Preneoplasia and Neoplasia of the colon
Juveniler Polyp

- Abundant stroma composed of inflamed often oedematous, granulation tissue surrounding cystically dilated glands containing mucin
- Most commonly in children (< 5 years)
- Dysplasia is very rare, but in increased in patients with juvenile polyposis syndrome
- May be sporadic or syndromic
- May present with bleeding
- Usually in rectum
Juveniler Polyp
Peutz-Jeghers Polyp

- Hamartomatous gastrointestinal polyp
- Mainly small intestine, rarely stomach
- Proliferation of glands intermingled with musculatur
- Can mimic invasion
Peutz-Jeghers Polyp
<table>
<thead>
<tr>
<th>Risikokategorie</th>
<th>Charakterisierung des/der Polypen (Histologie, Zusatzkriterien)</th>
<th>Koloskopie-Intervall</th>
<th>Koloskopie-Intervall, sobald Befund bland</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hyperplastische Polypen</td>
<td>Screening Koloskopie alle 10 Jahre²</td>
<td></td>
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<tr>
<td></td>
<td>. im Rektosigmoid und &lt;1 cm</td>
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<td></td>
<td>. im Rektosigmoid: &gt;1 cm oder</td>
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<tr>
<td></td>
<td>. oberhalb Rektosigmoid</td>
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<tr>
<td></td>
<td>Tubuläres Adenom</td>
<td>5 Jahre</td>
<td>Screening Koloskopie alle 10 Jahre²</td>
</tr>
<tr>
<td></td>
<td>. ≤ 2 Polypen und</td>
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<td></td>
<td>. ≤ 1 cm gross und</td>
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<td></td>
<td>. keine hochgradige Dysplasie</td>
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<tr>
<td></td>
<td>Sessiles serratiertes Adenom</td>
<td>5 Jahre</td>
<td>5 Jahre</td>
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<tr>
<td></td>
<td>&lt;1 cm und ohne Dysplasie</td>
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<tr>
<td>II</td>
<td>Tubuläres Adenom</td>
<td>3 Jahre</td>
<td>5 Jahre</td>
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<tr>
<td></td>
<td>. ≥ 3 Polypen oder</td>
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<td></td>
<td>. &gt;1 cm gross oder</td>
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<tr>
<td></td>
<td>. hochgradige Dysplasie</td>
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<td></td>
<td>(Tubulo-) villöses Adenom</td>
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<tr>
<td></td>
<td>Traditionelles serratiertes Adenom oder</td>
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<tr>
<td></td>
<td>Sessiles serratiertes Adenom</td>
<td></td>
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<tr>
<td></td>
<td>. ≥1 cm oder mit Dysplasie</td>
<td></td>
<td></td>
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<tr>
<td>III</td>
<td>pT1-Karzinom in sessilem Polyp</td>
<td>≤ 3 Monate zur Kontrolle der Resektionsstelle, dann 3 Jahre</td>
<td></td>
</tr>
<tr>
<td></td>
<td>. Polypektomie endoskopisch vollständig und</td>
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<tr>
<td></td>
<td>. Resektionsrand histologisch karzinomfrei und</td>
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<td></td>
<td>. Differenzierung G1-2 und</td>
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<td></td>
<td>. keine Angioinvasion und</td>
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<td></td>
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<tr>
<td></td>
<td>. &lt;1000 Mikrometer Invasion</td>
<td></td>
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<td></td>
<td>pT1-Karzinom in gestieltem Polyp</td>
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<tr>
<td></td>
<td>. Polypektomie endoskopisch vollständig und</td>
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<tr>
<td></td>
<td>. tumorfreier Stiel (Haggit Level 1-2)</td>
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<tr>
<td></td>
<td>. Differenzierung G1-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>. keine Angioinvasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>pT1-Karzinom im Polyp</td>
<td>Präsentation Tumorboard Chirurgische Resektion grundsätzlich indiziert</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nicht alle Kriterien Risikokategorie III erfüllt</td>
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</tbody>
</table>
Carcinoma of the colon and rectum

Adenocarcinoma
- Cribriform comedo-type adenocarcinoma
- Medullary carcinoma
- Micropapillary carcinoma
- Mucinous adenocarcinoma
- Serrated adenocarcinoma
- Signet ring cell carcinoma

