Risk stratification for colorectal cancer especially: the difference between sporadic disease and polyposis syndromes

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Why is risk stratification for colorectal cancer (CRC) essential?

Identification of pre-malignant lesions or early CRC

It helps to reduce

- incidence of CRC
- treatment-related impact on patient QoL
- healthcare-related costs
Which factors is the risk stratification of CRC based on?

- **Clinical symptoms**
  - Rectal bleeding/unexplained iron deficiency anemia
  - Weight loss
  - Palpable mass

- **Age**

- **Personal history**
  - adenoma(s) and/or colorectal cancer
  - inflammatory bowel disease
  - acromegaly (excessive levels of growth hormone/IGF-1)
  - known genetic mutation(s)

- **Family history**
  - adenoma(s) and/or colorectal cancer
  - extracolonic malignancy
  - known genetic syndrome
Colorectal cancer can arise in various family risk settings. Which are these forms?
Which patient groups can be defined by risk evaluation*?

- Average risk
- Moderate risk
- High risk

*according to the BGS guidelines
Patients are at average risk, if

- ≥50 yrs of age \textit{and}
- Asymptomatic \textit{and}
- No personal history of adenoma/CRC \textit{and}
- No family history of adenoma/CRC

(max. one second/third degree family member with CRC ≥60yrs of age at diagnosis)

Screening/surveillance recommendation?

- Colonoscopy every 10 yrs from age 50 preferred screening modality*
- \textit{Virtual colonoscopy is an option for failed colonoscopy}
- Annual (CH: biannual$^1$) fecal occult blood test (with three separate stools)

*An inadequate clean out of the colon reduces the ability to detect lesions during colonoscopy and mandates a repeated procedure at a shorter interval (colonoscopy acceptable if BBPS≥6)

$^1$Krebsliga Schweiz 2015
Patients are at **moderate** risk, if

- Family history of CRC or adenoma

**Characteristics of familial CRC are…**

- “Clustering” of colon cancer cases in the family (age > 50 at diagnosis) without clear dominant pattern
- Likely to be multiple low penetrant genes plus environmental factors
- No well-defined threshold between sporadic and familial CRC at this time
Patients are at *moderate* risk, if

- Family history of CRC or adenoma

Family history data for risk stratification?

- Number of family members with CRC or adenoma
- Degree of kinship
- Age of affected family member(s) at diagnosis of CRC or adenoma
- Histology of tumour
- Number of polyps/adenomas
- Extracolonic tumour(s) in the family
## Risk of Developing Colorectal Cancer

<table>
<thead>
<tr>
<th>Family History</th>
<th>Relative Risk for CRC</th>
<th>Absolute Risk of CRC by age 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>No family history</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>1 FDR with CRC</td>
<td>2.25</td>
<td>9%</td>
</tr>
<tr>
<td>1 FDR Dx &lt;45 yrs</td>
<td>3.87</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;1 FDR with CRC</td>
<td>4.25</td>
<td>16%</td>
</tr>
</tbody>
</table>

Surveillance strategies for patients with positive FH

General principles of surveillance are…

1. screening should begin earlier
2. screening should be performed more frequently
3. screening should be with the best available test, colonoscopy

Positive Family history

One first-degree relative with CRC or adenoma* at <60 yrs of age or ≥ 2 first-degree relative** FDR with CRC at any age

Begin colonoscopy at age 40 or 10 yrs before the youngest case in the family whichever is earlier
Repeat every 5 yrs

One first-degree relative with CRC or adenoma* at ≥60 yrs of age or Two second-degree relative with CRC at any age

Begin colonoscopy at age 40
Repeat every 10 yrs if normal

First-degree relatives are: parent, brother, sister, daughter or son
Second-degree relatives are: grandparents, aunts, uncles, cousins, niece, nephew

*adenoma: ≥1 cm of size, high-grade dysplasia, (tubulo)villous histology
** consider familial syndrome
Patients are at **high** risk, if

- Personal history of colorectal cancer *or*
- Personal history of adenoma(s) *or*
- Personal history of IBD (≥10 yrs after diagnosis) *or*
- Personal history of acromegaly *or*
- Genetic diagnosis of (A)FAP/suspected (A)FAP w/o genetic evidence *or*
- Genetic diagnosis/suspected hereditary polyposis syndromes (MAP, PJS, JP) *or*
- Serrated polyposis syndrome *or*
- Genetic or clinical diagnosis of HNPCC, individuals at increased risk of HNPCC
Patients are at high risk, if

- Personal history of colorectal cancer or
- Personal history of adenoma(s) or
- Personal history of IBD (≥10 yrs after diagnosis) or
- Personal history of acromegaly or
- Hereditary polyposis syndromes/HNPCC

Surveillance recommendation?

