives with colorectal cancer or an advanced adenoma diagnosed at any age</td>
<td>40 years or 10 years younger than the youngest affected relative’s age when diagnosed, whichever is earlier</td>
<td>5</td>
</tr>
</tbody>
</table>

NOTE: An advanced adenoma is defined as an adenoma that is 10 mm or larger, has villous elements, or has high-grade dysplasia.
Colorectal cancer surveillance

Table 3. Guidelines for Follow-Up Surveillance Colonoscopy

<table>
<thead>
<tr>
<th>Initial colonoscopy findings</th>
<th>Follow-up interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal²</td>
<td>10 years</td>
</tr>
<tr>
<td>No polyps or normal biopsy results</td>
<td></td>
</tr>
<tr>
<td>Hyperplastic polyps²</td>
<td></td>
</tr>
<tr>
<td>Small (&lt; 10 mm) hyperplastic polyps in rectum or sigmoid</td>
<td>10 years</td>
</tr>
<tr>
<td>Low-risk polyps²</td>
<td></td>
</tr>
<tr>
<td>1 or 2 small (&lt; 10 mm) tubular adenomas</td>
<td>5 to 10 years</td>
</tr>
<tr>
<td>Small sessile serrated polyp (&lt; 10 mm) without dysplasia</td>
<td>5 years</td>
</tr>
<tr>
<td>High-risk polyps¹</td>
<td></td>
</tr>
<tr>
<td>3 to 10 tubular adenomas</td>
<td>3 years</td>
</tr>
<tr>
<td>Tubular adenoma or serrated polyp that is ≥ 10 mm</td>
<td></td>
</tr>
<tr>
<td>Adenoma with villosus features or high-grade dysplasia</td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp with cytologic dysplasia</td>
<td></td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td></td>
</tr>
<tr>
<td>Other circumstances⁵</td>
<td></td>
</tr>
<tr>
<td>More than 10 adenomas</td>
<td>&lt; 3 years</td>
</tr>
<tr>
<td>Serrated polyposis syndrome*</td>
<td>1 year</td>
</tr>
<tr>
<td>Following piecemeal removal of a large (&gt; 15 mm) sessile adenoma or serrated polyp</td>
<td>Consider repeat in &lt; 1 year if question of residual polyp</td>
</tr>
<tr>
<td>Following curative resection of colorectal cancer¹</td>
<td>1 year after resection, then 3 and 5 years if normal</td>
</tr>
</tbody>
</table>

—Criteria for serrated polyposis syndrome: at least 5 serrated polyps proximal to the sigmoid with 2 or more that are > 10 mm, any serrated polyp proximal to sigmoid with a family history of serrated polyposis syndrome, or > 20 serrated polyps of any size throughout the colon.
Colorectal cancer not a single disease
Types of colorectal cancer

• 94% sporadic
  • Traditional pathway (80%)
    • Arise through APC mutation and chromosomal instability
    • Microsatellite stable, methylation negative, BRAF and KRAS WT tumors
    • Precursor lesions: conventional adenomas
    • These adenomas also typical in FAP & MutYH polyposis syndrome
    • (alternative: with KRAS mutations & low degree of methylation)
  • Serrated pathway (15%: elderly, right colon, women)
    • Arise through BRAF V600E mutation and, later, hypermethylation of the MLH1 promoter
    • High-level MSI and mismatch repair deficient (MLH1 and PMS2) or MSI-stable
    • Incompatible with Lynch syndrome
    • Precursor lesions: sessile serrated polyps (SSPs) with / without dysplasia
    • “hyperplastic” / “serrated” polyposis

• 5% hereditary
  • HNPCC / Lynch syndrome (conventional adenomas)
  • FAP & MutYH polyposis syndrome: conventional adenomas
  • Hamartomatous polyposis syndromes

• 1% dysplasia in IBD
CRC precursors: polyps

• Two endoscopic settings:
  • Single
  • Multiple → Polyposis syndrome?

