Colon

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Contents

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3.1 Anatomy and Physiology

3.1.1 Definition and Limits

- Definition
  - Colon = Intestinum crassum, part of the gastrointestinal tract
  - Distally from the small intestine, proximal from the rectum
- Limits
  - Proximal = ileocecal valve (= Bauhin); border between terminal ileum and colon
  - Distal = indistinct; transition zone between sigmoid colon and rectum = transition of the taenia into closed longitudinal muscles of the rectum

3.1.2 Tasks

- Transport of chyme
- Thickening of chyme
  - Active Na^+ resorption (with diffusion of H_2O)
  - Absorption capacity = up to 5 L/day (9 L in total in the whole gastrointestinal tract)
  - Active secretion of K^+, Cl^-, HCO_3^-
- Further development of chyme
  - Breakdown of the cellulose content by bacterial colonisation of the colon (10^{10} bacteria/g faeces)
  - Resorption of 40–50% of the fibres

3.1.3 Location and Classification

- Five colonic segments from proximal to distal:
  - Caecum (= appendix, coecum) with appendix vermiformis (= appendix)
  - Ascending colon
  - Transverse colon
  - Descending colon
  - Colon sigmoideum (= sigma)
- Position of the colon in relation to the peritoenum
  - Caecum (distal part) + appendix: Intraperitoneal
  - Caecum (proximal part): Secondary retroperitoneal
  - Ascending colon: Secondary retroperitoneal
  - Transverse colon: Intraperitoneal
  - Descending colon: Secondary retroperitoneal
  - Sigmoid colon: Intraperitoneal

3.1.4 Measured Values

- Colon length = 1/4 of the length of the intestine (in adults 140–160 cm)
- Lumen of the colon varies in size: in adults
  - Caecum = approx. 6.5 cm (maximum width approx. 9 cm)
  - Colon ascendens = approx. 5.5 cm
  - Transverse colon approx. 5 cm
  - Descending colon = approx. 4 cm
  - Sigmoid colon = approx. 5.5 cm

3.1.5 Characteristic Features of the Colon

- Taeniae coli
  - 0.5–1 cm wide light bands = shirred outer longitudinal muscles of the colon
  - Beginning at cecum-appendix junction to sigmoid colon
  - Three Taenia: libera, mesocolica, omentalis
- Haustra coli
  - Puffed sleeve-like protrusions of the colon between plicae semilunares coli
- Plicae semilunares coli
  - Crescent-shaped mucosal folds of the colon
- Appendices epiploicae
  - Small sac-like protrusions of the colonic serosa filled with fatty tissue from tela subserosa
  - Located near the Taeniae libera and mesocolica

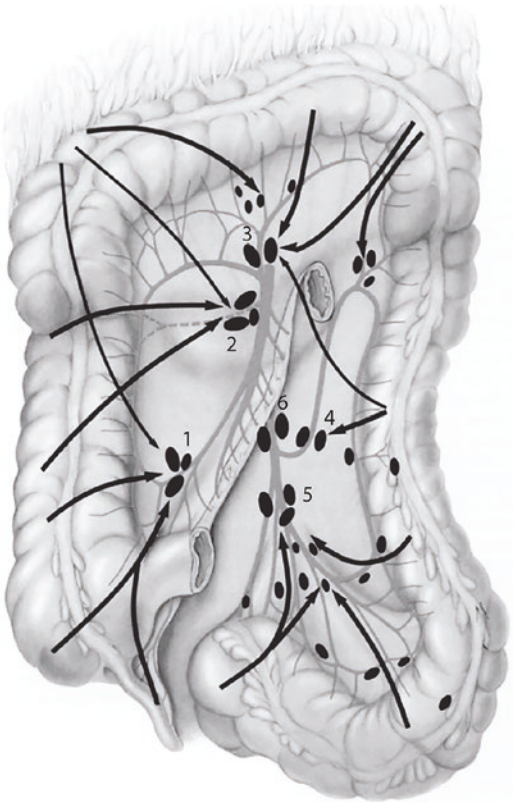


Fig. 3.1 Lymphatic drainage of the colon. *1* Ileocolic artery, *2* Right colic artery, *3* Middle colic artery, *4* Left colic artery, *5* Sigmoid arteries, *6* Inferior mesenteric artery

3.1.6 Blood Supply and Drainage

Arteries

- Superior mesenteric artery (ileocolic artery + right colic artery + middle colic artery): Caecum + appendix + ascending colon + transverse colon
- Inferior mesenteric artery (left colic artery + sigmoid artery): left half of transverse colon + descending colon + sigmoid colon
- Riolan anastomosis = anastomoses between two watershed areas: Between middle colic artery and left colic artery (Ramus ascendens), supply area superior and inferior mesenteric arteries

Veins

- Veins parallel to the arteries = portal vein/Henle loop

Lymphatic Drainage (Fig. 3.1)

- Along the associated arteries
- Paracolic at the small blood supply vessels (arcades)
- Intermediate: Along the main vessels
- Central: In the area of the aorta

Caution

Lymphatics along the marginal arteries = LN (lymph node) metastases to proximal and distal possible: safety distance to the proximal and distal resection border = 10 cm

3.2 Benign Diseases of the Colon

3.2.1 Diverticulosis and Diverticulitis

Key Points

- Acquired benign disease of the colon; incidence increasing with age
- Complications: Diverticulitis, hemorrhage, abscess, perforation, stenosis…
- Therapy: primarily conservative; surgery: in case of complications/recurrent diverticulitis

Definitions

Colon Diverticulum

- Acquired protrusion of the intestinal wall
- Diverticulum: Protrusion of the entire intestinal wall
- Pseudodiverticulum: Protrusion of the mucosa + submucosa through muscle-weak gaps of the colon wall

Diverticular Disease

- Occurrence of symptoms/complications in the context of diverticulosis

Diverticulitis (= Pathological)

- Peridiverticulitis: inflammatory process originating by the colonic diverticulum
- Pericolitis: spread to the intestinal wall (= focal pericolitis)

Epidemiology

- Prevalence of diverticulosis:
  - Increases with age
  - Under 40 years = rare
  - 60 years = approx. 30%
  - 85 years = approx. 65%
- Men:Women = 1:1
- Diverticular disease: clinical symptomatic = 10–25% of diverticular carriers (complications in 5%)
- Diverticulitis: incidence = 80–126/100,000 population/year

Etiology/Pathogenesis

- Multifactorial
- Increased intraluminal pressure
- Weakness of the intestinal wall: mostly passage of the vessels

Sigmoid colon = high pressure zone = increased intraluminal pressure; 90% of diverticula in the sigmoid.

Risk Factors

- Higher prevalence at older ages
- Genetic predisposition (e.g. Marfan syndrome, Ehlers-Danlos syndrome, polycystic kidney disease)
- Dietary fiber deficiency
- Higher body weight (BMI >30 kg/m^2)
- Recurrence rate after acute diverticulitis: depending on severity (between 2% and 35%) (= guideline)
- Complicated diverticulitis:
  - Relevant mortality (0–13%)
  - Special risk under immunosuppression (8–24%)

Increased prevalence of colorectal cancer in diverticulosis is not proven.

Complications

- Diverticulitis (see above)
  - Development due to stool retention = bacterial growth in the diverticulum = inflammation
  - Initial lesion before abscess, perforation
- Diverticular bleeding
  - In 5% of diverticula carriers (= hematochezia)
  - Independently of inflammation
  - Risk = age, nonsteroidal anti-inflammatory drugs, right-sided diverticula (Asian patients)
- Abscess and/or fistula formation
  - Severe complications
- Covered perforation/open perforation with peritonitis
- Stenosis

Symptoms

- Diverticulosis = asymptomatic
- Diverticulitis:
  - Left lower abdominal pain (abrupt onset, rapidly progressive)
  - Possibly pressure-painful roller (palpatory)
  - Fever, nausea, vomiting, dysuria
  - Change in bowel movements, possibly blood in the stool
  - Diverticular bleeding
  - Painless peranal bleeding
  - Sustained/Intermittent
  - Spontaneous healing (80% of cases)
  - High recurrence rate

Classifications

- Classification of diverticular disease according to the German S2k guideline of the AWMF (Classification of diverticular disease, CDD) (◘ Table 3.1)
- Classification according to Hinchey (for perforated sigmoid diverticulitis) (◘ Table 3.2)
- Classification according to Hansen and Stock (for sequence: diverticulosis, diverticulitis, complications) (◘ Table 3.3)

