

Clinical Practice Guideline

Colorectal Cancer

Diagnosis, Treatment, Prevention, and Long-Term Follow-Up Care

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Further guideline collabora-
tors are listed in eTable 8.

Summary

Background: Approximately 24 000 people die of colorectal cancer (CRC) in Germany each year. New developments in prevention, diagnosis, and treatment are improving long-term outcomes. These measures have been incorporated in the updated guideline and are presented here along with the findings of other new randomized controlled trials (RCTs).

Methods: A systematic search (2022–2023) was conducted for guidelines, reviews/meta-analyses, and primary studies (search term “colorectal cancer”; databases: international guideline registries, PubMed, Cochrane). 123 reviews were identified, evaluated, and used in the creation of the guideline.

Results: Early detection is performed with colonoscopy every 10 years, sigmoidoscopy every 5 years, or an immunological stool test for occult blood every 1–2 years; it can lower cancer-related mortality by up to 30%. Hereditary forms (Lynch syndrome, polyposis) require more intensive monitoring. All diagnosed cases must be presented to a tumor board. In the case of low-risk pT1 carcinoma, extended resection is not indicated after complete endoscopic removal. In a recent RCT, the recurrence rate was lower after robotic surgery than after laparoscopy (3-year recurrence rate 1.6% and 4.0% respectively; adjusted hazard ratio, 0.39; 95% confidence interval: [0.19; 0.80]). Treatment of patients with mismatch repair

deficiency (dMMR) or microsatellite instability-high (MSI-H) cancers with checkpoint inhibitors yields response above 90%. Further systemic therapies are based on the molecular tumor profile (dMMR/MSI-H, RAS, and BRAF). Organ sparing management may be an option for rectal cancer patients in complete remission after neoadjuvant therapy; however, this requires close follow-up monitoring.

Conclusion: The efficacy of early detection is undisputed. Less evidence is available concerning the optimal level of intensity of follow-up care. The clinical and molecular stratification of tumors enables differential treatment. Organ-preserving strategies after a complete response to therapy are an important area of current research.

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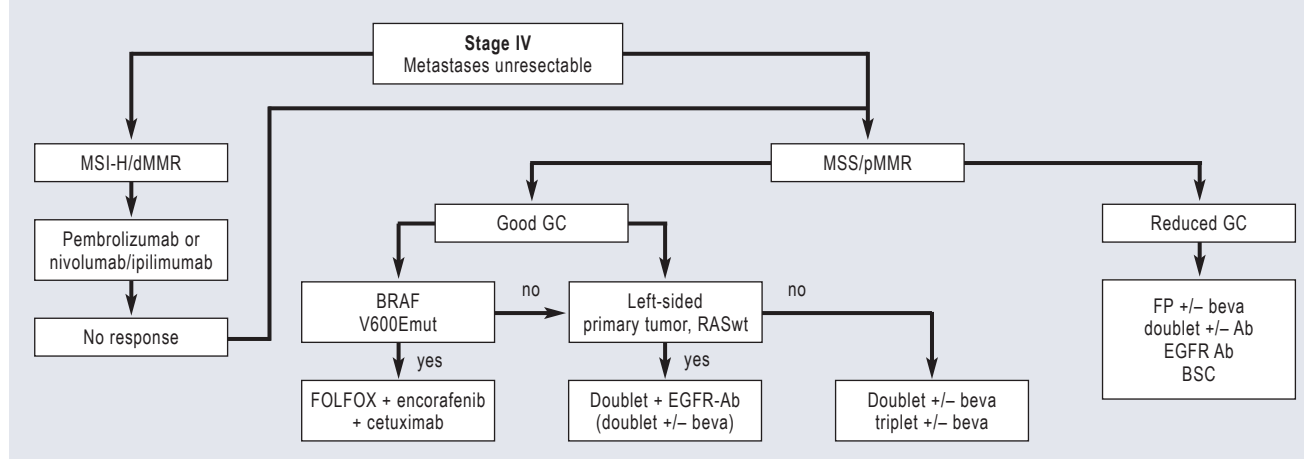
Colorectal cancer (CRC) is one of the most common malignant tumors in Germany, with approximately 55 000 new cases and around 24 000 deaths per year (1). CRC is predominantly a disease of the elderly, with a median age of diagnosis of 75 in women and 71 in men. In recent years, however, increased incidence rates in younger persons under the age of 50 have been reported, the cause of which is unclear (2).

The German (S3 level) clinical practice guideline on colorectal cancer has been updated to include new chapters on pathology, supportive treatment, rehabilitative care, and tertiary prevention. Management of high-risk groups (including hereditary/familial CRC), endoscopic therapy with differentiated polyp management, and surgical and multimodal treatment has been revised. Differentiated treatment of rectal cancer is another major focus.

Methods

In 2022 and 2023, a systematic search was conducted for guidelines, systematic reviews, and meta-analyses. Additional primary studies were included where aggregated evidence was unavailable (search term “colorectal cancer”; databases: international guideline registries, PubMed, Cochrane). A total of 123 systematic reviews reporting changes in professional practice were identified (eFigure 1) and assessed according to the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence, after which they were transferred into evidence tables to form the basis for classifying the levels of evidence and strength of recommendation in two consensus conferences (eTables 1 and 2).

Figure



Treatment algorithms in stage IV

Ab, antibody; GC, general condition; BSC, best supportive care; beva, bevacizumab; dMMR, mismatch repair deficiency; FP, fluoropyrimidine; MSI-H, microsatellite instability-high; MSS, microsatellite-stable; pMMR, mismatch repair proficiency; RASwt, RAS wild type

Methodological details, including a list of the most recent literature, are presented in the evidence report (3). Graphic elements (with the exception of the *Figure* and *eFigure 1*) and recommendations were taken from the updated version 3.0 of the German clinical practice guideline on colorectal cancer (4).

Results

Prevention and early detection

Significant overweight is associated with a 30% or greater increased risk of CRC, depending on its severity (5). Regular physical activity is therefore recommended to reduce the risk of CRC. Furthermore, around 10% of all cases of CRC are attributable to excessive alcohol consumption (6). The World Cancer Research Fund Third Expert Report confirms the direct association between alcohol consumption and an increased risk of CRC, while the consumption of dairy and whole grain products significantly reduces the risk. Therefore, to reduce the risk of CRC, the guideline recommends a diet rich in whole grains and fiber (for example, fruits and vegetables), plant-based foods, dairy products, and a diet low in highly processed foods as well as red and processed meat (expert consensus, EC) (7). A limiting factor, however, is that reliable data on the primary prevention of CRC through dietary interventions are not yet available. Furthermore, there are no confirmed data on the effectiveness of micronutrients, supplements, or medication in the primary prevention of CRC (8).