Adenosquamous carcinoma
Spindle cell carcinoma
Squamous cell carcinoma
Undifferentiated carcinoma
Histologic variants of Adenocarcinoma
Histological grading

<table>
<thead>
<tr>
<th>Gland formation in %</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 95%</td>
<td>Well</td>
</tr>
<tr>
<td>50-95%</td>
<td>Moderate</td>
</tr>
<tr>
<td>0-49%</td>
<td>Poor</td>
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</tbody>
</table>

If heterogeneous, grading is based upon the least differentiated component. The invading edge is regarded as suboptimal for grading.
Most CRCs are in the sigmoid colon and rectum
Proportion of CRC that are more proximal increases with age
MSI high frequently located in caecum, ascendens and transversum
Molecular analysis

**MSI-H Histology**

- Increased tumor-infiltrating lymphocytes
- Crohn’s like lymphocytic reaction
- Mucinous adenocarcinoma
- Signet ring cell differentiation
- Medullary adenocarcinoma
- Poorly differentiated carcinoma
- Aberrant CK20 expression

Test
IHC (MLH1, PMS2, MSH2, MSH6)
PCR (BAT25, BAT26, S2S123, D5S346, D17S250)
**Table 1 Amsterdam criteria II for Lynch syndrome (60)**

There should be at least three relatives with a Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter or renal pelvis)

All of the following criteria should be present

1. One should be a first-degree relative of the other two
2. At least two successive generations should be affected
3. At least one should be diagnosed before the age of 50 years
4. Familial adenomatous polyposis should be excluded in colorectal cancer case(s), if any
5. Tumors should be verified by pathological examination

**Table 2 Revised Bethesda guidelines for MSI testing (61)**

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumors, regardless of age
3. Colorectal cancer with the MSI-H histology, diagnosed in a patient who is less than 60 years of age
4. Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch syndrome-related tumor, with one of the cancers being diagnosed under age 50 years
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age

*Lynch syndrome-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract, and brain (usually glioblastoma) tumors, sebaceous gland adenomas, keratoacanthomas, and carcinoma of the small bowel; **Presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern
Molecular analysis

KRAS
- EGFR-Ab was only effective in KRAS wt patients.
- No EGFR-Ab treatment with KRAS mutations Therefore KRAS mutation testing for stage IV patients necessary.
- KRAS wt patients with resistance to EGFR-Ab treatment where shown to have mutations in NRAS (exon 2, 3 and 4)

BRAF
- BRAF mutations confer resistance to EGFR-inhibitors
- BRAF and KRAS mutations are mutually exclusive
Classification
• Adenomatous and
• Non-adenomatous polyposis syndromes

Adenomatous polyposis syndromes
• Familial adenomatous polyposis (FAP)
• Attenuated familial adenomatous polyposis (AFAP)
• MUTYH (MYH)-associated polyposis (MAP)

Hamartomatous polyposis syndromes
• Peutz-Jeghers syndrome (PJS)
• Juvenile polyposis (JP)
• Cowden syndrome (CS)
Familial polyposis syndrome

Prevalence: 1 in 10,000 individuals

Clinical characteristics
• Colonic manifestations
• Extracolonic manifestations in the GI tract
• Extraintestinal manifestations

Diagnosis
• >100 adenomatous polyps
• APC germline mutation
• FAP in family and any number of adenomatous polyps at young age

Colonic manifestations
• Presence of > 100 colonic adenomatous polyps
• Polyp development usually starts at an average age of 15y
• Nearly all patients with untreated FAP develop CRC by the age of 40
Familial polyposis syndrome

Extracolonic manifestations
• Polyps in the upper GI tract (duodenum, stomach)

Extraintestinal manifestations
• Desmoid tumors, Epidermoid cysts, Fibromas and osteomas, Dental abnormalities, congenital hypertrophy of the retinal epithelium (CHRPE)