• Four histological types:
  • Inflammatory
  • Hamartomatous
  • Hyperplastic
  • Neoplastic

• Five possible tasks for the pathologist:
  • Identify polyp type
  • Search for dysplasia & grade it
  • When dysplasia, look for cancer & type, grade and stage it
  • Assess completeness of cancer resection
  • Mention clinically relevant cancer features
Conventional adenomas
Conventional adenomas

• Circumscribed benign lesions with dysplastic epithelium (IEN)
• 12% in 5th decade, 50% lifetime risk
• LGD, HGD : architectural complexity, degree of nuclear atypia & stratification
• Villous component : finger-like projections overlying lamina propria
• TVA : 25-75% villous component
• Endoscopically : pedunculated / sessile / flat
• High risk: > 3 adenomas, > 1 cm, villous histology, HGD / intramucosal CA
Figure 2. Tubular adenoma (pedunculated).

Figure 3. Tubular adenoma (sessile).
Figure 4. Tubulovillous adenoma.

Figure 5. Tubular adenoma with high-grade dysplasia.
Villous component?
Degree of dysplasia?
HGD / cancer?

Figure 2: Spectrum of features that Western pathologists use to classify dysplastic changes in conventional adenomas. (A) Low-grade dysplasia characterized by polarized cells with pseudostratified, elongated and hyperchromatic nuclei arranged in simple non-complex crypts. (B) Gland crowding, loss of polarity and pleomorphic cells (arrowheads). (C) Full-thickness pseudostratification (asterisks) and areas suggestive of cribriforming (arrow). (D) Multiple crypts showing cribriforming/gland-in-gland change (asterisks). (B–D) are features that Western pathologists use to diagnose high-grade dysplasia. In contrast, many Eastern pathologists would consider these features compatible with carcinoma.
The initially negative polyp biopsy: what to do?

- Common problem: 15 - 20%
- Lymphoid aggregate, polypoid mucosal fold?
- Leave it – or deeper cut?
- One study (200+ samples)
  - Deeper levels 50 µm apart → lesion in 25%, this was a TA in 75%
  - Mean level 1.85 (range 1-9)
  - Typically small lesions, right hemicolon
- Adenoma detection rate!
- Scenarios:
  - In all?
  - If clinically relevant (= if finding a lesion would alter follow-up)?
  - Cost-effectiveness?

PMID: 26475150
Epithelial misplacement in adenomas
The problem, solutions

• Frequent, in 2-4% of conventional adenomas
• Common in the sigmoid (narrow & motile → polyp prolapse)
• Sometimes secondary to previous intervention (endoscopic / surgical)
• Mimics invasion, hence “pseudo-invasion”
• Diagnosis aided by several features:
  • Presence of lamina propria surrounding the dysplastic glands
  • Mixture of dysplastic and normal glands
  • Dysplastic epithelium has similar cytology as at polyp surface
  • Presence of haemosiderin macrophages
  • Mucin lakes
  • Lack of a desmoplastic reaction
• Immunohistochemistry not really useful
Pseudo-invasion: endoscopically suspicious
Pseudo-invasion: not endoscopically suspicious
The malignant polyp
Clinical & pathologic assessment

• Adenomas < 1 cm:
  • One large study in 23000 adenomas:
    • No cancers
    • HGD: 0.3 % if < 5 mm and 0.8 % if 6-9 mm
    • “Advanced features” (= HGD / villous growth): 2.1 % if < 5 mm and 5.6% if 6-9 mm
    • Resect and discard is safe?

• Adenomas 1-2 cm: 5% risk of cancer
• Adenomas > 2 cm: 10-20% risk of cancer

• Risk of metastasis:
  • Extremely low in intramucosal cancer (no lymph vessels)
    • Since this diagnosis is not reproducible & no clinical consequences: drop altogether!
  • Increases as soon as there is definite submucosal invasion

PMID: 27443490
Submucosally invasive cancer

Figure 3 Submucosally invasive adenocarcinoma arising in an adenoma, resected endoscopically during screening colonoscopy. Arrowheads highlight the cauterized submucosal margin. Residual muscularis mucosa is seen at the edges of the polyp. Asterisks mark the invasive front of the carcinoma in the submucosa. Double-headed arrow marks the distance of carcinoma at the invasive front to the closest submucosal margin, approximately 1 mm. Right inset shows detail of the invasive front of the carcinoma, with angulated irregular glands of carcinoma invading into desmoplastic stroma. Left inset shows detail of residual adenoma at the edge of the polyp.
What to report in a T1 cancer?

