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Rectal Cancer

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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1 Summary

Colorectal cancer is the second most common malignant tumor in women and the third most common cancer in men in German-speaking countries. The average age at onset is 70-75 years. People with a genetic or acquired predisposition may develop the disease in early adulthood.

For early detection, non-invasive tests for occult blood in the stool are available as a trigger for endoscopic examination or direct flexible endoscopic examination of the colon. Both procedures reduce cancer-specific mortality; in Germany, screening colonoscopy is the preferred recommendation.

The treatment of patients with rectal cancer is based on the stage of the disease at the time of initial diagnosis and the treatment goal. In stage I, surgery (optionally as local excision) is the first line of treatment. In stages II and III, preoperative radiochemotherapy (RChT) or radiotherapy (RT) is recommended for tumors in the lower and middle thirds; if there is a low risk of local recurrence, neoadjuvant chemotherapy or primary surgery is also recommended (treatment corridor). Total neoadjuvant therapy (TNT) is recommended if clinical risk factors are present. Rectal carcinomas in the upper third are usually resected primarily; if a microsatellite stable (MSS) tumor is present, neoadjuvant chemotherapy may be given (see below for possible indications). A recommendation for or against adjuvant chemotherapy cannot be made; the use of adjuvant therapy should therefore be discussed on an individual basis. The option of organ preservation should be discussed with the patient; the RT/RChT protocols used should be based on the tumor characteristics or stage.

For the majority of patients in stage IV, treatment aims at palliation, with relief of symptoms and prolongation of survival time. For a subgroup of patients, a cure is also possible in this situation. For systemic cancer treatment in stage IV, different cytostatic drugs, monoclonal antibodies and targeted therapies are available. The optimal combination and sequence are the subject of current clinical trials.

Advances in the diagnosis and treatment of colorectal cancer have led to a steady decline in mortality over the past 10 years.

2 Basics

2.1 Definition and basic information

The Union Internationale Contre le Cancer (UICC) defines rectal carcinomas as tumors whose aboral margin (distal margin) is 16 cm or less from the anocutaneous line when measured by rigid rectoscopy [1]. Carcinomas located more proximally up to and including the ileocecal valve are defined as colon carcinomas.

Histologically, adenocarcinoma is present in more than 95% of patients. Other, less common malignancies of the rectum are neuroendocrine tumors, lymphomas, sarcomas or squamous cell carcinomas.

Colon and rectal carcinomas share many common features in etiology and histology. However, they differ in their preoperative, surgical and adjuvant treatment strategies. Therefore, they are addressed in separate Onkopedia guidelines. The topic of this guideline is adenocarcinoma of the rectum. It accounts for 30-40% of colorectal cancer in Germany.