Table 3.1 Classification of diverticulitis/diverticular disease (CDD)

Type 0	**Asymptomatic diverticulosis**	
		Incidental finding; asymptomatic
		No disease
Type 1	**Acute uncomplicated diverticular disease/diverticulitis**	
Type 1a	Diverticulitis/diverticular disease without environmental reaction	Symptoms related to the diverticula
		Inflammatory signs (laboratory): optional
		Typical sectional imaging
Type 1b	Diverticulitis with phlegmonous bypass reaction	Inflammatory signs (laboratory): obligatory
		Sectional imaging: phlegmonous diverticulitis
Type 2	**Acute complicated diverticulitis** as 1b, additionally:	
Type 2a	Microabscess	Covered perforation, small abscess (≤1 cm); minimal paracolic air
Type 2b	Macroabscess	Para- or mesocolic abscess (>1 cm)
Type 2c	Free perforation	Free perforation, free air/liquid
		Generalized peritonitis
Type 2c1	Purulent peritonitis	
Type 2c2	Fecal peritonitis	
Type 3	**Chronic diverticular disease** Recurrent or persistent symptomatic diverticular disease	
Type 3a	Symptomatic uncomplicated diverticular disease (SUDD)	Typical clinical presentation
		Inflammatory signs (laboratory): optional
Type 3b	Recurrent diverticulitis without complications	Signs of inflammation (laboratory) present
		Cross-sectional imaging: typical
Type 3c	Recurrent diverticulitis with complications	Detection of stenoses, fistulas, conglomerate
Type 4	**Diverticular bleeding**	**Detection of the source of bleeding**

Table 3.2 Classification of perforated sigmoid diverticulitis according to Hinchey

Division	Definition
Hinchey I	Local pericolic abscess after perforation into the mesocolon
Hinchey II IIA IIb	Distant abscess Circumscribed, drainable distant abscess Diffuse abscess with fistula formation
Hinchey III	Purulent peritonitis
Hinchey IV	Fecal peritonitis

Table 3.3 Classification according to Hansen and Stock

Division	Definition
Stage 0	Asymptomatic diverticulosis
Stage 1	Diverticulitis without intestinal wall overflow, clinically unspecific complaints, inconspicuous CT findings
Stage 2a	Phlegmonous form, on CT extension into the pericolic fat tissue
Stage 2b	Spread of inflammation to adjacent organs by covered perforation, extraluminal gas inclusions in CT or abscess formation
Stage 2c	Free perforation, clinical signs of acute abdomen and evidence of free air
Stage 3	Chronic recurrent, development of intestinal wall fibrosis and luminal narrowing

Diagnosis

Medical History (Medication, Tobacco Consumption)

Clinical Examination

- Abdomen: palpation, auscultation, digital-rectal examination
- See below Symptoms
- Measurement of body temperature

Laboratory Tests

- Leucocytosis
- CRP elevation, accelerated blood sedimentation
- Urine analysis
- In sepsis: elevated procalcitonin

Diagnostic Imaging

- Ultrasound examination:
  - Bowel wall thickening
  - Dom sign: Hypo-echoic lesion, eccentric next to the intestinal wall (= inflammatory diverticulum)
  - Abscess, fatty tissue compression
- Cross-sectional imaging: CT with contrast agent = standard: confirmation of diagnosis + exclusion of complications
- Colonoscopy:
  - No colonoscopy to confirm the diagnosis of acute diverticulitis (risk of perforation!)
  - Important role in lower GI (gastrointestinal) bleeding and/or to exclude tumor
  - Colonoscopy after conservatively treated diverticulitis and planned elective sigmoid resection: (Usually after 4–6 weeks, to exclude other relevant pathologies

Caution

Colonoscopy in acute inflammatory situation = high risk of perforation.

Therapy

Prophylaxis of Diverticulitis

Primary Prophylaxis

- Regular physical activity
- High fiber diet
- Preservation of normal weight

Secondary Prophylaxis

- Insufficient data = no general recommendations possible
- Prophylaxis of recurrent diverticular disease:
  - Nutrition
  - Lifestyle
  - Physical activity
  - Medications (mesalazine, probiotics, rifaximin)

Conservative Therapy

Asymptomatic Diverticulosis

- Primary prophylaxis (see above)
- Acute uncomplicated diverticulitis without risk factors for a complicated course
  - Close clinical and laboratory control
  - Low recurrence rate
  - No indication for surgery

- Antibiotic therapy:
  - No acceleration of healing
  - No prevention of complications/recurrences
  - Exception = in the case of necessary immunosuppressive drug therapy after transplantation, collagenoses etc.

Complicated Diverticulitis

- Inpatient treatment
- If necessary, parenteral fluid substitution in case of insufficient oral fluid intake
- Oral intake of food if necessary (depending on clinical situation)
- Parenteral antibiotic therapy
- For retroperitoneal/paracolic abscesses = interventional drainage + control

Surgical Therapy

Surgery Indications

- Emergency surgery:
  - CDD Type 2c
  - Evidence of freely perforated sigmoid diverticulitis with clinical or radiological signs of peritonitis
  - Failure of conservative therapy in complicated diverticulitis (acute abdomen, sepsis)
  - Diverticular hemorrhage with circulatory effect or persistent Hb effect that cannot be controlled by interventions
- Elective surgery in the inflammation-free interval (>3–4 weeks):
  - Recurrent diverticulitis with structural changes and complications CDD type 3c (fistula formation, stenosis, unclear dignity)
  - After successfully treated complicated diverticulitis CDD type 2b (macroperforation, abscess)
  - Clinically uncomplicated symptomatic diverticular disease CDD type 3a or chronic recurrent diverticulitis CDD type 3b
  - Recurrent, localized, clinically relevant diverticular bleeding
  - Diverticular hemorrhage: endoscopic hemostasis or angiography with embolization not possible
- Surgery is not indicated:
  - Asymptomatic diverticulitis CDD type 0
  - Acute uncomplicated diverticulitis CDD type 1
  - In the interval after successful conservative therapy of complicated sigmoid diverticulitis with microabscess CDD type 2a
  - Self-limiting or interventional successfully treated diverticular bleeding

Surgical Strategy

- Objective = removal of the diverticulum (diverticulitis)-bearing intestinal segment
- Laparoscopic (or laparoscopic-assisted) vs. open resection: Laparoscopic = fewer local complications, wound infections, intra-abdominal abscesses, postoperative ileus and fascial dehiscence
- Standard procedure = sigmoid resection + primary continuity restoration (if necessary with protective ileostoma) also in case of perforated sigmoid diverticulitis
- Laparoscopic peritoneal lavage + drainage, without resection: if necessary also for Hinchey III
- Sigmoid resection with primary anastomosis superior to Hartmann's procedure in the haemodynamically stable and immunocompetent patient under 85 years of age (Lambrichts et al. (2019) Lancet 4(8), 599–610)

Caution

Continuity restoration after Hartmann resection (discontinuity resection with rectal blind closure and terminal stoma) occurs in only about 50% of patients and is associated with substantial morbidity (44%) and lethality (5%).

- Technical aspects:
  - Proximal resection margin: In any case proximal to the chronically or acutely inflammatory altered wall sections in the healthy intestine

  - Distal resection margin: In the upper rectum (better blood circulation) distal of the high pressure zone
  - Stapler vs. manual suture anastomosis = equivalent
- Preservation of the inferior mesenteric artery recommended = avoidance of damage to the sacral plexus (= tubular sigmoid resection preferred)
- In septic/instable patients with difficult mobilization of the left flexure = Hartmann's procedure

3.2.2 Colonic Polyps

Definition

- Growths of different genesis into the lumen of the colon

Epidemiology

- Accumulation with increasing age
- Men > Women
- Localization: >50% in the rectum

Classification (■ Table 3.4)

- Histological classification = behaviour/precancerous lesions

Symptoms

- Mostly incidental finding (= asymptomatic)
- Peranal mucus discharge: With large polyps
- Bleeding
- Complications:
  - Degeneration (adenoma-carcinoma sequence)
  - Obstruction
  - Invagination
  - Prolapse

Diagnosis

- Digital-rectal examination
- Rectoscopy/complete colonoscopy with biopsy/ablation
- Colon contrast imaging, CT colonography (rare, obsolete)

Therapy

Endoscopic Therapy

- If possible, always endoscopic
- Ablation of the polyp (thermal snare, forceps) in sano, goal = clean-colon
- Endoscopic mucosal resection (EMR)
- Submucosal resection/dissection (SMR/SMD)