• Polyp type (pedunculated vs sessile)
  • Usually easy, but CAVE fragmented excision!

• Depth of submucosal invasion: If > 1 mm, OR (N+) = 3.87

• Cancer grade: If G3, OR (N+) = 5.60
  • Based on % glandular growth (<5 / 5-50 / 50-95 / >95)
  • Difficult, not reproducible → use 2-tiered system

• Presence of lymnovascular invasion: if present, OR (N+) = 4.81
  • Use IHC in difficult cases

• Tumor budding: if high-grade, OR (N+) = 7.74
  • Which stain (HE, keratin?)
  • Which method (semiquantitative, quantitative in 1/10 HPFs?)
  • > 10 buds in 1 HPF???

• Margin
  • Usually easy if not fragmented & well-oriented
  • What is positive? Less than 2 mm, less than 1 mm, transsection?

PMID: 25531500
Depth of invasion?

- Ueno:
  - Width < 4000 µm : 2,5% N+
  - Width > 4000 µm : 18,2 % N+
  - Depth < 2000 µm : 3,9% N+
  - Depth > 2000 µm : 17,1% N+
Haggitt, Kikuchi

- Only pedunculated polyps!
- Difficult with piecemeal resection or poor orientation
- Level 3 and 4 = adverse
- Where do you draw the line?
- How thick can the line be?
- Inc N+ < 1% if Haggitt [1-3], completely removed & no other factors...

- Only sessile polyps (look at endoscopy report)!
- Can only be assessed if muscularis propria is present
- Virtually never in malignant polyps
- Exception: transanal minimal invasive surgery (TAMIS) for distal rectal adenoma
  - Report Kikuchi level AND measured depth of invasion
- Inc N+ 0-8% for (sm1 + sm2), and 12-25% for sm3
Treatment recommendations

Low risk
- Kikuchi level sm1/Haggitt levels 1–3/
  sm invasion <1,000 μm
  and
- No poor differentiation (G1/G2)
  and
- No lymph vessel invasion (L0)
  and
- Clear resection margin (R0)

Endoscopic therapy

High risk
- Kikuchi level sm3/Haggitt level 4/
  sm invasion ≥1,000 μm
  or
- Poor differentiation (G3)
  or
- Presence of lymphatic invasion (L1)
  or
- Positive resection margin (R1)

Surgical therapy
Fig. 1  Tumor budding. High-power image (×40) of tumor budding cells (→) at the invasive front of CRC in a standard H&E stain. Tumor budding is defined as the presence of single cells or small clusters of cancer cells in the tumor stroma and is frequently found in tumors with an invasive growth pattern and desmoplastic stromal response. Detection of tumor budding is frequently associated with lympho-vascular invasion (*) in the tumor microenvironment.

- Tumor buds are single cells or clusters of up to 5 cells (≤5 cells) present in the peritumoral stroma.
- Tumor buds show cytoplasmic reactivity to cytokeratin stains and a clearly identifiable nucleus.
- Cytoplasmic pseudofragments, ruptured glands, mucin pools, and necrosis are excluded.
MALIGNANT POLYPS – 1HPF METHOD

Field selection on low power

Counting buds in 1 high power field (1HPF)
Serrated polyps
Broad group of lesions

- Epithelial polyps with saw-toothed / stellate arrangement of the epithelium
- Three main forms:
  - Hyperplastic polyp (HP)
  - Sessile serrated adenoma/polyp (SSP), w/wo dysplasia
  - Traditional serrated adenoma (TSA)
Figure 1. Hyperplastic polyp.

Figure 6. Sessile serrated polyp.