Examinations for the prevention and early detection of CRC are recommended for all persons at average risk from the age of 50. Practical approaches for CRC prevention/early detection include: colonoscopy every ten years or sigmoidoscopy every five years, or an immunological stool test for occult blood (FIT, fecal immunochemical test) every one to two years. This can lower cancer-related mortality by up to 32% (9–11). The guideline clearly states that other imaging, biochemical, or molecular modalities should not be used for prevention or early detection in asymptomatic individuals (strength of recommendation B; level of evidence [LoE] grade 3b–4). Nor shall a FIT or any other procedure for CRC prevention/early detection be recommended for ten years after unremarkable screening colonoscopy in asymptomatic individuals at an average risk.

Persons at increased risk of developing CRC relative to the general population due to a specific predisposition typically belong to one of four defined risk groups (*eTable 3*). Genetic testing shall be offered when there is suspicion of monogenic hereditary cancer predisposition (Lynch syndrome, polyposis, risk group 2) (EC) (12). All other recommendations for individuals with specific predispositions are provided in *eTable 3* and *eTable 4*.

Diagnostic evaluation

As a rule, treatment for CRC should be planned based on comprehensive diagnostic testing to determine the tumor stage (*eTable 5*). The Union Internationale Contre le Cancer (UICC) classifies rectal cancer according to its distance from the anocutaneous line, or anal verge, in cancers of the upper third of the rectum (12 to 16 cm), the middle third (6 to <12 cm), and the lower third (<6 cm) (13). In general, all patients with CRC should henceforth be presented to a multidisciplinary tumor board, regardless of tumor stage. Before initiating treatment, referral to a multidisciplinary tumor board should be arranged for all patients with rectal cancer, stage IV colon cancer, with metachronous distant metastases, with local recurrence(s), and before any metastasis-directed therapy.

Endoscopy and polyp management

Colorectal polyps shall be assessed by their macroscopic endoscopic appearance prior to excision and described with reference to their morphology, vascular architecture, surface pattern, size, and location (EC) (14). The time for a follow-up colonoscopy after complete removal of adenomas and serrated lesions shall depend on number, size, and histology of the findings (*Table 1*) (15). There is a new recommendation that follow-up after 12 months is advised for macroscopically complete, but histologically unconfirmed, removal of adenomas measuring 4 to 20 mm (B, LoE 4). Clinically and endoscopically, T1 cancer is an

entity unto itself. As a rule, a distinction is made here between low-risk carcinomas (G1, G2, and L0) and high-risk carcinomas (G3 or G4 and/or L1). Deep submucosal invasion alone is associated with a low risk of lymph node metastases and is not considered a sole indicator for oncologic surgery (LoE 2) (16). The appropriate approach after resection of a pT1 carcinoma (low risk versus high risk) is summarized in *eFigure 2*.

Surgical and perioperative treatment

Surgical treatment of colon cancer should include complete mesocolic excision. Laparoscopic resection for colon and rectal cancer can be performed with the same oncological results as the open surgical approach, so it should be given preference because of the better early postoperative outcome (17). Furthermore, robotic procedures are regarded as equivalent to laparoscopic techniques. In a recent randomized controlled trial (RCT) by Feng et al., the three-year locoregional recurrence rate after robotic surgery was significantly reduced at 1.6% versus 4.0% after laparoscopic resection (adjusted hazard ratio 0.39; 95% confidence interval: [0.19; 0.80]) (18, 19). According to the SYNCHRONOUS and CCR-IV trials, resection of an asymptomatic primary tumor (no signs of stenosis, no clinically relevant bleeding) in patients with inoperable metastatic disease is obsolete (A, LoE 1b) (20). In cases of metastatic spread, hepatic metastases can be resected with curative intent. Furthermore, local ablative procedures can be used for both resectable and primarily non-resectable hepatic metastases.

Molecular testing is now routinely included in the initial diagnostic workup for CRC. All CRCs shall be tested for mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) at initial diagnosis (EC). RAS and BRAF mutation status shall also be determined before initiating systemic drug therapy in the metastatic setting and can now also be assessed using cell-free DNA from the plasma of patients with metastatic CRC (EC).

The results of a pooled analysis of six randomized trials by the IDEA collaboration enable stratification of adjuvant chemotherapy for stage III, while taking into account overall survival, risk of recurrence, treatment duration, and toxicity (21). A three-month course of oxaliplatin according to the CAPOX/XELOX regimen should be administered to patients with a low risk of recurrence (T1–3 N1). Treatment with FOLFOX should be planned for six months or CAPOX for three months for patients at high risk (T4 or N2 category). Comparison of the treatment arms with respect to the five-year overall survival rate did not produce non-inferiority of the three-month (82.4 %) versus the six-month (82.8 %) treatment duration, although the absolute difference of 0.4% in the five-year survival rate is to be regarded as small in the clinical context (HR 1.02; [0.95; 1.11]). Current evidence from the ATOMIC trial demonstrates an additional effect of atezolizumab on recurrence-free survival in stage III disease where there is evidence of MSI-H/dMMR (22). The participants were randomized to receive either atezolizumab and mFOLFOX6, with maintenance therapy with atezolizumab, or standard mFOLFOX6. This resulted in a significant benefit in disease-free survival for the atezolizumab treatment arm (HR 0.50; [0.35; 0.72], $p < 0.0001$). Treatment-related

Table 1

Follow-up intervals after polypectomy

Baseline situation	Recommended interval for follow-up colonoscopy
Conventional adenomas	
1 or 2 adenomas (<1 cm) without villous histology or high-grade intraepithelial neoplasia	7–10 years
3 or 4 adenomas (<1 cm) without villous histology or HG-IEN	3–5 years
≥ 1 adenoma ≥ 1 cm or villous histology or HG-IEN	3 years
≥ 5 adenomas	<3 years
Serrated polyps/sessile serrated lesions	
1–2 SSL <10 mm and without dysplasia	5–10 years
≥ 3 SSL, SSL ≥ 10 mm, SSL with dysplasia, traditional serrated adenoma, hyperplastic polyps ≥ 10 mm	3 years
Hyperplastic polyps <10 mm	No follow-up
Incomplete resection/piecemeal resection	
Macroscopically complete removal of 4–20 mm polyps, but histological confirmation not certain	12 months
Piecemeal resection of large polyps (> 20 mm)	Follow-up examination of the resection site after 6 months and 18 months 6 months und 18 months

SSL, sessile serrated lesion; HG-IEN, high-grade intraepithelial neoplasia

adverse events (≥ grade 3) occurred in 71.7% of patients in the atezolizumab group as opposed to 62.1% in the mFOLFOX6 group.