FAP (Familial Adenomatous Polyposis)

- First colonoscopy obligatory at the age of 10 years, then annually
- If adenomas are detected = proctocolectomy indicated between onset of puberty up to the age of 20 years
- Followed by annual pouchoscopy
- Human genetic counselling (diagnosis in the family)

■ **Table 3.4** Classification of colonic polyps

Designation	Definition
Adenoma	Epithelial neoplasia (precancerous lesion) with a tendency to degeneration
Hyperplastic polyp	Small benign mucosal change, low tendency to degeneration
Inflammatory polyp	Small benign mucosal change, without degenerative tendency (associated with chronic inflammatory bowel disease)
Familial adenomatous polyposis (FAP)	Obligate precancerous lesion; mutation of the APC gene (autosomal dominant); risk of degeneration = 100%
Hamartoma	Atypical differentiation of germinal tissue (mutation) = polyposis with a tendency to degeneration (e.g. Peutz-Jeghers syndrome; Cowden syndrome)
Serrated polyp	Epithelial neoplasia; adenoma with high malignant potency

Guideline: Polypectomy

Implementation

- Documentation of the localization
- Polyp >5 mm: complete resection by loop ablation
- Polyp ≤5 mm: complete resection with forceps or snare
- Endoscopic mucosal resection
- Endoscopic full-thickness resection
- Histology obligatory:
- Statement on the completeness of the removal
  - In case of carcinoma detection necessary: pT (in case of sessile polyps the sm invasion measurement in µm), grading, L-, R-classification (local complete removal in depth and to the side).
  - pT1 carcinomas: "low risk" = G1, G2, L0/ "high risk" = G3, G4, L1

Postpolypectomy Strategy

- High-risk pT1 carcinoma (even if R0 ablation) = oncological resection
- Low-risk pT1 carcinoma incompletely ablated = complete endoscopic/local surgical removal
- If R0 situation not achievable or doubt about pT1 situation = oncological surgical resection

Follow-up

- Low-risk pT1 carcinoma after complete endoscopic R0 ablation = endoscopy after 6 months, complete colonoscopy after 3 years
- After removal of small, single, non-neoplastic polyps = no need for follow-up = control colonoscopy after 10 years
- Complete ablation of neoplastic polyps
- Time of control colonoscopy depending on number, size and histology
- In case of 1–2 adenomas <1 cm without higher-grade intraepithelial neoplasia after 5–10 years

Surgical Therapy

- For large polyp with a large base
- For non-ablatable polyp
- In case of carcinoma detection, after polypectomy
- Technique:
  - Exploration, colotomy, ablation
  - Colonic segment resection
  - Transanal full wall excision

If carcinoma is detected in the histology, oncological resection of the colon segment bearing the polyp is essential (► Sect. 3.3).

Follow-Up Care After Colonoscopic Ablation

- Depending on the histology
- Control colonoscopy:
- After ablation of 1–2 adenomas with low-grade intraepithelial neoplasia: after 5–10 years
- After ablation of >3 adenomas or villous parts or high-grade neoplasia: After 3 years
- Sessile adenomas or questionable in-toto removal: After 2–6 months

3.2.3 Ulcerative Colitis

Key Points

- Chronic inflammatory bowel disease confined to the colon and rectum, continuous affection of the mucosa
- Risk of formation of DALM ("dysplasia associated lesion or mass") → colon carcinoma
- Cure through restorative proctocolectomy

Definition

- Inflammatory bowel disease
- Mucosa + submucosa of the colon and rectum affected
- Continuous spreading of the lesions = ulcerations
- Autoimmunity in the pathogenetic background = genetic predisposition + specific triggers (stress, infection)

Epidemiology

- Incidence: 3.0–3.9 per 100,000 population
- Prevalence: 160–250 per 100,000 population
- Age peak at 16–25 years
- Women > Men

Etiology

Etiopathogenesis

- Not fully clarified
- Autoimmune pathogenesis: genetic predisposition + specific triggers (stress, infection)
- Positive family history, currently more than 160 known gene loci
- Other factors: diet, psychosomatic causes, nicotine, intestinal microbiome

Course

- Onset of inflammation: In the rectum
- Spread in oral direction, restricted exclusively to rectal and colonic mucosa
- Acute phase: red edematous mucosa, contact bleeding, microscopy: granulocytic crypt abscesses
- Chronic phase: mucosa destruction with loss of fold relief = pseudopolyps; microscopy: lymphocytic histiocytic infiltration

Clinical Presentation

Intestinal Manifestations

- Bloody-mucous diarrhea = leading symptom
- Abdominal discomfort: Pain, tenesmus
- Systemic signs of infection (e.g. reduced general condition, fever)

Extraintestinal Manifestations (15–20%)

- Erythema nodosum
- Aphtae, pyoderma gangraenosum
- Episcleritis, uveitis
- Peripheral and axial arthritis (ankylosing spondylitis)
- Primary sclerosing cholangitis (PSC), increased risk for development of chronic sclerosing cholangitis (CSC)

Course

- Acute-fulminant (5%): Sudden onset of illness (diarrhea, septic temperatures, septic shock); complications: Toxic megacolon; lethality approx. 30%
- Chronic-Continuous (10%): Without complete remission
- Chronic-recurrent (85%): Recurrent exacerbations; periods of complete remissions

Complications

- Massive bleeding
- Toxic megacolon
- Growth disorder
- Backwash ileitis (in up to 10% of patients spread to the ileum DD Crohn's disease)

Caution
Risk of colon cancer development due to ulcerative colitis!

Diagnosis

Anamnesis

- Type and onset of symptoms, food intolerances, medications, etc.
- Stool anamnesis

Complete Physical Examination

- Digital-rectal examination (blood detection)
- Extraintestinal manifestations (especially skin)

Lab

- Inflammatory status (leukocytosis, blood sedimentation rate, CRP, α_2-globuline)
- Hemoglobin, iron balance (exclusion of bleeding)
- Kidney function

- Transaminases, cholestasis parameters (bilirubin, alkaline phosphatase, γ-glutamyltransferase) in primary sclerosing cholangitis
- p-ANCA (antineutrophil cytoplasmic antibodies): 60–70% of cases
- Calprotectin/Lactoferrin in stool: progression parameter in any inflammatory bowel disease)
- Exclusion of intestinal infection: e.g. Clostridium difficile, CMV (cytomegalovirus), travel history
- Stool diagnosis

Imaging

- Colon double contrast enema:
  - Loss of the mucosal relief = "bicycle tube"
  - Pseudopolyps
- Sonography: Thickened colonic mucosa
- Hydro-MRI

Endoscopy

- Rectoscopy, ileocolonoscopy
- Biopsies of all intestinal sections
- Danger of perforation in case of inflammation

Endoscopic Classification

- Proctitis (limited to rectum)
- Left-sided colitis (to left flexure)
- Extensive colitis

Differential Diagnosis

- Crohn's disease
- Diverticulitis
- Infectious colitis
- Ischemic colitis
- Drug-toxic colitis
- Colon Cancer
- Irritable Bowel Syndrome

Therapy

Conservative-Medical Therapy

Long-term remission maintenance therapy should be given to all patients after successful relapse therapy

Uncomplicated Ulcerative Colitis

Proctitis

- Mesalazine ≥1000 mg/day as suppository
- Plus topical steroids (budenoside-rectal foam) or additional oral administration of mesalazine, if necessary

Left-Sided Colitis

- Rectal mesalazine as an enema or foam (≥1 g/day) in combination with oral mesalazine-releasing preparations (≥3 g/day)
- If necessary, systemic steroid therapy 0.5–1 mg/kg body weight/day prednisolone equivalent

Cancer Prevention

- Significantly increased risk of cancer = colonoscopy annually in patients with ulcerative colitis (after 8 years of disease)
- Risk reduction: Aminosalicylate long-term therapy
- In case of high-grade IEN (intraepithelial neoplasia) = proctocolectomy

Complicated/Severe Ulcerative Colitis

- Inpatient treatment, interdisciplinary
- Thrombosis prophylaxis
- Parenteral fluid and electrolyte balance
- No motility inhibiting drugs
- Systemic steroid therapy, e.g. 1 mg/kg body weight/day prednisolone equivalent
- In case of contraindication for system. Steroid therapy, Infliximab, Ciclosporin A or Tacrolimus can be used
- In case of insufficient clinical efficacy of steroids, these can be supplemented with TNF antibodies, tofacitinib, or with ciclosporin A or tacrolimus. In the case of infliximab, combination therapy with a thiopurine should preferably be used
- Surgical proctocolectomy
- Definition of severe colitis = criteria of Truelove and Witts:
  - More than six bloody diarrhea per day

- Fever
- Tachycardia
- Anemia
- BSR >30 mm/h

- Always interdisciplinary therapy

Time-Adapted Approach

- Time points for response to therapy, onset of remission, time point for discontinuation of medication in remission (Table 3.5)

Infliximab and ciclosporin are comparable as salvage therapy in acute severe steroid-insensitive ulcerative colitis.