Figure 7. Traditional serrated adenoma.
Figure 3. Sessile serrated adenoma with cytological dysplasia—72-year-old woman, right colon. (a) A typical SSA/P is present, with characteristic deep crypt lateral spread. (b) Focally, there is a sharp clonal-type demarcation with a component that resembles a tubular adenoma morphologically, felt to represent a subclone arising in the SSA/P. (c) The subclone is not simply an adjacent tubular adenoma as it has lost hMLH1 immunoreactivity, reflective of the dysplastic area arising through hMLH1 promoter methylation—usual tubular adenomas would retain hMLH1 immunoreactivity. The SSA/P component characteristically retains hMLH1 activity. (d) The presence of BRAF immunoreactivity, reflective of BRAF V600E mutation, in both the SSA/P and the dysplastic subclone, is further evidence that the dysplastic subclone is not just an adjacent tubular adenoma as tubular adenomas would not demonstrate BRAF mutations.
Issues with serrated polyps

- What are the minimum morphological criteria for SSP versus mvHP?
  - mvHPs and SSPs have similar molecular alterations, but different locations...
  - You can find large areas of mvHP in an SSP
  - Arbitrary: one convincing boot-shaped crypt is enough

- Can size and location help to distinguish between mvHPs and SSPs?
  - Usually mvHPs are small < 5 mm and left-sided

- What is an SSP with “cytological dysplasia”?
  - Term chosen to emphasize that dysplasia develops within the SSP
  - Not an adjacent tubular adenoma!

- Relation between SSP and traditional serrated adenoma (TSA)?
  - None, except the name...
  - TSAs are rare (< 1% of all colon polyps), usually left-sided & different histologically
  - MR enzymes retained; often KRAS mutations; development of HGD associated with P53 mutations

- What is a goblet cell HP?
  - Unrelated to mvHP
  - Often distal, rare BRAF mutations, 50% KRAS mutations

- What is serrated polyposis syndrome?
  - Former hyperplastic polyposis syndrome
  - Multiple mvHPs and SSPs (generalized methylation) → endoscopic surveillance, surgery?
Figure 4  Traditional serrated adenoma (TSA). (a) On low power, they typically have a villiform appearance with conspicuous serrations. (b) Many of the serrations are associated with "ectopic crypts", which are felt to represent abortive attempts at forming new crypt bases throughout the polyp. Goblet cells are present in variable numbers as shown here. (c) Ki67 immunostaining tends to be strongest in the ectopic crypt bases. (d) Hyperchromatic pencillate-shaped nuclei are present; the cytoplasm is often intensely eosinophilic as shown here, although mucin may be present as well (as shown in panel b).

Figure 5  Goblet cell type hyperplastic polyp (GC HPP). Mostly flat and usually small, they can be histologically subtle as serrations may be minimal (as shown here) to non-existent. Elongated crypts with a dense population of goblet cells from crypt base to surface but little mitotic activity are typical features.
“Mixed” polyps?

- One polyp with SSP regions, TSA regions & classical adenomatous dysplasia
- When in the right colon: probably SSP with dysplasia
- When in the left colon: “collision” of SSP and classical adenoma?

PMID: 25934843
## Surveillance intervals after finding serrated lesions

Table 3  Cross-tabulation of recommendations for surveillance intervals after detection of serrated lesions

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic (serrated) polyposis syndrome</td>
<td>Serrated polyposis syndrome</td>
<td>Serrated polyposis syndrome</td>
<td>N/A</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Sessile serrated adenoma (SSA)/polyp &gt;10 mm, SSA/ polyp with dysplasia, or traditional serrated adenoma (TSA)</td>
<td>SSA/P or TSA &gt;10 mm or 3 or more in number. Two or more SSA/P 10 mm in size† or any SSA/P with dysplasia†</td>
<td>Serrated polyps ≥10 mm, or with cytological dysplasia at any size*</td>
<td>–</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>SSA/polyp &lt;10 mm with no dysplasia</td>
<td>≥4 HPs any size proximal to sigmoid, or any proximal HP &gt;5 mm in size, or 1–2 SSPs or TSAs &lt;10 mm</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Distal serrated polyp &lt;10 mm</td>
<td>–</td>
<td>HP &lt;10 mm in recto-sigmoid, or ≤3 HP ≤5 mm proximal to sigmoid</td>
<td>Serrated polyp &lt;10 mm with no dysplasia</td>
<td>All serrated lesions of any size without adenomatous dysplasia (no recommendation for surveillance)</td>
<td>10 (routine screening)</td>
</tr>
</tbody>
</table>

*This proposed strategy considers hyperplastic polyps (HPs), SSA/SSPs, and traditional serrated adenomas as serrated polyps.
†1–3 years recommended depending on clinical circumstances. SSPs should be considered.