In stages II and III, microsatellite status shall always be determined before establishing the indication for adjuvant chemotherapy. Adjuvant chemotherapy should not be administered in stage II disease with confirmed dMMR/MSI-H status. If a locally advanced mismatch-repair-proficient (pMMR) and/or microsatellite-stable CRC is present, then neoadjuvant/perioperative chemotherapy with FOLFOX or CAPOX can be administered (0, LoE 2). The FOxTROT study demonstrated an advantage of preoperative therapy with respect to the R0 resection rate (94% versus 89%, $p = 0.001$) as well as two-year recurrence-free survival (16.9% versus 21.5%; HR 0.72; [0.54; 0.98]) (23). The results of neoadjuvant immunotherapy in locally advanced dMMR/MSI-H CRC are even more impressive (0, LoE 3). In a phase II trial, Chalabi et al. reported on the response of these tumors to checkpoint blockade with ipilimumab and nivolumab. Of 111 evaluable patients, 105 (95%) demonstrated a major pathological response (≤ 10% residual tumor cells) and 75 a pathological complete response (24).

Treatment for stage IV

The five-year survival rate in stage IV is around 10 to 14%. Stratifying therapy based on clinical and molecular factors, however, results in long-term survival and potential cure, provided that the tumor shows an appropriate response, for example, to immunotherapy in dMMR/MSI-H disease and/or to the use of curatively intended resections. Consultation with the tumor board is therefore necessary for all patients, both initially and during ongoing treatment, to select the

Table 2

Scheduled follow-up examinations for follow-up care of colorectal carcinoma (UICC I–III)

Examination	Months*1										
	3	6	9	12	15	18	21	24	36	48	60
Medical history, physical examination		X		X		X		X	X	X	X
Colonoscopy*2		(X)		X							X
Abdominal ultrasound				X				X	X	X	X
Spiral computed tomography*3				X							

*1 Duration of follow-up (3 or 5 years) should be determined individually

*2 Colonoscopy: within 6 months, if not already performed before surgery

*3 Follow-up monitoring by spiral computed tomography or abdominal ultrasound to be determined individually
UICC, Union Internationale Contre le Cancer

appropriate therapy—particularly to assess whether local therapeutic procedures, possibly in combination, can be integrated into the treatment strategy with curative intent. Other local therapeutic procedures may also be considered, in addition to resection of metastasis (EC). Apart from determining the molecular tumor profile (dMMR/MSI-H, RAS, and BRAF, see above) (A, LoE 1a), a mutation in the four most important dihydropyrimidine dehydrogenase (DPD) gene loci shall be excluded before implementing fluoropyrimidine-based (FP) therapy (A, LoE 2a). As a general rule, all patients with metastatic dMMR/MSI-H CRC shall receive checkpoint inhibitor therapy (EC). The effectiveness of treatment with pembrolizumab and/or nivolumab/ipilimumab has been demonstrated in RCTs. Whereas treatment with pembrolizumab (KEYNOTE177 trial) resulted in, amongst other endpoints, improvement of progression-free survival after two years from 18.6% [12.1; 26.3] to 48.3% [39.9; 56.2] (25), combination treatment with nivolumab plus ipilimumab resulted in a two-year progression-free survival of 72% [64; 79%] in comparison with 14% [6; 25%] on chemotherapy alone (26). There was a considerable difference between immunotherapy and chemotherapy with respect to treatment-related adverse events. In the KEYNOTE-177 trial, the following (predominantly immune-mediated) adverse reactions (grade ≥ 3) were due to pembrolizumab: increased transaminases, colitis, diarrhea, and fatigue (2%). Decreased neutrophil count (17%), neutropenia (15%), diarrhea (10%), and fatigue (9%) developed in the chemotherapy arm (25). The *Figure* presents further treatment options for patients without dMMR/MSI-H, stratified by their RAS and BRAF status. In the BREAKWATER trial involving BRAF-mutated CRC, progression-free survival and overall survival were significantly longer after encorafenib, cetuximab, and mFOLOFOX6 (median 12.8 versus 7.1 months, HR 0.53 [0.41; 0.68] and median 30.3 versus 15.1 months, HR 0.49 [0.38; 0.63] respectively), in comparison with standard care (chemotherapy $\pm$ bevacizumab, at the physician's discretion) (27). Trifluridine/tipiracil should be used in combination with bevacizumab in patients who have received all available chemotherapies/antibodies, or who are not suitable candidates for them.

Other approved options include fruquintinib, regorafenib, and, with evidence of NTRK1–3 fusion, NTRK inhibitors (28).

Rectal cancer

Diagnostic evaluation of rectal cancer is conducted similar to that for colon cancer (*eTable 5*), while taking into account additional modalities for local tumor staging, including determination of correct tumor height. Accurate determination of the distance of the distal tumor margin from the dentate line is essential prior to treatment and should be achieved preferably by rigid proctoscopy, or alternatively and with appropriate expertise, by magnetic resonance imaging (MRI) or using flexible endoscopy. The MRI report should include the following parameters: tumor size/infiltration (cT category), locoregional lymph nodes (cN category), involvement of the mesorectal fascia (MRF), of the lateral pelvic lymph nodes, and/or extramural vascular invasion (EMVI). Various treatment options are available for UICC stages I to III: surgery alone (local excision or total/partial mesorectal excision), neoadjuvant chemotherapy, or short-course radiotherapy, or chemoradiotherapy. New additions include total neoadjuvant therapy and organ-preserving strategies in cases of complete or near-complete therapeutic response, for example after multimodal therapy and/or immunotherapy for MSI-H/dMMR tumors. All 12 participants with dMMR rectal cancer in the phase II trial by Cercek et al. demonstrated complete clinical remission (100%; [74%; 100%]) (29). No adverse events of grade 3 or higher were reported. Mild adverse reactions (grade 1 or 2) were dermatitis (31%), pruritus (25%), and fatigue (25%). A larger, more recent phase II trial confirmed complete clinical remission in all 49 patients (30). Therefore, in confirmed MSI-H/dMMR disease, therapy with an immune checkpoint inhibitor alone can be provided for six months without radio- or chemoradiotherapy, with no need for surgery if a clinical complete remission (cCR) is achieved (EC) (29, 30). Selection of the best treatment for the patient should be based on therapeutic goals, as well as clinical, imaging, and molecular factors. When curatively equivalent treatment options are available, factors such as

the patient's baseline clinical and functional status (for example, sphincter function), comorbidities, and personal preferences regarding treatment side effects and symptom profiles become the focus of attention during shared decision-making (31, 32).