Caution

- Before anti-TNF-α therapy: exclude latent tuberculosis!
- Before immunosuppressive therapy in chronic inflammatory bowel disease patients with a negative VZV (varicella-zoster virus) history (chickenpox/herpes zoster) or negative VZV serology, perform vaccination:
  - HPV (human papillomavirus) vaccination in girls and young women
  - Pneumococcal vaccination

Surgical Therapy

Surgery Indications

- Free or covered perforation
- Therapy refractory bleeding
- Drug-therapy refractory relapse
- Conservative-therapy refractory course
- Colon stenosis (of unclear dignity)
- Suspicion or detection of carcinoma, DALM

Important: Intraepithelial neoplasia (IEN) (WHO criteria) → continence-preserving proctocolectomy

- Histopathologically graded (low/high grade)
- In flat, non-inflamed mucosa
- Secondary assessment by reference pathologists
- DALM (inflammatory bowel disease-associated): Dysplasia-associated lesion or mass
- ALM: "adenoma like mass"

Standard Surgery: Restorative Proctocolectomy

- Laparoscopic or conventional open surgery
- If necessary, staged surgery: e.g. 3-stage procedure
  - Subtotal colectomy with terminal ileostomy
  - Residual proctocolectomy (with ileo-anal pouch anastomosis) + double barrel ileostomy

Table 3.5 Time-adapted approach, time points for response to therapy, onset of remission, time point for discontinuation of medication in remission

Drug	Response after	Remission after	Time of weaning
5-aminosalicylic acid	2–4 weeks	8–12 weeks	After 2 years
Budenoside	2 weeks	8–10 weeks	(After 6–12 months)
Systemic steroids	1 week	4 weeks	No permanent therapy
Anti-TNF-α	1st–2nd gift	8 weeks	After 2 years
Azathioprine, 6-mercaptopurine, methotrexate	8 weeks	12–16 weeks	After >3.5 years
Calcineurin inhibitors	5–7 days	3 months?	After 6–12 months

TNF tumour necrosis factor

- Reversal of Ileostomy
- In case of ileoanal pouch = leave not longer than 2 cm rectal mucosa, if necessary secondary transanal mucosectomy

- Contraindications:
  - Severe sphincter insufficiency (check sphincter function, e.g. enema)
  - Perianal fistula
  - Age >60 years (relative CI)

Surgical Procedure

Restorative Proctocolectomy

- Transabdominal total colon and rectum resection (comparable to FAP Procedure—► Sect. 3.3.3)
- Peranal exposure of the rectal stump (Parks retractor)
- Injection of the mucosa above the dentate line
- Dissection the mucosa cranially
- Transanal/transabdominal transection of the rectal wall (with/without preservation of a rectal cuff)
- Mobilization of the ileum = tension-free anastomosis
- Reservoir formation: Formation of a 15-cm ileum J-pouch with stapling suture device (GIA 90 mm), via antimesenteric incision in the ileum loop
- Peranal anastomosis: machine/hand anastomosis
- Hand anastomosis: pull-through of the reservoir through rectal cuff + pouch-anal anastomosis (single stitch suture, all-layer)
- Protective double barrel loop ileostomy

Follow-Up

- Ileostomy reversal (after 2–3 months): Only after checking the reservoir tightness (pouchoscopy + CM imaging) + continence check (e.g. enema).
- Pouchoscopy: annually = exclusion of cancer or pouchitis

Alternative Procedure

- In case of cancer: surgery according to oncological criteria
- Turnbull procedure (creation of ileostoma and colostoma) for toxic megacolon
  - Double barrel ileostomy
  - Two colonic fistulas (transverse colon + sigmoid colon)
  - Lethality = 2–5% vs. 30% for subtotal colectomy
- Subtotal colectomy
  - Emergency surgery
  - Blind closure of the rectum (Hartmann operation)
  - Interval proctocolectomy
  - High lethality

Preventive Care (Cancer Prophylaxis)

- Indication
  - Ulcerative pancolitis that has been present for >8 years
  - Left-sided colitis persisting for more than 15 years
  - Synchronous primary sclerosing cholangitis (PSC)
  - If the rectum is left in place or if there is a terminal ileostomy with rectal stump
- Complete colonoscopy with step biopsies
  - At least four biopsies every 10 cm
  - Annually
- Primary prevention of colorectal carcinoma (CRC) = aminosalicylates

3.2.4 Chronic Constipation

In Short

- Rule out laxative abuse
- Neuronal pathologies: usually very early manifestation
- Rule out rectocele

Definition

- Subjectively unsatisfactory (<3 bowel evacuation per week or ≥2 leading symptoms of constipation: heavy straining,

lumpy or hard stool, subjectively incomplete defecation, subjective obstruction, manual maneuvers to facilitate defecation)
- For at least 3 months

3

Epidemiology

- Western countries: incidence = approx. 15%
- Women > Men
- Age-associated: Increases with age

Etiology

- Low-fiber diet: association, but no causal relationship
- Reduced fluid intake
- Lack of exercise
- Neuromuscular factors: enteric neuropathy: Cajal cells, myopathy: intestinal smooth muscle
- Diseases that can lead to secondary constipation (◘ Table 3.6)
- Medications with constipation potency (◘ Table 3.7)

◘ Table 3.6 Diseases that can lead to secondary constipation

Endocrinopathies	Diabetes mellitus Hypothyroidism Hyperparathyroidism MEN 1 and MEN 2
Neurological diseases	Parkinson's disease Multiple sclerosis Apoplexy Paraplegic Syndrome Paraneoplastic intestinal Neuropathies
Psychiatric diseases	Depression Somatization disorder
Other diseases	Ovarian carcinoid Scleroderma Amyloidosis Myotonic dystrophy Obstructive/Stenosing Intestinal disorders

MEN Multiple endocrine neoplasia

Diagnosis

Anamnesis

- Defecation disorder
- Medication

◘ Table 3.7 Drugs with constipation potency

Drug group	Drugs
Analgesics	Opiates
Antacids	Aluminium hydroxide, calcium carbonate
Antidepressants (anticholinergics)	Tricyclics (imipramine, clomipramine, amitriptyline, dibenzepine), tetracyclics (maprotiline, mianserine)
Antiepileptic drugs	Carbamazepine
Antihypertensives	β-blockers (e.g. atenolol), calcium antagonists (e.g. verapamil), clonidine
Anti-Parkinson's medication	Anticholinergics (e.g., biperiden), amantadine, bromocriptine
Antiemetics	5-HT3 antagonists (e.g. ondansetron)
Antitussives	Preparations containing codeine
Chemotherapeutics	Vincristine, vinblastine
Diuretics	Thiazides, sulfonamides
Iron supplements	Iron(II) and iron(III) salts
H_2 blocker	Cimetidine, Famotidine, Ranitidine
Lipid-lowering agent	Ion exchangers (e.g. colestipol, colestyramine)
Neuroleptics	Phenothiazines (e.g. chlorpromazine), thioxanthenes, butyrophenones, dibenzodiazepine (clozapine)
X-ray contrast agent	Barium salts
Spasmolytics	Butylscopolamine, trospium chloride