Single crypt adenoma
Familial polyposis syndrome

**Gardner`s syndrome**
- Combination of polyposis, epidermoid cysts, osteomas, desmoid tumor

**Turcot´s syndrome**
- Combination of polyposis and tumours of the CNS (medulloblastoma)

**Genetics**
- Autosomal dominant inherited disease
- Germline mutation of the APC gene in chromosome 5
- Mutations detectable in 80 % of patients with FAP
- New or de novo mutations are responsible for 25 % of FAP cases

**Treatment**
- Prophylactic surgery is performed in the majority of patients before 20y
Approximately 10% of FAP patients present with an attenuated form of FAP

**Clinical characteristics**
- **Colonic manifestations**
- **Extracolonic manifestations** (rare in comparison to FAP)

**Colonic manifestations**
- 10-100 colorectal polyps with a predominance in the proximal colon
- Tendency to polyp and CRC development at a later age; AFAP is mostly diagnosed in patients older than 45 years
- Without therapeutic interventions the estimated CRC risk is 70-80%

**Extraintestinal manifestations** (rare)
- Desmoid tumours
- Epidermoid cysts
- Fibromas and osteomas (mandibula)
- Dental abnormalities, CHRPE
MUTYH-associated polyposis (MAP)

Autosomal recessive disorder, accounts for < 10 % of early-onset CRC

Clinical characteristics

Colonic manifestations

✓ Multiple colorectal adenomas (>10) and carcinomas (phenotype difficult to distinguish from FAP/AFAP)
✓ Most patients older than 45 years at diagnosis
✓ Adenomatous polyps predominate, hyperplastic polyps and serrated polyps are common

Extracolonic manifestations rare

• Gastric and duodenal polyps in 11 and 17 %
• Increased risk for ovarian, bladder, skin, sebaceous gland tumors, possible breast cancer
MUTYH-associated polyposis (MAP)

Genetics
Biallelic germline mutation of the base excision repair (BER) gene *MUTYH* on chromosome 1

Two hot spot mutations representing 80% of all mutations (Y179C, G396D)
- Germline mutation testing is indicated in patients with 10 or more adenomas after exclusion of an APC mutation
Juvenile polyposis syndrome (JPS)

Autosomal dominant familial cancer syndrome 1:100’000

Multiple hamartomatous polyps (3-200) of the colorectum (98%), stomach (13%) and the small bowel (6%)

Definition
• Five or more juvenile polyps in the colon or rectum; or
• One juvenile polyp and positive family history of JP, or
• Juvenile polyps outside the colon or rectum (stomach or small bowel, any number)

Congenital abnormalities (cardiovascular, urogenital or CNS abnormalities) in about 15 % of patients

Genetic
SMAD4, BMPR1A in 50-60% of the cases
Peutz-Jeghers syndrome

Incidence: 1/50000-1/120000

Peutz-Jeghers polyps and mucocutaneous melanin pigmentation (pigment lesions in 95% of patients)

10-fold increase in CRC
Predisposition to develop cancer of: breast, pancreas, testis (Sertoli cell)

Genetics
Autosomal dominant
Germline mutation in LKB1/STK11 tumor suppressor gene
Cowden syndrome (CS)

Intestinal hamartomatous polyposis (stomach, colon, oesophagus)

Germline mutation in PTEN gene.
- Juvenile polyps, lipomas, inflammatory polyps, ganglioneuromas, lymphoid hyperplasia
  - Cutaneous hamartomas (Facial trichilemmomas, oral papillomas, hyperkeratotic skin lesions) and oesophageal glycogenic acanthosis
  - Increased lifetime risk for breast cancer (50%) and thyroid cancer (15%)
  - Gastrointestinal cancer risk is not increased

Genetics
- Autosomal dominantly inherited disease
- Germline mutations of the tumour suppressor gene PTEN (approximately 80% of patients)

Surveillance
- Should focus on breast and thyroid cancer
Lynch syndrome (HNPCC)

- Autosomal dominant disease
- Caused by germline mutations in the DNA mismatch repair (MMR) genes.
- Proximal colon predilection
- Earlier age onset
- Accelerated progression (adenoma-carcinoma)
- Extra colonic cancer (endometrium, ovaries, sebaceous glands)
- Favorable survival
- Turcot variant (brain tumors)
- Muir-Torre variant (sebaceous glands)
References

• WHO Classification, Blue Book, Tumours of the Digestive System