- Personal h/o colon cancer: colonoscopy 12 months after resection* (T1-4 M0)
  or as soon as possible if colon not fully visualized prior surgery (according to our SOP within 6 mo)

- Personal h/o rectal cancer: rectosigmoidoscopy in 6 months-interval in the first 2 yrs
- Annual thoracic and abdominal CT scan in the first 5 yrs
- CEA-titer
  annual in the first 5 years in colon cancer T1-2
  3 monthly in the first year, 6 monthly in years 2 and 3, then annual in colon cancer T3-4/ rectum cc

*if colonoscopy at one year is negative, repeat at 3 yrs and then every 3-5 yrs if normal
Patients are at high risk, if

- Personal history of colorectal cancer or
- Personal history of adenoma(s) or
- Personal history of IBD (≥10 yrs after diagnosis)
- Personal history of acromegaly
- Hereditary polyposis syndromes/HNPCC

Risk stratification for polyps/adenomas?

<table>
<thead>
<tr>
<th>No risk («and»)</th>
<th>Low risk («or»)</th>
<th>Low risk («and»)</th>
<th>Intermediate risk («or»)</th>
<th>Intermediate risk («or»)</th>
<th>High risk («and»)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic</td>
<td>Hyperplastic</td>
<td>1-2 polyp(s)</td>
<td>(Tubulo)vilous</td>
<td>pT1 carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>≤1 cm of size</td>
<td>≥1 cm of size</td>
<td>≤1 cm of size</td>
<td>Serrated</td>
<td>complete resection</td>
<td></td>
</tr>
<tr>
<td>Rectosigmoideum</td>
<td>proximal to</td>
<td>tubular/serrated</td>
<td>&gt;1 cm of size</td>
<td>no angioinvasion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rectosigmoideum</td>
<td>no dysplasia</td>
<td>High grade dysplasia</td>
<td>G1/2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no FA</td>
<td>positive FA (FDR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 yrs</td>
<td>5 yrs</td>
<td>5 yrs</td>
<td>3 yrs</td>
<td>3 yrs</td>
<td></td>
</tr>
<tr>
<td>3 mo then 3 yrs</td>
<td>3 yrs</td>
<td>3 yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patients are at high risk, if

- Personal history of colorectal cancer or
- Personal history of adenoma(s) or
- Personal history of IBD (≥10 yrs after diagnosis)
- Personal history of acromegaly
- Hereditary polyposis syndromes/HNPCC

Risk stratification in IBD patients?

**Lower risk («or»)**

Extensive* colitis NO ACTIVE end./hist. Inflammation or Left-sided colitis or Crohn’s colitis of ≤50% colon

**Intermediate risk («or»)**

MILD ACTIVE extensive* colitis or Post-inflammatory polyps or FH of CRC in FDR aged 50+

**High risk («or»)**

MODERATE/SEVERE ACTIVE Extensive* colitis or Stricture in past 5 yrs or Dysplasia in past 5 yrs or PSC/transplant for PSC or FH CRC in FDR aged <50

- Extensive disease defined as E3 (proximal to the splenic flexure) and L3 (at least 50% of the colon) according to the Montreal classification
Biopsy protocol in IBD patients?

Pancolonic dye spray
- targeted biopsy of abnormal areas
- 2-4 random biopsies from every 10 cm of the colorectum

Post-colectomy surveillance in IBD patients?

**Lower risk**
- None of the higher risk factors

↓

5 yrs

**Higher risk («or»)**
- Previous rectal dysplasia
- Dysplasia/cancer at time of pouch surgery
- Persistent atrophy & severe inflammation
- PSC

↓

1 yr
Patients are at **high risk**, if

- Personal history of colorectal cancer *or*
- Personal history of adenoma(s) *or*
- Personal history of IBD (≥10 yrs after diagnosis)
- Personal history of acromegaly
- Hereditary polyposis syndromes/HNPCC (hereditary CRC)

**Surveillance recommendation?**

- **Colonoscopy starting at 40 yrs of age**

**Lower risk («or»)**
- Negative first screening
- Hyperplastic polyp found at first screening
- Normal IGF-1/growth hormone levels

5-10 yrs

**Higher risk («or»)**
- adenoma found at first screening
- IGF-1 > max. of age-corrected normal

3 yr
Patients are at high risk, if

- Personal history of colorectal cancer or
- Personal history of adenoma(s) or
- Personal history of IBD (≥10 yrs after diagnosis)
- Personal history of acromegaly
- Hereditary polyposis syndromes/HNPCC (hereditary CRC)

Characteristics of hereditary CRC are…

- Multiple relatives with colorectal cancer
  - One or more diagnosed at an early age (<50)
- Sequential generations affected
  - Except in autosomal recessive syndromes (MAP)
- Other cancers in the family known to be associated with CRC (uterine, ovarian, GI)
- Multiple primary tumors or polyps
Compared to sporadic cancer people with hereditary cancer have…

- A higher risk of developing cancer
- A younger age of onset of cancer
  - Generally < 50 years of age
- Multiple primary cancers
- Generally have a family history of cancer

Hereditary cancer is less common in the general population than sporadic cancer

For risk stratification is genetic testing in suspected hereditary colon cancer syndromes essential
Who are eligible for genetic testing?