Physical Examination

- Rectal digital examination
- Gynaecological examination if necessary

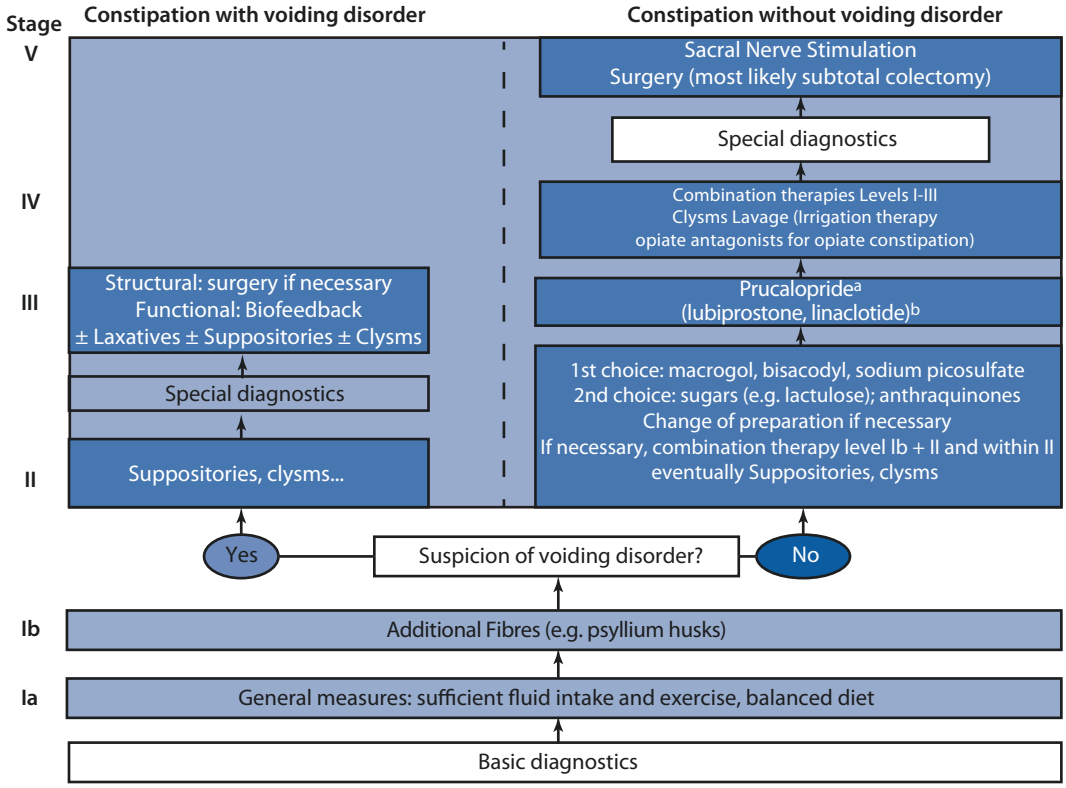
Further Diagnosis

- Abdominal Ultrasound
- Colonoscopy after the age of 55
- Anorectal manometry
- MRI Defecography
- Colonic transit time

Therapy

Step-By-Step Therapy (◘ Fig. 3.2)

- First stage: General recommendations = high-fibre diet, if necessary addition of psyllium husks, wheat bran
- Second stage:
  - Suppositories and clysms, plentiful fluid intake, adequate exercise, refraining from suppressing the urge to defecate
  - First choice: macrogol (osmotic laxative), bisacodyl, narium picosulfate (stimulate colonic motility and water secretion)
  - Second choice: sugars e.g. lactulose, anthraquinones
- Third Stage:
  - Prucalopride: e.g. Resolor®: prokinetic serotonin (5 HT4) receptor agonist = promotion of intestinal motility
  - Lubiprostone: e.g. Amitiza®: direct chloride channel activator = increase water and chloride secretion
  - Linaclotide: e.g. Constella®. Agonist = guanylate cyclase agonist = increase water and chloride secretion
- Fourth stage: Combinations of stages 1–3 (after special diagnosis)
- Fifth Stage: Sacral nerve stimulation



◘ **Fig. 3.2** Therapeutic algorithm for chronic constipation. 1st choice Approved for constipation in women if laxatives are ineffective or intolerant. 2nd choice Available through international pharmacies, linaclotide approved for obstipation-predominant IBS

Surgery

- Rarely indicated, after careful consideration most likely subtotal colectomy (80–90% improvement)
- Estimation of the potential effect: Temporary ileostoma or permanent ileostoma on patient's request
- Alternative: Antegrade irrigation via appendix or caecal stoma

3.2.5 Guidelines

AWMF guideline: S2k guideline diverticular disease/diverticulitis, register number 021/20. Currently under revision, planned completion 31.07.2021

AWMF guideline colorectal cancer January 2019, registration number 021/007OL.

S3 guideline ulcerative colitis 8/19, AWMF registration number 021/009

3.3 Colon Cancer and Hereditary CRC Syndromes

3.3.1 Colon Carcinoma

In Short

- Adenoma-carcinoma sequence: screening colonoscopy
- Standard procedure: Surgery with adjuvant chemotherapy (from T3/N+)

Definition

- Epithelial malignancy of the colon (between the caecum and rectosigmoid junction)
- Upper limit (level) of rectum (rigid rectoscopy) = 16 cm from ano (in Europe)

Epidemiology

- Second most common tumor in western industrialized nations
- Incidence in Germany = 80/100,000 inhabitants per year
- Men = Women
- Multiple synchronous colorectal carcinomas = 2–5%
- From 50 years of age: doubling of incidence and mortality per decade of life

Etiology and Pathogenesis

- Interaction of genetic factors and environmental influences

Risk Categories

- Sporadic: approximately 70%, acquired somatic mutation associated with:
  - Higher age (>40 years)
  - Tobacco consumption, alcohol consumption
- Risk-increasing diseases: Colorectal adenomas, chronic inflammatory bowel diseases (► Sect. 3.2.3 Ulcerative colitis), ureterosigmoideostomy, carcinomas of other organs (mamma, uterus, ovary, urinary bladder)
- Familial: approx. 20–30%, polymorphisms and gene loci with lower penetrance
- Hereditary: approx. 5%, hereditary mutation with high penetrance (► Sect. 3.3.2 Hereditary CRC syndromes)

Protective Factors

- High-fiber, low-fat, low-meat diet
- Fast stool passage
- Aminosalicylates
- Vitamin C, folic acid

Pathogenesis

- Adenoma-carcinoma sequence (90%): Due to increasing mutations over years
- De novo carcinomas (10%): Without adenoma manifestation (e.g. ulcerative colitis)
- Hereditary forms: Germline mutations already existing = carcinoma at a young age

Classification

TNM Classification (2017)

- T (tumor)
  - Tx Primary tumor not assessable
  - T0 No evidence of primary tumor
  - Tis carcinoma in situ: intraepithelial or invasion of the lamina propria
  - T1 Invasion of the submucosa
  - T2 Invasion of the muscularis propria
  - T3 invasion of the subserosa, or pericolic fat tissue
  - T4a Perforation of the visceral peritoneum
  - T4b Invasion of adjacent organs
- N (lymph nodes)
  - N0 No regional lymph node metastases
  - N1a 1 affected lymph node
  - N1b 2–3 affected lymph nodes
  - N1c Tumour nodule in the pericolic fat tissue
  - N2a 4–6 affected lymph nodes
  - N2b More than 6 affected lymph nodes
- M (metastases)
  - M0 No distant metastases
  - M1a Metastases in another organ
  - M1b Metastases in more than one other organ

UICC Staging of Colorectal Cancer

UICC stage	T (tumor)	N (lymph nodes)	M (metastases)
0	Tis	N0	M0
I	T1, T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
III	Each T	N1, N2	M0
IIIA	T1, T2	N1a	M0
	T1	N2a	M0
IIIB	T3, T4a	N1	M0
	T2, T3	N2a	M0
	T1, T2	N2b	M0
IIIC	T4a	N2a	M0
	T3, T4b	N2b	M0
	T4b	N1, N2	M0
IVA	Each T	Each N	M1a
IVB	Each T	Each N	M1b

Histological Grading

- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated (e.g. mucinous)
- G4: Undifferentiated (e.g. small cell, signet ring cell)
- V0/V1: Vein intrusion present/absent
- L0/L1: Intrusion into lymphatic vessels present/absent
- Pn0/Pn1: Perineural sheath infiltration present/absent

Symptoms

- Mostly uncharacteristic features
- Blood in the stool
- Change in bowel habits
- B-symptoms (fever, night sweats, weight loss)
- Performance drop, fatigue
- Tumor Anemia
- Rare abdominal pain

Complications

- Ileus
- Tumor perforation
- Fistulas
- Relevant bleeding

Diagnosis

Standard Investigations

- Anamnesis
  - Stool habits, body weight, blood in the stool, pain

  - Family history: for risk assessment of hereditary colorectal cancer (■ Tables 3.8, 3.9, and 3.10)
- Clinical examination of the abdomen
  - Digital rectal examination
  - FOBT (Fecal Occult Blood Test = Haemoccult®)
- Lab
  - Blood count, electrolytes, kidney function, coagulation status
- Complete colonoscopy