Long-term follow-up care

Taking a symptom-oriented medical history and performing a physical examination are still basic components of long-term follow-up care. The intensity and duration of care, as well as the role of further diagnostic procedures, including imaging studies and tumor markers, remain topics of ongoing debate (33–35). The meta-analysis by Pita-Fernandez et al. showed, for example, a clear benefit of intensive aftercare for CRC patients (11 RCTs, 4055 patients; HR = 0.75; [0.6; 0.86]) (33), while the more recent Cochrane analysis by Jeffrey et al. involving 19 trials and 13 216 patients produced no significant survival benefit for intensive follow-up care (HR 0.91; [0.80; 1.04]; I² = 18%) (34). If levels of the tumor marker carcinoembryonic antigen (CEA) were elevated before treatment, then they can be re-assessed after curative-intent treatment. It is also recommended that full colonoscopy be performed within six months of surgery if a complete examination was not achieved preoperatively. All recommendations for follow-up care are summarized in Table 2. Structured follow-up should be recommended after curative metastasis-directed therapy: computed tomography of the chest and abdomen every three months in the first year and then every six months until the fifth year.

Palliative care and rehabilitation

The recommendations for palliative care adhere to the German Clinical Practice Guideline on Psycho-oncological Diagnostics, Counseling and Treatment of Adult Cancer Patients. Patient-centered provision of information about psycho-oncological support services shall be ensured early and in all phases of the disease (EC). As regards optimized nutrition, regular monitoring of food intake, weight changes, and body mass index using established methods (for example, NRS 2002 [Nutritional Risk Screening], MUST [Malnutrition Universal Screening Tool]) should be carried out from the time of cancer diagnosis. Dietary intervention should then be recommended for all CRC patients affected by malnutrition or at risk of malnutrition.

Regular physical activity is recommended (36). In the RCT by Courneya et al., a structured exercise program administered after completion of adjuvant chemotherapy was associated with significantly longer recurrence-free survival (HR 0.72; [0.55; 0.94]; *p* = 0.02). Every patient should be asked as early as possible and repeatedly throughout follow-up care about the use of complementary measures and specifically informed about possible interactions between these applications and cancer therapy. On completion of primary therapy, a post-acute convalescence program shall be offered to all patients capable of rehabilitation (EC). In their meta-analysis of 12 RCTs with 1669 patients, Scott et al. found a significant improvement in the SF-36 physical health component scores (mean difference 2.22; [0.12; 4.31]) (37). It should be ensured that, when indicated, adjuvant chemotherapy is promptly initiated, even in these cases.

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Conflict of interest statement

ME is a member of the Executive Committee of the DGVS. He has received fees for lecturing activities from the FALK Foundation.

CP received fees for lecturing activities from Falk, Fuji, Merck, and MSD. He is secretary of the Gastro-Liga (German Society for the Fight against Stomach, Intestine, Liver and Metabolic Diseases as well as Eating Disorders)

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Clinical practice guidelines in the *Deutsches Ärzteblatt*, as in many other journals, are not subject to peer review because clinical practice (S3 level) guidelines are texts that have already been evaluated, discussed, and widely agreed upon multiple times by experts (peers).

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Supplementary material

Complete list of full references, eTables, eFigures
www.aerzteblatt-international.de/m2025.0196

CLINICAL SNAPSHOT



Incarcerated Jejunal Hernia Following Lumbar Vertebral Fracture

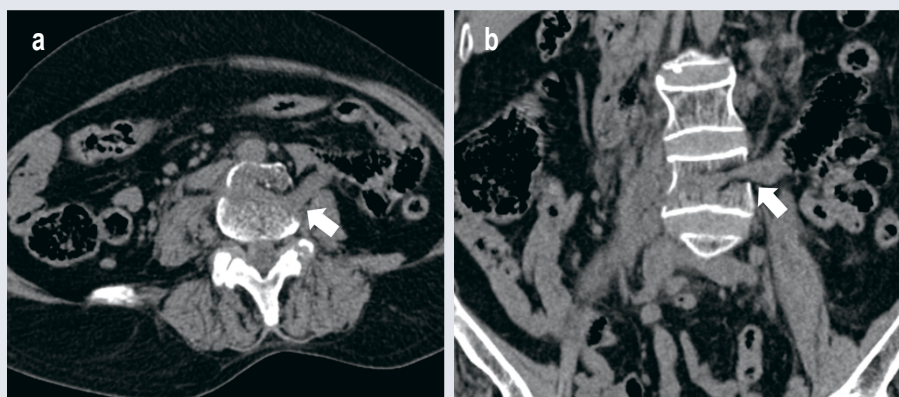


Figure: Abdominal CT showing discontinuity of the L4 vertebral body with fracture fragments. Jejunal loop trapped in the fracture gap (arrows), exhibiting wall thickening and edema, accompanied by proximal jejunal dilation and an air fluid level.

A patient in their 60s presented in September 2024 with a 3-day history of progressive weakness, malaise, decreased appetite, and non-projectile post-prandial vomiting, without motor deficits or fever. The patient had sustained an L4 vertebral fracture 1 month earlier, which had been managed conservatively without surgical intervention. Abdominal CT (Figure A, B) demonstrated discontinuity of the L4 vertebral body with separated fracture fragments. Emergency laparotomy revealed jejunal incarceration at the L4 fracture site, with necrosis and perforation of an approximately 6-cm long section of the bowel. Resection of the necrotic segment with jejunojunctionostomy was performed. At 2-week follow-up, bowel function was restored without evidence of anastomotic leakage. This case illustrates a rare hernia variant: jejunal incarceration within a lumbar vertebral fracture (only 12 cases reported globally between 1979 and 2016). It underscores the need to consider traumatic or spinal abnormalities in atypical intestinal obstructions.