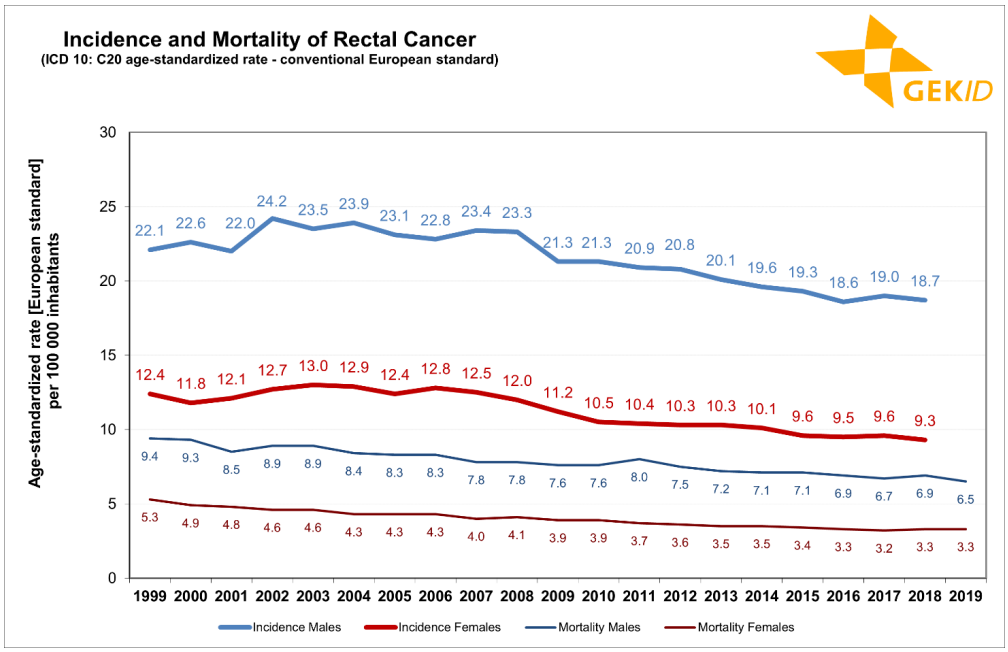
2.2 Epidemiology

Almost 20,000 new cases of rectal cancer are diagnosed in Germany every year. Almost 12,000 men and around 7,000 women are annually diagnosed with this type of cancer in Germany, which corresponds to around 4.3% and 3.0% of all malignant tumors. The prognosis of rectal cancer is similar to that of colon cancer and is in the middle range compared to other cancers. Every year, slightly less than half as many individuals die from rectal cancer than are diagnosed (i.e., approx. 7,600) [3].

The median age at diagnosis for men is 70 years, which is the same as for cancer overall (70 years), while for women it is 73 years, i.e., four years higher than for cancer overall (69 years). The median age at death is 74 years (men), one year below and 78 years (women), one year above the median age at death from cancer overall (75 years and 76 years, respectively).

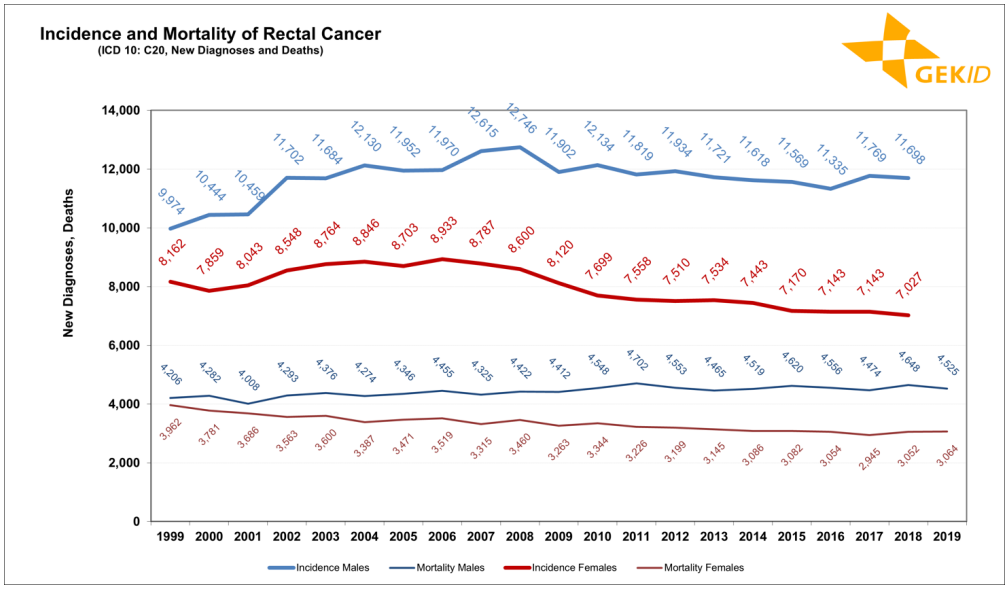
The age-standardized morbidity rates - i.e., the probabilities of developing the disease - as well as the age-standardized mortality rates - the probabilities of dying - show a decreasing trend over the past 15 years both for men and women, see Figure 1. This is also confirmed by a joinpoint analysis [4, 5], according to which the incidence rates in men decrease by an average of 1.8% per year and those in women by as much as 2.1%. The declines in mortality rates are similar, averaging 1.6% (men) and 2.3% (women) per year.