NIH, national institutes of health (USA); SSP, sessile serrated polyp.

[^98]: Terdiman J, McQuaid K. Surveillance intervals after finding serrated lesions.
[^29]: US multisociety taskforce.
[^19]: NIH working group.
[^99]: ESGE.
[^100]: European Union/IARC.
Dysplasia in IBD
Cautionary note: inflammatory polyps in IBD

• Mucosal / submucosal damage & regeneration in severe inflammatory diseases, such as IBD

• Single or multiple

• “Inflammatory polyposis”
  • Stenosis
  • Avoid misdiagnosis: DD familial adenomatous polyposis, hyperplastic polyposis, dysplasia / cancer in IBD
  • Typically surgery

• Although an inflammatory polyp is not neoplastic in itself, its presence may point to an inflammatory milieu that promotes the formation of cancer...
Inflammatory polyposis in IBD

PMID: 25624746
Dysplasia in IBD: the clinical problem

- Risk factors for cancer in IBD (UC and CD):
  - Young age at disease onset, duration of disease, extent of disease
  - Family history of CRC
  - Concomittant PSC
  - Severity of current or prior inflammation
  - Dysplasia = unequivocally neoplastic changes of the epithelium (Riddell classification)

- Traditional standard screening for dysplasia:
  - Random biopsies every 10 cms, up to 33 biopsies
  - = 1% of mucosal surface

- However most dysplasia is visible:
  - Therefore targeted biopsies
  - High-definition white-light colonoscopy/ chromoendoscopy

- Start screening after 8-10 yrs of disease
<table>
<thead>
<tr>
<th>Society</th>
<th>Low risk (5 years)</th>
<th>Intermediate risk (3 years)</th>
<th>High risk (1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSG</td>
<td>Extensive colitis with no active endoscopic or histologic inflammation OR left-sided colitis OR Crohn’s colitis with &lt;50 % involvement</td>
<td>Extensive colitis with mild active endoscopic or histologic inflammation OR post-inflammatory polyps OR family history of CRC in FDR &gt; 50 years</td>
<td>Extensive colitis with moderate to severe active endoscopic or histologic inflammation OR stricture in past 5 years OR dysplasia in past 5 years without surgery OR PSC OR family history of CRC in FDR &lt; 50 Stricture or dysplasia detected within past 5 years OR PSC OR extensive colitis with severe active inflammation OR family history of CRC in FDR &lt; 50</td>
</tr>
<tr>
<td>ECCO</td>
<td>Neither intermediate nor high-risk features</td>
<td>2–3 years</td>
<td></td>
</tr>
</tbody>
</table>
In almost all dysplasia
More in HGD

PMID: 27567189
Current management of dysplasia in IBD

• Don’t use the DALM / non-DALM terminology anymore

• Visible dysplastic lesion in healthy colon: standard polypectomy

• Visible polypoid dysplastic lesion in IBD area:
  • Not endoscopically resectable → colectomy
  • Complete endoscopic resection (biopsy proven) → close surveillance

• Visible non-polypoid dysplastic lesion in IBD area:
  • High risk of malignancy, may be difficult to resect
  • Consider colectomy, in any case take biopsy

• Invisible dysplasia:
  • If LGD: already 22% risk of synchronous cancer
    • Consider for colectomy, especially if multifocal LGD
  • If HGD: 45-67% risk of synchronous cancer
    • Always colectomy
Serrated polyps in IBD?

- Serrated polyps in inflamed colon in IBD: 1-2%
  - Serrated, no dysplasia ≈ sporadic sessile serrated polyps
    - 11% prevalent and 0% 10 yr incident neoplasia
    - Predominantly ♀, right colon
    - 2/3rds BRAF V600E mutation
  - Serrated, indefinite for dysplasia (heterogeneous group)
  - Serrated, LG dysplasia ≈ sporadic traditional serrated adenoma
    - 76% prevalent and 17% 10 yr incident neoplasia
    - Comparable to 23% 10 yr incidence rate for conventional non-serrated dysplasia at baseline
    - Predominantly ♂, left colon
    - Almost half KRAS mutations (exon E2, codons 12 & 13)