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Supplementary material to accompany the article

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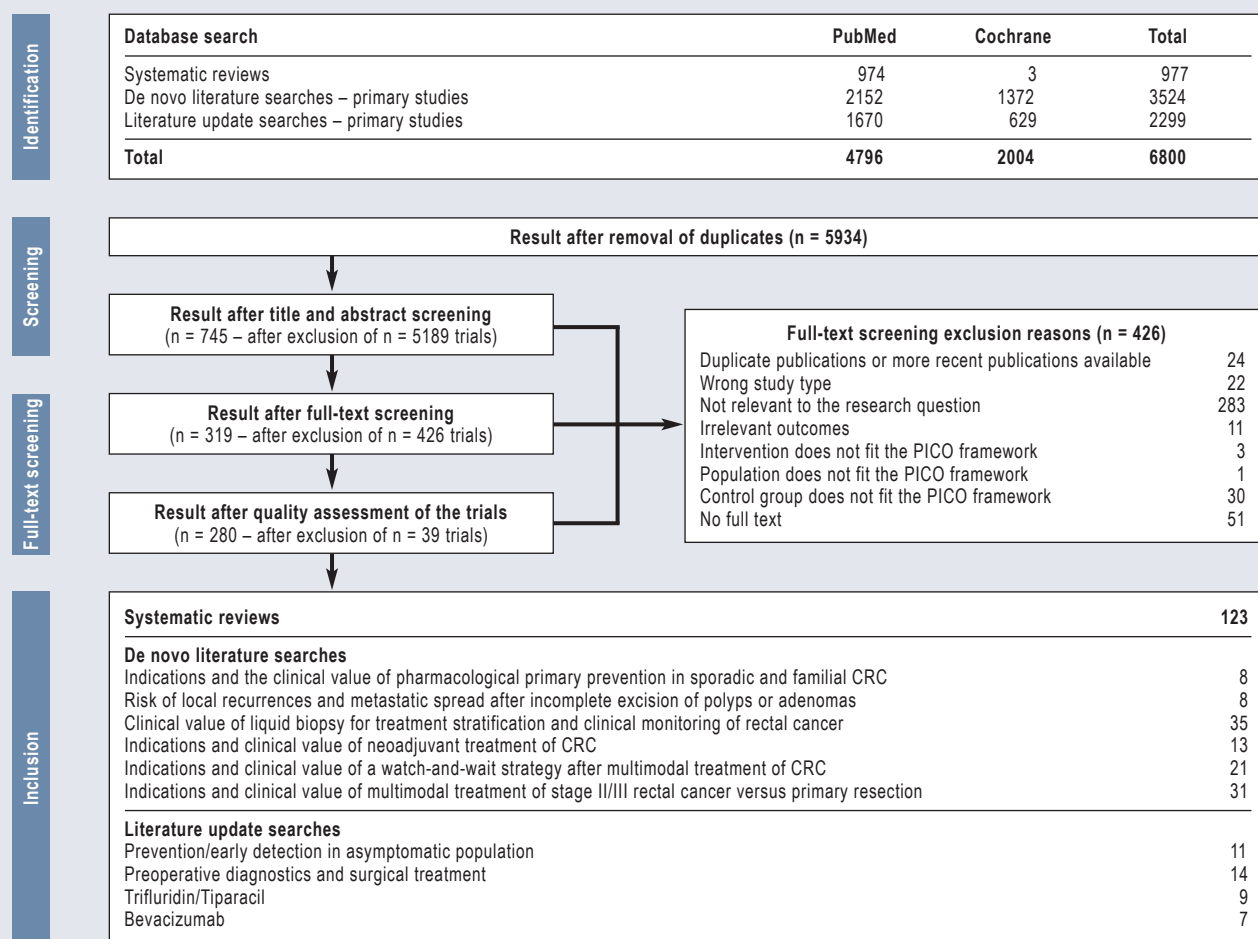
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eFigure 1

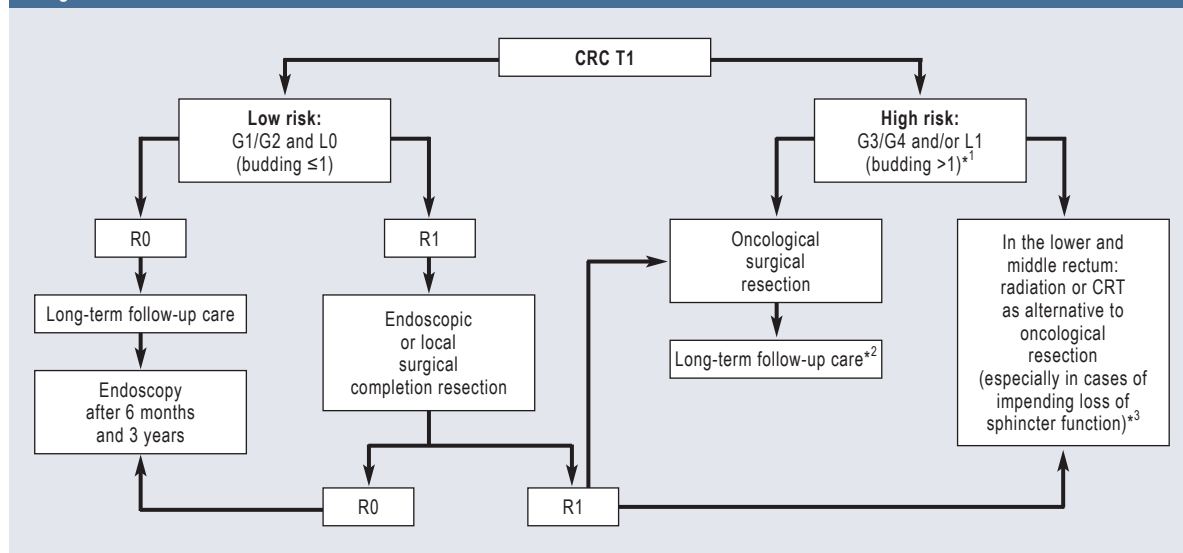


PRISMA flow chart—overview of identification and selection of studies

Initially, a systematic literature search was conducted to identify reviews and meta-analyses addressing all de novo key questions and to update existing evidence-based recommendations. After evaluating the reviews, six searches for primary studies were conducted for de novo key questions for which no aggregated evidence was available, or for which the available aggregated evidence alone was considered insufficient. For revisions of evidence-based recommendations for which no aggregated evidence was available, four additional update searches were conducted to identify primary studies.