Figure 1: Estimated incidence and mortality of malignant neoplasms of the rectum (ICD 10: C20) in Germany – age-standardized rates (old European standard) [3]



While the age-standardized rates new of new diagnoses are a measure of the probability of disease and largely independent of the population structure, the number of new cases also depends on the age structure and population size. Due to the shift in the age structure towards an older society and the fact that the baby boomers are reaching the age cohorts most likely to develop the disease, the courses of new cases and deaths differ from the course of the rates. The higher the age at which the disease is first diagnosed, the stronger the effect. This effect is more pronounced in men than in women. Despite declining morbidity and mortality rates, the number of new cases and deaths from colorectal cancer in men has remained almost constant since 2003. For women, as with the rates, decreasing numbers are also observed for incidence and mortality, but the decline of 1.5% per year (incidence) and 1.2% per year (mortality) is lower than for the rates (Figure 2).

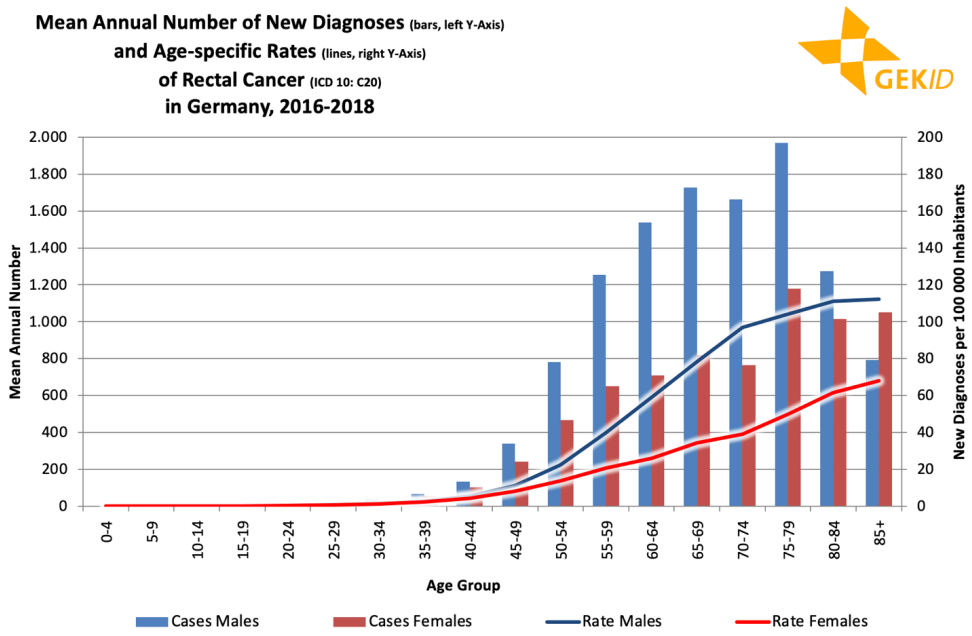
Figure 2: Estimated incidence and mortality of malignant neoplasms of the rectum (ICD 10: C20) in Germany – case numbers [3]



In individuals up to the age of 40 years, rectal cancer is almost neglectable. From then on, the disease rates increase steadily in both sexes and reach their peak in the highest age group (85 years and older) (see Figure 3 [lines]). From the beginning, the rate for men is always higher