Guideline-Based Preoperative Diagnostic of Tumor Staging

- Digital-rectal examination
- Complete colonoscopy + biopsy
- Tumor not passable = colonoscopy 3–6 months postoperatively or intraoperatively
- Pneumocolon CT if necessary
- Abdominal ultrasound (especially liver)
- Chest X-ray in 2 planes

■ **Table 3.8** Amsterdam I criteria[a]

1	CRC was diagnosed in at least 3 relatives
2	One of you should be a first degree relative of the other two
3	At least 2 consecutive generations are affected
4	At least 1 CRC was diagnosed before the age of 50 years
5	Familial adenomatous polyposis (FAP) was excluded
6	CRC are verified by histopathological examination

CRC colorectal carcinoma
[a] Families must meet all criteria

■ **Table 3.9** Amsterdam II criteria[a] (risk assessment of hereditary colon carcinoma)

1	Lynch syndrome-associated carcinoma has been diagnosed in at least 3 relatives[b]
2	One of you should be a first degree relative of the other two
3	At least 2 consecutive generations are affected
4	At least 1 tumor was diagnosed before the age of 50 years
5	Familial adenomatous polyposis (FAP) was excluded
6	Tumors are verified by histopathological examination

[a] Families must meet all criteria
[b] Colorectal tumor or tumor of the endometrium, small intestine, ureter, or renal pelvis

■ **Table 3.10** Revised Bethesda guidelines (risk assessment of hereditary colon carcinoma[a])

1	CRC before the age of 50
2	Presence of synchronous, metachronous CRC (or Lynch syndrome)-associated tumors[b], regardless of age
3	CRC with MSI-H histology[c] diagnosed in patients <60 years of age
4	CRC diagnosed in patients with one or more first degree relatives with Lynch syndrome-associated tumor, one of whose carcinomas was diagnosed before age 50 years
5	CRC diagnosed in a patient with 2 or more first or second degree relatives with Lynch syndrome-associated tumor, regardless of age

[a] MSI investigation required if only one criterion is met
[b] Endometrial, gastric, ovarian, pancreatic, biliary, small bowel, brain tumors (usually glioblastoma in Turcot syndrome), seborrheic gland adenomas, and keratoankanthomas in Muir-Torre syndrome, hepatobiliary carcinomas, transitional cell carcinomas of the renal pelvis or ureter
[c] Presence of tumor-infiltrating lymph nodes, Crohn's disease-like lymphocytic infiltration, mucinous/seal-ring differentiation, or medullary growth pattern

- CEA (carcinoembryonic antigen) determination
- Useful in individual cases: spiral CT or MRI abdomen, spiral Chest CT

Colorectal Cancer Screening (in the Asymptomatic Population)

- Colonoscopy = standard procedure
  - From the age of 50
  - If the findings are unremarkable = repetition after 10 years
- Alternative: Sigmoidoscopy every 5 years + yearly FOBT (Guajak procedure)
- FOBT = consisting of 3 test letters with 2 order fields each for 3 consecutive stools
- Positive FOBT test = colonoscopy check!

Caution

In first degree relatives of patients with CRC or colorectal adenomas, a complete colonoscopy should be performed before the age of 50 years approximately 10 years before the age of onset of the cancer in the index patient, latest at the age of 50 years.

Guideline: Polypectomy

- ► Section 3.2.2

Therapy

Treatment Strategy

- Colon cancer = indication for surgery
- Always aim for R0 resection
  - Contraindication to surgery:
  - General inoperability of the patient
  - Inoperability of the tumor (R0 not achievable): Diffuse peritoneal carcinomatosis with distant metastases, infiltration of the great vessels

Surgical Therapy

Principles of Surgical Therapy

- Oncological resection principles
- Laparoscopic vs. open: equivalent if oncologic principles are adhered to
- Extent of resection (◘ Fig. 3.3) depending on resection of the supplying vessels and the lymphatic drainage areas
- Right Hemicolectomy:
  - Indication: cancer of the caecum, ascending colon; for cancer of the right flexure = extended right hemicolectomy
  - Complications: Injury to the branches of the superior mesenteric artery, injury to the right ureter, injury to the duodenum, tearing of the pancreatic head veins (loop of Henle)
  - CME = complete mesocolic resection
- Left Hemicolectomy:
  - Indication: cancer of the descending colon, of the proximal sigmoid; in case of cancer of the left flexure = extended left hemicolectomy
  - Complications: Injury to the spleen, hemorrhage from splenocolic ligament, injury to the left ureter
- Colon transversum resection
  - Indication: Cancer of the middle of the transverse colon; for tumors close to the flexure = hemicolectomy
  - Complications: Insufficient anastomotic perfusion = anastomotic leakage
- Colon sigmoideum resection
  - Indication: Cancers of the middle/distal sigmoid colon
  - Complications: Injury to the left ureter, inadequate anastomotic perfusion = anastomotic leakage

Surgical Procedure

Right Hemicolectomy

- Longitudinal laparotomy vs. upper abdominal transverse laparotomy vs. laparoscopic approach
- Complete mesocolic excision (CME)
- Exploration, marking (e.g. vessel loops) of the colon at the level of the resection margins (proximal margin = 10–20 cm of the Bauhin valve)
- Mobilization of the caecum and ascending colon; exposure of the right ureter; detachment of the colon/mesocolon from Gerota's fascia