1. Patients with $\geq 10$ adenomatous polyps or $\geq 2$ hamartomatous polyps
2. Patients at age $\leq 40$ yrs with adenomatous polyps AND high-grade dysplasia
3. Patients with diagnosis of CRC and/or endometrium cancer at age $< 50$ yrs
4. Multiple colorectal and/or extracolonic carcinomas (synchronous or metachronous)
5. Family members of patients with known genetic mutation of hereditary tumour sy.
6. Positive family history of CRC and/or extracolic cancers in $\geq 2$ first-degree relatives
Suspected polyposis syndrome

Colonoscopy:
Number, size, localisation and histological type of polyps

EGD, Enteroscopy/ Capsule enteroscopy of the small intestine

Extraintestinal manifestations? (tumours, skin lesions, CHRPE, osteom)

Family history (autos. dominant/ recessive inheritance, sporadic)

Suspected diagnosis

Adenomatous polyposis FAP/AFAP, MAP

Hamartomatous polyposis PJS, JP, CS

Serrated polyposis SPS

Genetic counselling (general information, risk of recurrence/carcinoma)

Genetic testing (detection/screening of mutation(s))

Mutation found
Confirmation of diagnosis
Predictive testing of patients at risk

No mutation found
Predictive testing of patients at risk not possible

Screening, therapy
Endoscopy, polypectomy, colectomy

Risk stratification for colorectal cancer November 18, 2015
Serrated polyposis syndrome

Multiple/large hyperplastic lesion throughout the colon

Concomittant concorruence with adenomatous polyps (number of lesions ~ CRC-risk)

Less is known about etiology, natural history and incidence
(serrated pathway predominates over WNT pathway: CpG-islet hypermethylation (CIMP) →transkriptional/epigenetic silencing of hMLH1 gen, w/wo BRAF mutation)

WHO criteria for diagnosis 2010 («or»):
- ≥20 cumulative hyperplastic lesion of any size distributed throughout the colon
- ≥5 hyperplastic lesion proximal to the sigmoid colon with at least 2 being greater than 10 mm in diameter
- ≥1 hyperplastic colonic lesion with a 1st-degree relative with HPP
Which genetic testing for risk stratification?

**Suspected HNPCC**

**Modified Amsterdam criteria**
- 3 or more relatives with a Lynch Syndrome–associated cancer;
- 2 or more successive generations affected;
- 1 or more relatives diagnosed before age 50 years;

One family member should be a first-degree relative of the other 2 members
FAP excluded

**Revised Bethesda Criteria**
- Colorectal cancer diagnosed in a patient less than 50 years of age
- Presence of synchronous or metachronous colorectal or other HNPCC-associated tumours, regardless of age
- Colorectal cancer with MSI-H histology diagnosed in a patient less than 60 years of age
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under the age of 50 years
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

Hoffmann R et al *Gastroenterology & Endoscopy News* 2010;61[5]:1,19-20,22
Genetic testing of the index patient in suspected Lynch syndrome

- **Immunohistochemistry**
  - Absent staining of MLH1/PMS2
  - Absent staining of MSH2/MSH6 or Absent staining of PMS2 (MLH1 intact)
- **Intact MMR-protein expression**
- **PREMM-Score ≥5%**
- **MSI testing**
  - Normal
  - MSI-high
  - No further testing
- **Genetic counselling and testing**
- **BRAF mutation V600E/MLH1-promoter-hypermethylation testing**
  - Absent MMR protein expression in 10% of sporadic CRC
  - BRAF mutation present/MLH1-promoter-hypermethylation
- **Sporadic cancer**

**NOTE:** up to 5-10% false negative testing results of IHC and MSI-PCR
Surveillance strategies for patients with hereditary CRC?

- Genetic diagnosis of FAP or suspected FAP w/o genetic evidence
  - Annual colonoscopy starting at age 12
  - Consider prophylactic colectomy
- Genetic diagnosis of AFAP/MAP or suspected AFAP/MAP w/o genetic evidence
  - Annual colonoscopy starting at age 18-20
- Genetic or clinical diagnosis of HNPCC or individuals at increased risk of HNPCC
  - Annual colonoscopy starting at age 20-25 yrs or 10 yrs before onset of the youngest HNPCC-associated tumour case
- Genetic/clinical diagnosis of PJS
  - Biannual colonoscopy starting at age 25
- Genetic/clinical diagnosis of JP
  - Annual colonoscopy starting at age 18-20 consider prophylactic colectomy
- Clinical diagnosis of SPS
  - Annual/Biannual colonoscopy prophylactic colectomy when polyps become unmanageable