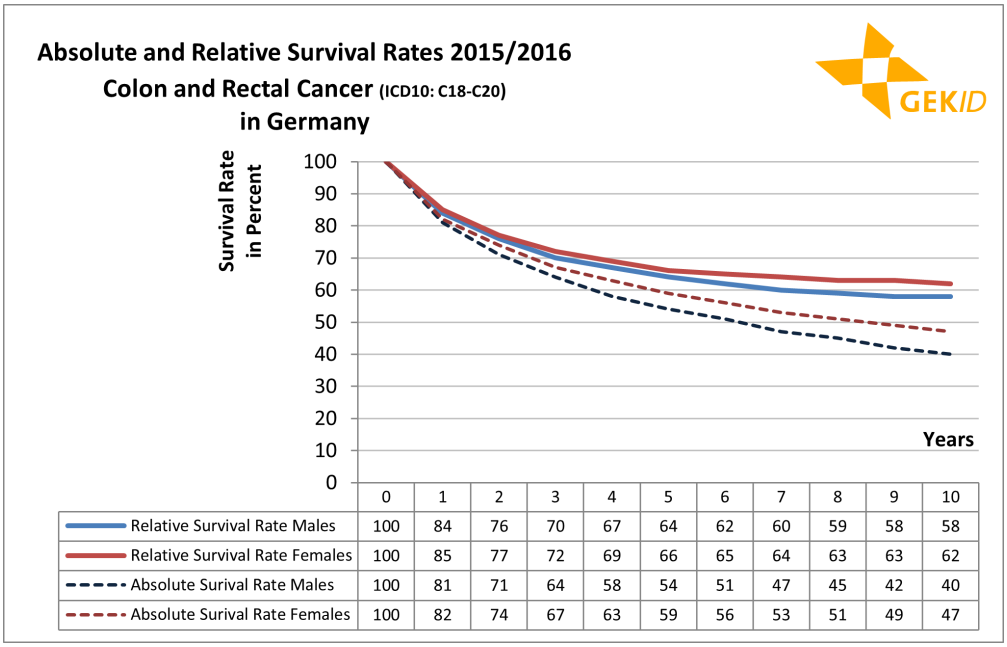
than that for women. The number of cases is somewhat different due to the population distribution. The number of new cases increases in men up to the age group of 75-79 years (see Figure 3 [bars]). After that, the number of cases halves, which is due to the fact that the number of men declines due to their shorter life expectancy. For women, a steady increase in the number of cases can be observed up to the age of 70 years. Around 800 new cases are currently diagnosed in the eighth decade of life. After that, the number of cases rises by around 50% to 1,200 new cases and then remains at around this level.

Figure 3: Age distribution of the incidence of malignant neoplasms of the rectum (ICD 10: C20) – age-specific case numbers and rates [3]



As mentioned above, the prognosis of colorectal cancer is in the middle range of all malignancies. It is 54% of men and 59% of women who are still alive five years after diagnosis. Figure 4 shows the survival rates for colon (C18) **and** rectal cancer (C19, C20) combined (Figure 4). The difference between the entities is only slight. There are differences in the absolute survival rates - i.e., the percentage of patients who survive a certain time - and the relative survival rates - i.e., the ratio of absolute survival to the expected survival in the general population. Although only 40% (men) and 47% (women) are still alive 10 years after diagnosis, the relative survival rate is still 58% (men) and 62% (women), as a number of individuals in the general population have also died in these 10 years. There are only minor differences between the sexes, with slight advantages for women.

Figure 4: Absolute and relative survival rates for malignant neoplasms of the colon and rectum (ICD 10: C18-C20) [3]



	0	1	2	3	4	5	6	7	8	9	10
Relative Survival Rate Males	100	84	76	70	67	64	62	60	59	58	58
Relative Survival Rate Females	100	85	77	72	69	66	65	64	63	63	62
Absolute Surival Rate Males	100	81	71	64	58	54	51	47	45	42	40
Absolute Surival Rate Females	100	82	74	67	63	59	56	53	51	49	47

Based on the current incidence of the disease and the 14th coordinated population projection of the Federal Statistical Office (G2L2W2, moderate development), the number of cases can be expected to increase by around 22% to almost 23,000 new cases (2050) over the next 30 years, solely due to the shift in the age structure of the population.

2.3 Pathogenesis

Colorectal carcinoma is biologically heterogeneous. The "classic" pathway of the adenoma-carcinoma sequence is molecularly associated with primary mutations in the *APC* gene and chromosomal instability. Another pathogenic pathway is via so-called serrated adenomas with epigenetic promoter (CpG) methylation and high microsatellite instability, and there are also mixed forms. There is a broad biological diversity within these groups, also depending on the anatomical localization within the colon.