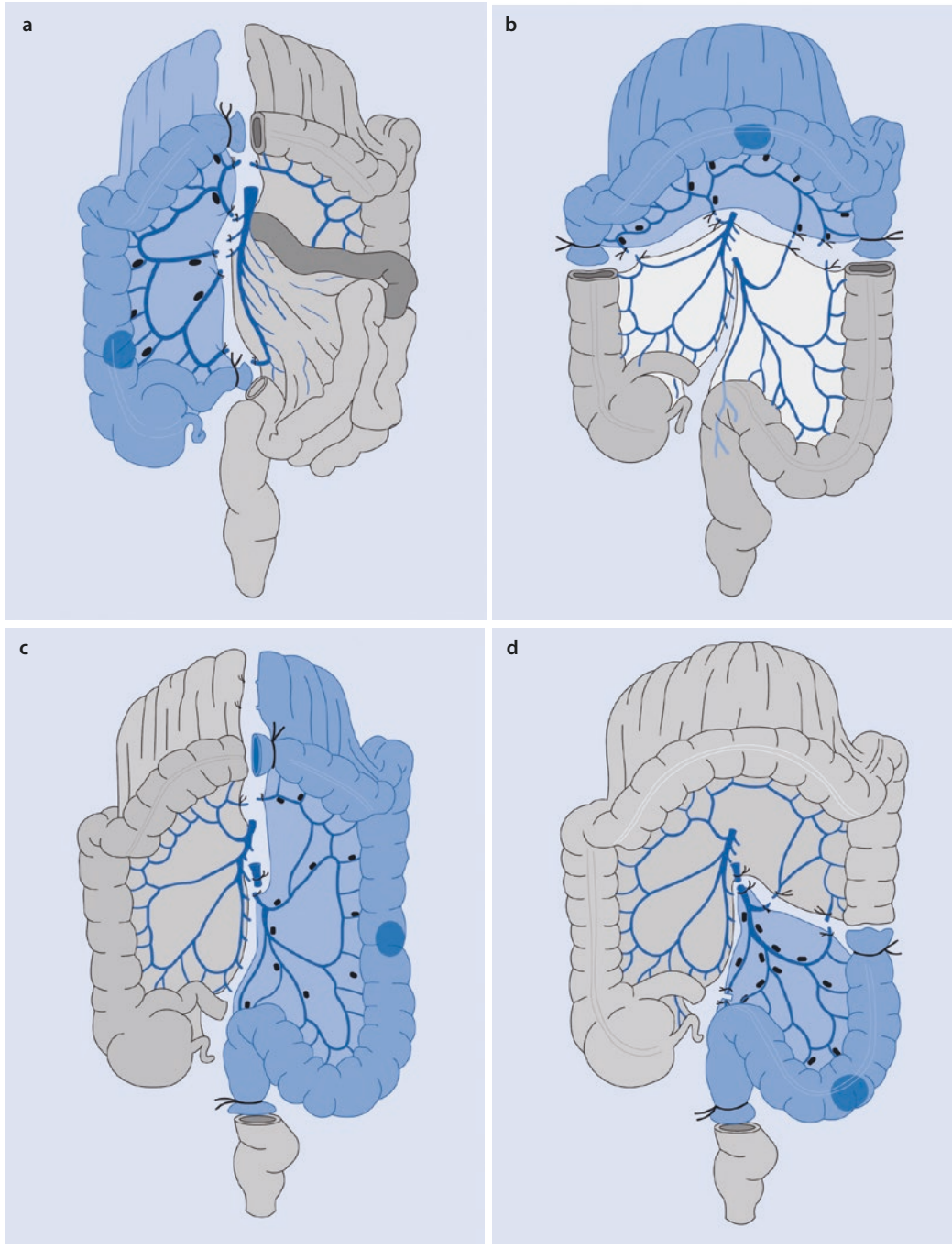


Fig. 3.3 **a**–**d** Extent of resection of various colon cancers. **a** Carcinoma of the appendix, caecum and ascending colon. Right hemicolectomy and lymphadenectomy. **b** Carcinoma of the transverse colon. Resection of the transverse colon including the flexurae coli dextra and sinistra and lymphadenectomy. **c** Carcinoma of the descending colon. Resection of the distal half of the transverse colon, descending colon, sigmoid colon, and lymphadenectomy. **d** Carcinoma of the sigmoid colon. Resection of the distal descending colon, sigmoid colon, proximal rectum, and lymphadenectomy

- Mobilization of the right flexure (transection of the hepatocolic and duodenocolic ligaments)
- Transection of gastrocolic ligament for distal resection border
- Transection of the great omentum at the level of the distal resection margin; omentum remains en bloc on the specimen
- Transection of the mesentery (with mesenteric vessels) between ligatures
- Ligation of the ileocolic vessels close to superior mesenteric vein and colic arteries and the right branch of the colic artery and vein close to Henle's loop (CME)
- Remove the bowel at the level of the resection margins
- Side-to-side ileotransversostomy
- Closure of the mesenteric gap

Surgical Procedure
Left Hemicolectomy

- Longitudinal laparotomy vs. laparoscopic approach
- Complete mesocolic excision (CME)
- Exploration, marking of the colon at the level of the resection margins (proximal: depending on tumor location; distal: above the peritoneal fold)
- Incision of the white line (Toldt) and mobilization of the descending colon + sigmoid; exposure of the left ureter
- Dissection of the left mesocolon from Gerota's fascia medially
- Transection of the great omentum at the level of the proximal resection margin; omentum remains en bloc on the specimen
- Mobilization of the left colonic flexure (transection of the splenocolic and phrenocolic ligaments)
- Severing the mesentery between ligatures
- Transection of the inferior mesenteric vein at the inferior border of the pancreas (lateral to lig. Treitz), transection of the inferior mesenteric artery centrally
- Pay attention to the course of the parasympathetic nerves
- Remove the bowel at the level of the resection margins
- Transversorectostomy (usually circular end to end anastomosis)
- Closure of the mesenteric gap

Surgical Procedure
Colon Transversum Resection

- Longitudinal laparotomy vs. upper abdominal transverse laparotomy vs. laparoscopic approach
- Complete mesocolic excision (CME)
- Exploration, marking of the colon at the level of the resection margins
- Transection of the gastrocolic ligament
- Mobilization of the right colonic flexure and the ascending colon
- Mobilization of the left colonic flexure
- Radicular resection of the A. and V. colica media
- Transection of the transverse mesocolon at the lower border of the pancreas; including lymphadenectomy
- Transection of the mesentery between ligatures
- Remove the bowel at the level of the resection margins
- Ascendodescendostomy as end-end anastomosis
- Closure of the mesenteric gap

Surgical Procedure
Oncological Colon Sigmoideum Resection

- Median lower abdominal laparotomy vs. laparoscopic approach
- Complete mesocolic excision (CME)
- Exploration, marking of the colon at the level of the resection margins (proximal: transition descending colon—sigmoid; distal: rectosigmoid transition)

- Incision of the white line (Toldt) and mobilization of the descending colon + sigmoid; exposure of the left ureter
- Dissection/Mobilization of the mesosigmoid from Gerota fascia medially
- Exposure and resection of the inferior mesenteric artery (preservation/non-preservation of the left colic artery); check of the blood supply of the proximal end of the intestine
- Transection of the inferior mesenteric vein at the inferior border of the pancreas
- Medial incision of the mesenteric peritoneum at the insertion along the aorta and blunt detachment from the retroperitoneum; Attention: protection of the autonomic nerves
- Resection of the superior rectal artery
- Transection of the mesosigma between ligatures
- Mobilization of the proximal rectum
- Incision of the pelvic floor peritoneum
- Exposure of the rectum, dorsally in the Waldeyer space, then ventrally and laterally (paraproctia).
- Transection of the upper mesorectum up to the level of the distal resection border (No **Coning** = thinning of the distal mesorectum)
- Resection of tumor bearing colon segment
- Circular end-to-end descendorectostomy (usually mechanically with transanal CEEA ("circular end-to-end anastomosis") stapler)

Postoperative Complications

- Suture insufficiency = anastomotic insufficiency
  - With peritonitis: relaparotomy, lavage, Hartmann resection or resection + anastomosis, creation of protective ileostoma
- Abscess: drainage (possibly CT-guided), irrigation, if necessary creation of protective ileostoma
- Fecal fistula without peritonitis (infraperitoneal): stoma creation + Endo-VAC-application until cleaning of the cavity, waiting for spontaneous healing.
- Postoperative bleeding
- Mechanical ileus due to adhesive small bowel obstruction = relaparotomy + adhesiolysis
- Hernia
- Cancer Recurrence

Principles for Specific Situations

- Multivisceral resection:
  - In case of adherence of the tumor to adjacent organs = en bloc multivisceral resection
- **Caution:** Biopsies should be strictly avoided = risk of tumor cell dissemination (spillage)
- Carcinoma in FAP: Restorative proctocolectomy with small bowel pouch + lymph node dissection according to the location of the carcinoma
- Carcinoma in HNPCC:
  - Proceed in the same way as for sporadic CRC
  - If necessary subtotal colectomy + prophylactic hysterectomy + salpingoovarectomy at the time of abdominal surgery
- Carcinoma in ulcerative colitis: restorative proctocolectomy + systematic oncologic lymphadenectomy with CME

Principles in Metastatic Colon Cancer

- Liver metastases
  - If R0 resection for liver and all other lesions possible = liver resection
  - Neoadjuvant systemic chemotherapy if necessary
- Pulmonary metastases
  - If R0 resection possible = resection
  - For synchronous liver and lung metastases → resection of liver metastases first
- Peritoneal carcinomatosis
  - If R0 (CC-0) resection possible = cytoreductive surgery (CRS) + peritonectomy + hyperthermic intraperitoneal chemotherapy (HIPEC) indicated

Adjuvant Chemotherapy

Caution

- Prerequisite is the oncological R0 resection!
- Indication based on histology with TNM classification (pN0 classification possible if at least 12 regional lymph nodes in specimen) (see above)

Indications

- Stage III (UICC)
- Stage II (UICC) (with microsatellites instability) or with risk factors:
  - pT4 tumor, tumor perforation/rupture
  - Emergency Operation
  - Number of examined lymph nodes too low
- Adjuvant chemotherapy may be considered after R0 resection of synchronous or metachronous liver metastases

Contraindications

- Poor general condition
- Uncontrolled infection
- Liver cirrhosis Child B/Child C
- Severe coronary heart diseases (CHD); heart failure: NYHA (New York Heart Association) III/IV
- Preterminal/terminal renal failure
- Limited bone marrow insufficiency

Standard Chemotherapy = FOLFOX (5-FU/Folinic Acid/Oxaliplatin)

- Protocol Examples:
  - FOLFOX4: folinic acid, 5-FU (5-fluorouracil), oxaliplatin every 2 weeks for 12 cycles
  - Guideline states that patients over 70 years of age should not receive oxaliplatin-containing therapy
  - In case of contraindication to oxaliplatin-containing regimens = monotherapy with fluoropyrimidines: oral 5-FU prodrug capecitabine, 8 cycles of 3 weeks each
  - In R0-resected stage III colon cancer, additional administration of cetuximab does not add benefit to FOLFOX even in KRAS wild type

No age restriction for adjuvant chemotherapy (general contraindications to be considered) = patients ≥75 years of age in stage III have survival benefit from adjuvant chemotherapy; oxaliplatin provides little additional benefit.