CRC, colorectal cancer

eFigure 2



Flow chart for the therapeutic approach to T1 colorectal cancer

*1 budding: no obligatory high-risk criterion

*2 see chapter on long-term follow-up care

*3 followed by local excision or watch-and-wait approach after achieving (near) clinical full remission

CRC, colorectal cancer; CRT, chemoradiotherapy

eTable 1

Grading of recommendations system

Strength of recommendation	Description
A	strong recommendation for or against a measure; expression used = shall/shall not
B	recommendation for or against a measure; expression used = should/should not
O	open recommendation (option) for a measure; expression used = can

eTable 2

Classification of consensus strength

Consensus strength	Description
No approval	<50% approval of those eligible to vote
Consensus	>75–95 % approval of those eligible to vote
Majority approval	>50–75% approval of those eligible to vote
Strong consensus	>95% approval of those eligible to vote

eTable 3

Risk groups with predisposition to colorectal cancer

Risk group with definition	Preventive measure
● Risk group 1: Confirmed carriers of a monogenic hereditary cancer predisposition with an increased risk of CRC (Lynch syndrome [LS]; gastrointestinal/colorectal polyposis)	Syndrome-specific
● Risk group 2: Persons with suspected monogenic hereditary cancer predisposition based on clinical or molecular-pathological findings, or with clinically confirmed polyposis, but without evidence of a causative germline variant	
a) Patients with CRS who fulfil one of the criteria listed below (revised Bethesda criteria) and their first-degree relatives: – patients with CRC under the age of 50 – patients with two LS tumors^{*1} – CRC patients with a first-degree relative with LS tumor^{*1} under the age of 50 – CRC patients with two first or second-degree relatives with LS tumors^{*1} regardless of onset age	Colonoscopies starting 10 yrs. prior to age of onset of the youngest CRC in family, from the age of 40 at the latest; every 3 to 5 yrs. ^{*2}
b) Patients with MSI-H/dMMR-KRK without evidence of a tumor-specific (somatic) cause: – loss of MMR gene expression and/or microsatellite instability – additionally, in cases with MLH1 loss: no MLH1 promoter methylation, no BRAF p.Val600Glu mutation in the tumor tissue	
c) Patients with clinically suspected or confirmed polyposis: – patients with (suspected) adenomatous polyposis – patients with (suspected) hamartomatous polyposis (juvenile polyposis, Peutz-Jeghers syndrome) – patients with (suspected) serrated polyposis syndrome	Individual early detection screening and preventive surgery, depending on the clinical findings
● Risk group 3: Persons with a positive family history of polyps/CRC with no clinical suspicion of monogenic hereditary cancer predisposition	
a) First-degree relatives of CRC patients who do not fall into risk group 2	Colonoscopy starting 10 yrs. prior to age of onset of the youngest CRC in the family, from the age of 40 at the latest ^{*2} , every 10 yrs.
b) First-degree relatives of patients with isolated adenomas under the age of 40	Colonoscopy starting 10 yrs. before age of onset of the youngest adenoma in the family ^{*2} , every 10 yrs.
● Risk group 4: Persons with any other underlying condition that predisposes to CRC	
a) Patients with inflammatory bowel disease	See corresponding ulcerative colitis GL or Crohn's disease GL
b) Patients with cystic fibrosis (mucoviscidosis)	Colonoscopy from the age of 40

^{*1} Colon/rectum, endometrium, stomach, ovaries, pancreas, urothel, bile duct, and brain (usually glioblastoma), as well as sebaceous gland neoplasias (adenomas, epitheliomas, carcinomas), and keratoacanthomas

^{*2} This is rarely necessary before the age of 18. Therefore, if the affected relative developed the disease at a very young age, the 10-year interval should be discussed critically with at-risk persons and shortened if necessary.

GL, guideline; MSI-H, microsatellite instability-high

eTable 4

Hereditary and familial colorectal cancer: New recommendations and statements

No.*	Statement/Recommendation	Recommendation grade	LoE	Consensus
5.3	The first step in the diagnostic workup for suspected Lynch syndrome is molecular testing of the tumor tissue for abnormalities typical of Lynch syndrome, provided this has not been done already.	EC		strong
5.4	All patients with MSI-H/dMMR CRC with no evidence of a sporadic malignant neoplasm (in cases of MLH1 loss: no evidence of MLH1 promoter methylation or BRAF p.Val600Glu mutation) shall be offered germline genetic testing for Lynch syndrome.	A	2b	strong
5.5	Patients with early-onset CRC (<50 years) should be offered germline genetic testing for a monogenic hereditary tumor predisposition, regardless of their molecular-pathology results.	B	2	strong
5.6	All patients with suspected hereditary polyposis syndrome shall be offered germline genetic testing (multigene panel testing). Since there is considerable overlapping in number of polyps and their histology across the various clinically defined subtypes, it is recommended that all genes relevant to the colorectal phenotype and relevant differential diagnoses be included.	EC		strong
5.7	Detection of a causative germline mutation (pathogenicity class 4 or 5) in an established gene for monogenic hereditary cancer predisposition enables the diagnosis of hereditary CRC (Lynch syndrome, polyposis) to be made and allows (predictive) genetic testing to be offered to at-risk family members. If a known familial germline mutation has been excluded in an at-risk family member, then the same recommendations for general cancer screening and early detection apply to this person.	EC		strong
5.10	Patients with clinically suspected monogenic hereditary cancer predisposition (risk groups 2a and 2c), as well as their first-degree relatives, shall be referred to a human genetics clinic or to a center for hereditary cancer syndromes, regardless of the results of the molecular pathology or molecular genetic tests.	EC		strong
5.15	Furthermore, the possibility of preventive measures against other extraintestinal malignancies shall be discussed with Lynch syndrome carriers, especially with respect to endometrial cancer, ovarian cancer, and pancreatic cancer (see S3 guideline Endometrial Cancer, S3 guideline Ovarian Cancer, S3 guideline Pancreatic Cancer).	EC		strong
5.30	- All polyps ≥ 5 mm and all polyps macroscopically suspicious of dysplasia should be removed endoscopically in patients with serrated polyposis syndrome. - The surveillance interval should be one year for advanced polyps (SSL ≥ 10 mm in diameter and/or dysplasia or advanced adenoma) or non-advanced polyps of ≥ 5 mm in diameter (adenomas or SSLs ≥ 5 mm). - The interval should be two years for patients with no evidence of advanced polyps or <5 non-advanced polyps.	EC		strong
5.31	Screening colonoscopy should be offered to first-degree relatives of patients with serrated polyposis syndrome, beginning at 40 years of age, or 10 years prior to the age at diagnosis of the affected relative.	EC		strong
5.34	Lynch syndrome cannot be reliably excluded in patients with abnormalities typical of Lynch syndrome detected in the molecular pathology analysis of the tumor tissue (dMMR and/or MSI-H; in cases of MLH1 loss: no MLH1 promoter methylation, no BRAF p.Val600Glu mutation), in whom no causative germline mutation has been identified. However, patients and their first-degree relatives who do not fulfil the clinical suspicion criteria for Lynch syndrome are unlikely to have a significantly increased risk of (metachronous) CRC.	EC		strong
5.40	Patients with cystic fibrosis (mucoviscidosis) have a significantly increased risk of CRC relative to the general population.	EC		strong
5.41	Patients with cystic fibrosis (mucoviscidosis) should be advised to undergo colonoscopy every five years from the age of 40, depending on their general condition and prognosis.	EC		strong