- Biological similarity with sporadic serrated polyps?
Lynch syndrome
Lynch syndrome (HNPCC)

- 1/370, most common cause of hereditary CRC
- Aut Dom, germline mutation in one of the MMR genes
  - MLH1, PMS2, MSH2, MSH6
  - Patterns:
    - MLH1 and PMS2 loss
    - MSH2 and MSH6 loss
    - Solitary MSH6 loss
    - Solitary PMS2 loss
  - Rarely: 3’ deletions of EPCAM → MSH2 hypermethylation
- CRC > endometrial cancer
- Younger age (50s-60s), multiple tumors, high-level microsatellite instability (MSI)
- More than 90% of LS tumors are MSI-H / have absent MMR proteins by IHC
- Most common somatic cause of MMR deficiency = MLH1 hypermethylation
Identification of LS patients?

- Clinical (family history, age, tumor histology) : sub-optimal
- Test the index cancer
  - IHC directs to appropriate gene
  - However, MSI = insensitive to neoadjuvant chemoradiation (rectal cancer, MSH6)
- Colorectal polyps in LS (HNPCC)?
  - One or more (up to 20) classical adenomas frequently detected at colonoscopy
  - Evolve quickly (dwell time 2-5 yrs instead of 10-15 yrs)
  - About half is advanced (> 1 cm, villous component, HGD)
- Test colorectal polyps in case of suspected LS?
  - MSI occurs early in LS carcinogenesis (in aberrant crypt foci & even in normal mucosa !)
  - Detection threshold : number of accumulated genetic defects
  - Therefore detection dependent on growth rate of the polyp → easier in advanced adenomas
  - Typically 40-80%, both IHC and molecular (technique-dependent)
  - Test polyps only if no cancer tissue is available!
Lynch syndrome: MMR deficiency in polyps

Fig 6. High concordance between IHC and MSI results using LMRs. There was 96% (79/82) concordance between MSI results using LMR repeats and loss of MMR expression by IHC. For example, tubular adenoma 26/8 was unstable at all five markers and lacked MSH2 and MSH6 expression. Note that when MSH2 is lost, the level of binding partner MSH6 is often significantly lower due to reduced stability. The area indicated by the rectangle in the H&E panel is enlarged 2x in each of the lower panels. Size bar for H&E, 500μm.

PMID: 26252492
Lynch syndrome: test algorithm for cancers

Universal Testing of Colorectal Cancers for Lynch Syndrome

Initial Screen: DNA Testing for MSI or IHC for MMR Proteins

Test for MSI

- MSS
- MSI-H

MLH1

- MLH1 Methylation
- BRAF testing

BRAF WT and MLH1 not methylated

No Further Evaluation

MMR IHC

MMR Protein Loss

Genetic Counseling

Germline Testing for Specific MMR Mutation

- MSH2, MSH6, PMS2

PMID: 26664327
Polyposis syndromes
(Attenuated) Familial Adenomatous Polyposis (FAP)

• 1/7000-1/30000, up to 0,5% of all CRCs
• Germline mutation in APC gene (10-30% de novo)
• FAP 100s-1000s of adenomatous polyps, AFAP 0-470 mean 25
• Younger age (40s-50s)
• Also polyps in stomach & duodenum, desmoid tumors (Gardner syndrome)
• Test for APC mutations if > 20 adenomas (hepatoblastoma, desmoid tumor ?)
MUTYH-associated Polypsosis (MAP)