Palliative Chemotherapy

- Stage IV: Indicated for primary irresectability, independently of metastasis-related symptoms
- For example, FOLFOX, FOLFIRI, bevacizumab, cetuximab…
- Regorafenib (small molecule multikinase inhibitor) = survival benefit in metastatic colorectal cancer after failure of all standard therapies

Oncologic Follow-up

- Stage I: Not indicated
- Stage II and III: Follow-up indicated after R0 resection
- Principles of oncologic follow-up: Table 3.11

Prognosis

- Cumulative 5-year survival rate = 60%
- 5-year survival rate by UICC stage:
  - UICC I = approx. 70–100%
  - UICC II = approx. 60–91%
  - UICC III = approx. 44–60%
  - UICC IV = approx. 3–7% (without therapy)

3.3.2 HNPCC (Hereditary Non-polyposis Colorectal Cancer): Lynch Syndrome

Key Points

- Hereditary disease associated with colorectal cancer
- Also associated with other cancers (including endometrial cancer)
- Defect in mismatch repair genes

Table 3.11 Programmed follow-up for colon cancer UICC II and III (S3 Guidelines Colorectal Carcinoma)

Investigation	Months										
	3	6	9	12	15	18	21	24	36	48	60
Medical history, physical examination, CEA		x		x		x		x	x	x	x
Colonoscopy		x[a]		x[b]					x[b]		
Abdominal Sonography[c]		x		x		x		x	x	x	x
Sigmoidoscopy (rectoscopy)[d]		x		x		x		x			
Spiral CT[e]	x										
Chest X-ray (no consensus)											

[a] If a complete preoperative colonoscopy has not been performed
[b] If the findings are unremarkable (no adenoma, no carcinoma) next colonoscopy after 5 years
[c] A meta-analysis showed an advantage for an imaging procedure to detect liver metastases in follow-up. For this reason, application of the simplest and less expensive procedure
[d] Only for rectal cancer without adjuvant or neoadjuvant radiochemotherapy
[e] Only for rectal cancer 3 months after completion of tumor-specific therapy (surgery or radiation/chemotherapy) as initial findings

Definition

- HNPCC = Lynch syndrome
- Most frequent form of hereditary colorectal cancer
- Autosomal-dominant inheritance, no 100% penetrance

Epidemiology

- Approx. 1–3% of all CRC patients
- 2% of all endometrial cancers
- Most common form of hereditary CRC
- Lynch syndrome: Compared to sporadic CRC
  - Younger patient age
  - Better prognosis
  - Much lower metastatic tendency: synchronous CRC 18%, metachronous CRC 30% after 10 years, 50% after 15 years, right-sided CRC 60%
  - Lifetime risk of CRC (up to 75 years) (Table 3.12)

Etiology

- HNPCC: "hereditary non-polyposis colorectal cancer" (introduced in 1985)
- Bethesda/Amsterdam criteria for the diagnosis of HNPCC
- Lynch syndrome: mutation identified
- Mismatch repair (MMR) gene: mutation (MSH2, MLH1, MSH6, PMS2)
- Malignancies in LS (Lynch syndrome) patients: Due to somatic mutation of the second gene = microsatellite instability (MSI)
- Lynch I: CRC only

Table 3.12 Cumulative lifetime risks in patients with Lynch syndrome

Cancer	Lynch syndrome (%)	General population (%)
CRC male	54–74	5
CRC female	30–52	5
Endometrium	28–60	2
Ovary	6–7	1
Stomach	6–9	<1
Small intestine	3–4	<1
Pancreas	<1–4	1
Hepatobiliary	1	Rarely
Urinary tract	3–8	Rarely
Brain	2–3	<1
Seborrhoeic skin tumour/keratoankanthoma	1–9	Rarely

- Lynch II: CRC + cancer of the genitourinary tract
- Muir-Torre syndrome: Lynch syndrome + sebaceous gland cancers or keratoacanthomas

Diagnosis

Anamnesis

- Amsterdam criteria I + II (Tables 3.8 and 3.9)
- Bethesda criteria (Table 3.10)

Test for Mismatch Repair Defect

- If Bethesda criteria met
- By PCR, much cheaper = immunohistochemistry
- Histology
- In biopsy of CRC, MSI can be identified with almost 100% sensitivity and specificity
- Increased incidence of mucinous carcinomas, signet ring carcinomas, medullary carcinomas

Caution

A significant proportion of loss of MLH1 expression is the result of promoter methylation (BRAF V600 mutation) and not an MMR defect

Prevention

- Monitoring of Lynch syndrome mutation carriers (Table 3.13)
- Complete colonoscopy: annually from the age of 25, in any case 5 years before the lowest age of onset of the disease in the family
- Females at risk: From the age of 25 annual gynaecological examination + transvaginal US
- If there is a positive family history of gastric cancer: annual EGD from the age of 25
- Upper abdominal Ultrasound annually

Surgical Therapy

Despite regular monitoring, the relative risk of developing a tumor is 5.8 times higher compared to a mutation-negative cohort.

Table 3.13 Recommendations for surveillance of Lynch syndrome mutation carriers by the German S3 guideline (compared with the recommendations of the Mallorca group (European branch of InSIGHT, ► http://www.mallorca-group.eu), EGAPP (► https://www.egappreviews.org/recommendations/Lynch.htm), and NCCN (► https://www.nccn.org)

	Colonoscopy interval (years)	Lower age limit	Gastroscopy interval (years)	Lower age limit	Abdominal ultrasound interval (years)	Lower age limit	Gynecology Interval (years)	Lower age limit	Other
S3 guideline	1	25[a]	1[b]	25	1	25	1	25	Genetic counseling at the age of 18
Mallorca Group	1–2	20–25	1–2[b]	30–35	1	30–35	1–2, TVU, aspiration biopsy…	30–35	Urinalysis and cytology if there is a family history of urinary tract cancer.
EGAPP	1–2	20–25					1–2, TVU, endometrial biopsy…	30–35	Genetic counselling
NCCN	1–2	20–25[c]					1–2, TVU or endometrial aspirate	30–35	

TVU transvaginal ultrasound

[a] Same age or at least 5 years younger than the youngest age at diagnosis in the family

[b] When cancer runs in the family

[c] Same age or 10 years younger than youngest age at diagnosis in the family

- Oncological resection: According to the standard rules for CRC
- Extended resection: e.g. subtotal colectomy + ileosigmoidostomy = justified in individual cases
- If necessary prophylactic hysterectomy + salpingo-oophorectomy at the time of abdominal surgery

3.3.3 Other Hereditary CRC Syndromes

Familial Adenomatous Polyposis (FAP)

Definition

- Obligate precancerous lesion
- Risk of cancer = almost 100% from the age of 15 onwards
- About 1% of all CRC
- Other extracolic manifestations

Etiology

- Mutation APC gene
- Autosomal dominant inheritance (75% of cases)
- New mutation (25% of cases)

Tumour Spectrum

- Duodenal and papillary adenomas
- Gastric Adenomas
- Abdominal and extraabdominal desmoid tumors
- Thyroid cancers
- Malignant CNS tumours (mostly medulloblastomas)
- Hepatoblastomas
- Osteomas, epidermoid cysts, pigmentary abnormalities of the retina

Prevention

- From the age of 10, after human genetic counselling predictive genetic diagnosis
- If mutation confirmed:
  - Rectosigmoidoscopy annually from the age of 10 at the latest
  - If adenomas are detected = complete colonoscopy
  - Until proctocolectomy annual repetition of complete colonoscopy
- Esophagogastroscopy (EGD) with inspection of the papilla region: At the latest from the age of 30 every 3 years, if necessary annually in case of changes
- Extracolic manifestations: Annual ultrasound of the abdomen, from the age of 10 onwards annual ultrasound of the thyroid gland

Therapy

- Sphincter-preserving proctocolectomy (► Sect. 3.2.3)

Follow-Up

- Pouchoscopy yearly
- If preserved rectal stump = rectoscopy every 4 months

Hamartomatous Polyposis Syndromes

Definition

- Peutz-Jeghers Syndrome
- Juvenile polyposis coli
- Cowden syndrome: PTEN ("phosphatase and tensin homolog") gene

Prophylaxis

- No general recommendations due to sparse evidence available

Diagnosis and Therapy

- See above (CRC)
- No general recommendations due to sparse evidence available

3.3.4 Guidelines

S3 Guideline Colorectal Carcinoma 1/2019, AWMF Register Number 021/007/OL

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