* The numbers correspond to the recommendation numbers in the original clinical practice guideline, Version 3.0; accessible online at: www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Kolorektales_Karzinom/Version_3/LL_KRK_Langversion_3.0.pdf
A, strength of recommendation shall/shall not; B, strength of recommendation should/should not; EC, expert consensus; CRC, colorectal carcinoma; LoE, level of evidence; MSI-H, high microsatellite instability; SSL, sessile serrated lesion

eTable 5

Colorectal cancer staging

Examination	Colon cancer	Rectal cancer
Digital rectal examination	X	X
Full colonoscopy	X	X
Chest/Abdominal CT, including pelvis	X	X
Rigid proctoscopy		X
MRI rectum (pelvis)		X
Rectal endoscopic ultrasound for locally confined tumors		X
Contrast-enhanced ultrasound or MRI with a liver-specific contrast agent in cases of unclear hepatic M situation after CT	X	X

CT, computed tomography; MRI, magnetic resonance imaging; M situation, metastases

eTable 6

Working groups and their members

Working group	Members of the working group
WG 1: Prevention—asymptomatic population (Chapter 3)	Prof. Dr. Johann Ockenga Dr. Thomas Maibaum, Dr. Stefanie Reichermeier, Prof. Dr. Jürgen F. Riemann, Prof. Dr. Diana Rubin
WG 2: Prevention/Early detection—asymptomatic population (Chapter 4)	Prof. Dr. Frank Kolligs Prof. Dr. Hermann Brenner, Dr. Günther Egidi, Prof. Dr. Michael Neumaier, Prof. Dr. Kristina Ringe
WG 3: Risk groups (Chapter 5)	Prof. Dr. Stefan Aretz, Dr. Robert Hüneburg Dr. Frank Dannel, Dr. Günther Egidi, Prof. Dr. Alois Fürst, Prof. Dr. Jens Neumann, Nicola Reents, Dr. Verena Steinke-Lange
WG 4: Endoscopy: Implementation and polyp management (Chapter 6)	Dr. Dietrich Hüppe, Dr. Andreas Probst Prof. Dr. Hendrik Bläker, Prof. Dr. Ulrike Denzer, PD Dr. Dipl.-Phys. Anjali A. Röth
WG 5: Preoperative diagnostics and surgical treatment (Chapter 7)	PD Dr. Christine Koch, Prof. Dr. Thomas Schiedeck Prof. Dr. Hojjat Ahmadzadehfard, Prof. Dr. Dirk Arnold, Prof. Dr. Cihan Gani, Prof. Dr. Christoph-Thomas Germer, Erich Grohmann, Maria Hass, Dr. Christian Hillert, Prof. Dr. Markus Juchems, Prof. Dr. Andreas Jung, Prof. Dr. Josef Menzel, Prof. Dr. Michael Neumaier, Prof. Dr. Stefan Post, Prof. Dr. Carolin Tonus, Prof. Dr. Tim Vilz, Dr. Maria Kröplin
WG 6: Pathology (Chapter 8)	Prof. Dr. Jens Neumann Prof. Dr. Dirk Arnold, Prof. Dr. Hendrik Bläker, Dr. Annika Kurreck, Prof. Dr. Michael Neumaier, Dr. Verena Steinke-Lange, Prof. Dr. Sebastian Stintzing
WG 7: Neoadjuvant and adjuvant therapy (Chapter 7)	Prof. Dr. Claus Rödel, Prof. Dr. Thomas Seufferlein Dr. Christian Hillert, Prof. Dr. Ralf-Dieter Hofheinz, Prof. Dr. Stefan Holdenrieder, Prof. Dr. Matthias Miederer, Prof. Dr. Beate Rau, Prof. Dr. Anke Reinacher-Schick, Prof. Dr. Sigmar Stelzner, Prof. Dr. Thomas J. Vogl
WG 8: Treatment for metastatic spread and in the palliative situation (Chapter 10)	Prof. Dr. Ulrich Graeven, Prof. Dr. Claus-Henning Köhne Prof. Dr. Emmanouil Fokas, Prof. Dr. Volker Heinemann, Dr. Christian Hillert, Prof. Dr. Stefan Holdenrieder, PD Dr. Kia Homayounfar, Michael Höckel, PD Dr. Gunther Klautke, Prof. Dr. Philipp Lenz, Prof. Dr. Andreas Mahnken, Prof. Dr. Beate Rau
WG 9: Follow-up care (Chapter 11)	Prof. Dr. Leopold Ludwig PD Dr. Reiner Caspari, Prof. Dr. Robert Grützmann, PD Dr. Holger Hass, Dr. Christian Hillert, Prof. Dr. Stefan Holdenrieder, Dr. Jürgen Körber, Dr. Thomas Maibaum, Prof. Dr. Oliver Waidmann
WG 10: Psycho-oncology, supportive and complementary medicine, palliative care, rehabilitation (Chapters 12 and 13)	Prof. Dr. Diana Rubin PD Dr. Reiner Caspari, Erich Grohmann, PD Dr. Holger Hass, Maria Hass, Dr. Jürgen Körber, Dr. Bernd Oliver Maier, Viktoria Mathies, Prof. Dr. Alexander Stein
WG 11: Research issues (Chapter 14)	Prof. Dr. Matthias Ebert PD Dr. Dr. Lena Conradi, Prof. Dr. Stefan Holdenrieder, Prof. Dr. Sebastian Stintzing
WG 12: Healthcare facilities and quality indicators (Chapter 15)	PD Dr. Christian Pox Prof. Dr. Stefan Rolf Benz, Erich Grohmann, Maria Hass, Michael Höckel, Dr. Stefanie Reichermeier, Prof. Dr. Carolin Tonus, Dr. Thomas Weihkopf

Working group leaders are indicated in bold.