- Less common than FAP and AFAP
- Biallelic mutations in MUTYH gene
- Typically 20-100 colonic adenomas, but HPs and SSPs may be found in 50%
- Younger age (50s-60s), 28x ↑ risk
- Test for mutations if > 20 adenomas (simultaneously with APC testing)
<table>
<thead>
<tr>
<th>Syndrome: Inheritance</th>
<th>Gene(s)</th>
<th>Associated Cancers (Lifetime Risk, %)</th>
<th>Nonmalignant Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS: Autosomal dominant</td>
<td><strong>MLH1, MSH2, EPCAM</strong></td>
<td>Colorectal (22%–74%), Endometrial (14%–54%), Stomach (0.2%–13%), ovary (4%–20%), urinary tract (0.2%–25%), hepatobiliary tract (0.02%–4%), small bowel (0.4%–12%), brain (1%–4%), sebaceous tumors (0.4%–4%)</td>
<td>Some colon adenomas; sebaceous gland adenomas and epitheliomas</td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td>Colorectal (10%–22%), Endometrial (17%–71%), Other malignancies possibly increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PMS2</strong></td>
<td>Colorectal (9%–20%), Endometrial (10%–15%), Other malignancies possibly increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAP: Autosomal dominant</td>
<td><strong>APC</strong></td>
<td>Colorectal (~100%), Duodenal/periampullary (4%–12%), thyroid (1%–2%) gastric (0.5%–1%), hepatoblastoma (&lt;1%), medulloblastoma (1%–2%), other cancers: pancreatic, biliary, distal small bowel</td>
<td>Colonic adenomatous polyposis, gastric polyposis (fundic gland), Duodenal polyps (adenomas), Desmoid tumors, epidermoid cysts, fibromas, osteomas, congenital retinal pigment epithelial hypertrophy, adrenal adenomas, dental abnormalities, pilomatrixomas, nasal angiofibromas</td>
</tr>
<tr>
<td>AFAP: Autosomal dominant</td>
<td></td>
<td>Colorectal (69%), Duodenal/periampullary (4%–12%), thyroid (1%–2%)</td>
<td>Colonic adenomatous polyposis, gastric polyposis (fundic gland), duodenal polyps/polyposis (adenomas)</td>
</tr>
<tr>
<td>MAP: Autosomal recessive</td>
<td><strong>MUTYH</strong></td>
<td>Colorectal (80%), Duodenal (4%), Other malignancies possibly increased</td>
<td>Colonic polyposis (adenomas, hyperplastic, and sessile serrated polyps), sebaceous gland adenomas, and epitheliomas</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Management Recommendations</td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **LS: MLH1, MSH2, and EPCAM**         | Colonoscopy every 1–2 y at age 20–25 y  
Consider prophylactic hysterectomy and bilateral salpingo-oophorectomy if childbearing complete  
Consider esophagogastroduodenoscopy every 3–5 y at age 25–30 y  
Annual physical/neurologic examination at age 25–30 y |
| **LS: MSH6 and PMS2**                 | Colonoscopy every 1–2 y at age 25–30 y  
Consider prophylactic hysterectomy and bilateral salpingo-oophorectomy if childbearing complete |
| **FAP**                               | Annual colonoscopy/sigmoidoscopy by 10–12 y until colectomy (total colectomy with IPAA often preferred)  
Upper endoscopy with side-viewing instrument every 1–4 y by 25–30 y  
Annual physical examination, with particular attention to the thyroid |
| **AFAP**                              | Colonoscopy every 2–3 y by late teens  
Total colectomy with ileal rectal anastomosis often preferred with advanced polyph/ polyposis  
Upper endoscopy with side-viewing instrument every 1–4 y by 25–30 y  
Annual physical examination, with particular attention to the thyroid |
| **MUTYH-associated polyposis**        | Colonoscopy every 2–3 y by 25–30 y  
Upper endoscopy with side-viewing instrument every 1–4 y by 30–35 y |
Hamartomatous polyposis syndromes

• **Peutz-Jeghers syndrome:**
  - Aut Dom, germline mutation in tumor suppressor gene LKB1 / STK11
  - Mucocutaneous pigmentation, intestinal polyposis, familial history
  - Colon polyps 1/3rd
  - Additional somatic mutations: dysplasia in PJ polyp, carcinoma
  - Lifetime colon cancer risk 40%

• **Juvenile polyposis syndrome:**
  - Aut Dom? Germline mutation in SMAD4 / BMPR1A, incomplete penetrance
  - Colorectum always affected, > 5 polyps
  - Development of conventional adenomas...
  - Lifetime colon cancer risk 20%

• **PTEN hamartomatous tumor syndrome**
  - AD, germline mutation in tumor suppressor gene PTEN / others?
  - Pediatric variant: Bannayan-Riley-Ruvalcaba syndrome
  - Adult variant: Cowden syndrome
  - Facial trichilemmomas, oral mucosal papillomatosis, hand / feet keratosis
  - Hamartomatous colon polyps (juvenile, ganglioneuroma, intramucosal lipoma) in 1/3rd – 3/3rds of pts
  - Adenomas common, 10x ↑ risk of colorectal cancer
Hamartomatous polyposis syndromes
Dysplasia in a PJS polyp

**Figure 2.** Endoscopic view of the flat, sessile rectal polyp (3.0 cm × 3.5 cm).

**Figure 3.** Histopathology image indicating a typical Peutz-Jeghers polyp and an adenoma with high-grade intramucosal neoplasia (HE staining × 100).
# Hamartomatous polyposis syndromes

## Table 2: Clinical features and colon cancer risk in Hamartomatous Polyposis Syndromes, according to literature series

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main clinical features polyp distribution</th>
<th>Increased risk of other tumors</th>
<th>Colon cancer risk</th>
</tr>
</thead>
</table>
| Juvenile Polyposis        | Juvenile polyps  
                        Distribution: large bowel (mainly), small bowel, stomach | Gastric and colorectal                                             | 39%-68%           |
| Peutz-Jeghers             | Peutz-Jeghers polyps  
                        Typical melanotic oral and dermic pigmitions  
                        Distribution: small bowel, large bowel, stomach | Gastric, small bowel, pancreas, colorectal, ovary, uterus, breasts, sex cords | 39%-57%           |
| PTEN                      | Mucocutaneous tumors (multiple trichlemmomas)  
                        Distribution: Small bowel, large bowel, stomach | Breast, thyroid, retina and uterus cancer                           | 18%               |

## Table 1: Genetic features and prevalence of pure Hamartomatous Polyposis Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mode of inheritance</th>
<th>Gene</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile Polyposis</td>
<td>AD</td>
<td>SMAD4/DPC4</td>
<td>1:100 to 1:160 thousand</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>AD</td>
<td>BMPIA, STK11/LKB1</td>
<td>1:60 mil a 1:300 thousand</td>
</tr>
<tr>
<td>Cowden</td>
<td>AD</td>
<td>PTEN, SDH and KLLN epimutations</td>
<td>Rare</td>
</tr>
</tbody>
</table>

## Table 3: Cumulative cancer risk by site and age in Peutz-Jeghers Syndrome (Hearle et al\(^{[18]}\))

<table>
<thead>
<tr>
<th>Cancer/Age</th>
<th>20 yr</th>
<th>30 yr</th>
<th>40 yr</th>
<th>50 yr</th>
<th>60 yr</th>
<th>70 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>2</td>
<td>5</td>
<td>17</td>
<td>31</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>-</td>
<td>1</td>
<td>9</td>
<td>15</td>
<td>33</td>
<td>57</td>
</tr>
<tr>
<td>Breast</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>13</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td>Gynecological</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Pancreas</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Lung</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>4</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>

BRRS: Bannayan-Riley-Ruvalacaba syndrome; AD: Autosomal dominant; SDH: Succinate dehydrogenase (B and C subunits); KLLN: p53 target gene.
Hamartomatous polyposis syndromes: recommendations

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Screening</th>
<th>Work-up</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jeghers</td>
<td>18-25 yr</td>
<td>Endoscopy (upper/lower)</td>
<td>2-3 yr</td>
</tr>
<tr>
<td>25 yr</td>
<td></td>
<td>MRI and mammography</td>
<td>Annual</td>
</tr>
<tr>
<td>10 yr</td>
<td></td>
<td>Testicular examination</td>
<td>Annual</td>
</tr>
<tr>
<td>30 yr</td>
<td></td>
<td>MRI or CT (pancreas)</td>
<td>1-2 yr</td>
</tr>
<tr>
<td>Juvenile Polyposis</td>
<td>15-18 yr</td>
<td>Upper endoscopy</td>
<td>1-3 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonoscopy</td>
<td>1-3 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper endoscopy and video capsule endoscopy</td>
<td>3 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for HHT</td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>After 25 yr</td>
<td>Colonoscopy</td>
<td>3-5 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mamography/thyroid US</td>
<td>Annual</td>
</tr>
</tbody>
</table>
That’s all for now
Questions?
Break!