eTable 7

Participating professional societies and organizations

Participating professional societies and organizations	Persons
Working Group on Imaging within Oncology of the German Cancer Society (ABO)	Prof. Dr. Matthias Miederer
Working Group of German Tumor Centers (ADT)	Prof. Dr. Stefan Rolf Benz
Working Group on Medical Oncology within the German Cancer Society (AIO)	Dr. Annika Kurreck Prof. Dr. Anke Reinacher-Schick Prof. Dr. Alexander Stein
Working Group on Oncological Pharmacy (OPH)	Michael Höckel
Working Group on Oncological Rehabilitation and Social Medicine within the German Cancer Society (AGORS)	PD Dr. Reiner Caspari Dr. Jürgen Körber
Working Group on Palliative Medicine within the German Cancer Society (APM)	Dr. Bernd Oliver Maier Dr. Parvis Sadjadian
Working Group on Prevention and Integrative Medicine in Oncology within the German Cancer Society (PRiO)	Viktoria Mathies
Working Group on Radiological Oncology within the German Cancer Society (ARO)	Prof. Dr. Emmanouil Fokas
Working Group on Supportive Measures in Oncology within the German Cancer Society (AGSMO)	Prof. Dr. Alexander Stein
Working Group on Oncological Pathology within the German Cancer Society (AOP)	Prof. Dr. Jens Neumann
Association of Surgical Oncology	Prof. Dr. Christoph-Thomas Germer Prof. Dr. Carolin Tonus
Professional Association of German Pathologists (BDP)	Prof. Dr. Hendrik Bläker Prof. Dr. Andreas Jung Prof. Dr. Jens Neumann
German Society for General and Visceral Surgery (DGAV)	PD Dr. Dr. Lena Conradi Prof. Dr. Alois Fürst Prof. Dr. Christoph-Thomas Germer Prof. Dr. Robert Grützmann PD Dr. Kia Homayounfar Prof. Dr. Beate Rau Dr. Dipl.-Phys. Anjali A. Röth Prof. Dr. Thomas Schiedeck Prof. Dr. Sigmar Stelzner Prof. Dr. Tim Vilz
German College of General Practitioners and Family Physicians (DEGAM)	Dr. Günther Egidi Dr. Thomas Maibaum
German Society for Epidemiology (DGEpi)	Prof. Dr. Hermann Brenner
German Society for Nutritional Medicine (DGEM)	Prof. Dr. Diana Rubin
German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS)	Prof. Dr. Ulrike Denzer Prof. Dr. Matthias Ebert Prof. Dr. Ulrich Graeven Dr. Robert Hüneburg Dr. Dietrich Hüppe PD Dr. Christine Koch Prof. Dr. Frank Kolligs Prof. Dr. Leopold Ludwig Prof. Dr. Johann Ockenga PD Dr. Christian Pox Dr. Andreas Probst Dr. Stefanie Reichermeier Prof. Dr. Thomas Seufferlein
German Society of Human Genetics (GfH)	Prof. Dr. Stefan Aretz Dr. Verena Steinke-Lange
German Society for Hematology and Medical Oncology (DGHO)	Prof. Dr. Dirk Arnold Prof. Dr. Volker Heinemann Prof. Dr. Ralf-Dieter Hofheinz Prof. Dr. Claus-Henning Köhne Prof. Dr. Sebastian Stintzing Prof. Dr. Oliver Waidmann
German Society for Internal Medicine (DGIM)	Prof. Dr. Matthias Ebert

German Society for Interventional Radiology and Minimally Invasive Therapy (DeGIR)	Prof. Dr. Markus Juchems Prof. Dr. Andreas Mahnken
German Society for Clinical Chemistry and Laboratory Medicine (DGKL)	Prof. Dr. Stefan Holdenrieder Prof. Dr. Michael Neumaier
German Society for Coloproctology (DGK)	Prof. Dr. Stefan Post
German Society for Nuclear Medicine (DGN)	Prof. Dr. Hojjat Ahmadzadehfard
German Society for Palliative Medicine (DGP)	Prof. Dr. Philipp Lenz
German Society for Pathology (DGP)	Prof. Dr. Hendrik Bläker Prof. Dr. Andreas Jung Prof. Dr. Jens Neumann
German Society of Radiation Oncology (DEGRO)	Prof. Dr. Cihan Gani PD Dr. Gunther Klautke Prof. Dr. Claus Rödel
German Society of Rehabilitation Science (DGRW)	PD Dr. Holger Hass
German Society of Ultrasound in Medicine (DEGUM)	Dr. Christian Hillert Prof. Dr. Josef Menzel
German ILCO Association (patient organization for stoma carriers)	Erich Grohmann Maria Hass
German Crohn's Disease/Ulcerative Colitis Association	Dr. Frank Dannel
German Radiology Society (DRG)	Prof. Dr. Markus Juchems Prof. Dr. Andreas Mahnken Prof. Dr. Kristina Ringe Prof. Dr. Thomas J. Vogl
Invited experts (without voting rights)	Dr. Joachim Reibetanz Dr. Thomas Weihkopf Dr. Maria Kröplin
Methodology, coordination	Dr. Markus Follmann Celia Inselmann PD Dr. Petra Lynen Jansen Dipl.-Troph. Lars Klug Dipl.-Soz.Wiss. Thomas Langer Dr. Cathleen Muche-Borowski Dr. Monika Nothacker Dr. Stefanie Reichermeier Dr. Nadine Steubesand Dipl. Biologie Gregor Wenzel
SemiColon, Family Support for CRC	Nicola Reents
Lebensblicke Foundation (engaged in cancer prevention)	Prof. Dr. Jürgen F. Riemann

eTable 8

Colorectal Cancer Steering Group: List of working group leads (Collaborators)

Members of the working group	Institute/Department	Hospital
Prof. Dr. Stefan Aretz	Institute for Human Genetics	University Hospital Bonn
Prof. Dr. Matthias Ebert	Medical Department II	University Medical Center Mannheim
Prof. Dr. Ulrich Graeven	Clinic for Hematology, Oncology and Gastroenterology	Maria Hilf Hospitals Mönchengladbach
Dr. Robert Hüneburg	Medical Department I	University Hospital Bonn
Dr. Dietrich Hüppe	Gastroenterological Group Practice Herne	Herne
PD Dr. Christine Koch	Medical Department I	University Hospital Frankfurt
Prof. Dr. Claus-Henning Köhne	Department for Internal Medicine – Oncology and Hematology	University Hospital Oldenburg
Prof. Dr. Frank Kollegs	Department for Internal Medicine and Gastroenterology	Helios Clinic Berlin-Buch
Prof. Dr. Leopold Ludwig	Gastroenterological Subspecialized Practice	Dornstadt
Prof. Dr. Jens Neumann	Institute for Pathology	Nuremberg University Hospital
Prof. Dr. Johann Ockenga	Medical Department II	Bremen-Mitte University Hospital
PD Dr. Christian Pox	Medical Department	St. Joseph-Stift Hospital, Bremen
Dr. Andreas Probst	Medical Department III	University Hospital Augsburg
Prof. Dr. Claus Rödel	Department of Radiation Therapy and Oncology	University Hospital Frankfurt
Prof. Dr. Diana Rubin	Center for Nutritional Medicine	Vivantes Humboldt Hospital Berlin
Prof. Dr. Thomas Schiedeck	Department of General, Visceral, Thoracic and Pediatric Surgery	Ludwigsburg Hospital
Prof. Dr. Thomas Seufferlein	Department for Internal Medicine I	University Hospital Ulm