2.4 Risk factors

The risk of developing colorectal cancer is increased by the following factors:

- Defined genetic disease patterns (about 3% of new cases)
  - Hereditary colorectal cancer without polyposis (HNPCC, Lynch syndrome [OMIM ID # 120435] [6] with mutations in the genes:
    - *MSH2* (HNPCC1): approximately 60% of patients
    - *MLH1* (HNPCC2): approx. 30% of patients
    - *PMS1* (HNPCC3), *PMS2* (HNPCC4), *MSH6* (HNPCC5), *TGFBR2* (HNPCC6), *MLH3* (HNPCC7)
  - Familial adenomatous polyposis (FAP) with germline mutations within the *APC* gene (1%) [OMIM ID # 175100] [6]
  - Attenuated familial adenomatous polyposis (AAPC) with germline mutations in the 5' end of the APC gene and complete loss of function [OMIM ID # 175100] [6]
  - Peutz-Jeghers syndrome with germline mutations in the *STK11* gene
  - Cowden syndrome with germline mutations in *PTEN* genes

- History of familial disposition
    - Colorectal cancer in one or more first-degree relatives under 50 years of age
- Colorectal adenomas as precursors of sporadic carcinomas (adenoma-carcinoma sequence)
- Chronic inflammatory bowel disease
    - Ulcerative colitis
    - Crohn's disease
- Toxic
    - High alcohol consumption
    - Smoking
- Diet
    - Low fiber intake
    - High fat consumption
    - High proportion of red meat and processed sausage products
    - Low intake of vegetables
- Lifestyle
    - Obesity
    - Lack of physical exercise

**Due to methodological limitations (study design, different cultural and social backgrounds, self-assessment by participants, multifactorial events, etc.), the data on toxic, dietary, and lifestyle-related risk factors are not as reliable as the data on the other risk factors listed above.*

3 Prevention and early detection

3.1 Prevention

The recommendations for the prevention of colorectal cancer refer to the acquired risk factors identified to date:

- Removal of adenomas
    - Removal of adenomas is a preventive measure that involves removing the precursor stages of the cancer. This procedure is performed as part of endoscopic early detection measures.
- Lifestyle
    - Weight reduction in overweight individuals
    - Regular physical exercise
    - Avoiding excessive alcohol consumption
    - Avoiding tobacco consumption
- Diet
    - High in fiber (30 g/day)
    - Rich in folic acid, calcium, and vitamin B6
    - Increased consumption of fruits and vegetables
    - No red or processed meat every day

The most extensive data on drug prevention is available for acetylsalicylic acid (ASA). Regular consumers of ASA at a dose of ≥75 mg/day have a colorectal cancer rate that is approximately

half that of comparator groups [7]. In HNPCC gene carriers, daily intake of 300-600 mg ASA reduces the risk of colorectal cancer by 37%.

These and numerous other studies on the association between colorectal cancer and certain forms or components of the diet, micronutrients, electrolytes such as calcium or magnesium, or medications such as low-dose ASA or COX-2 inhibitors have not yet been sufficiently validated for a specific positive recommendation for prevention [8].

3.2 Early detection

3.2.1 Population (screening)

The usually long time between the appearance of polyps and their malignant transformation offers an opportunity for early detection and prevention. Testing stool for occult blood using the guaiac test (gFOBT) reduces cancer-specific mortality [8]. Immunochemical tests for occult blood (iFOBT) have a higher sensitivity. In Germany, the gFOBT has been replaced by the iFOBT since January 1, 2017. A multi-test for DNA changes and human hemoglobin leads to a further increase in sensitivity but also in the rate of false positive results.

Sigmoidoscopy with prophylactic polypectomy reduces rectal cancer-specific mortality [8]. The effect is stronger than that of testing stool for occult blood. Total colonoscopy increases the detection rate of carcinomas and precancerous changes, but has not yet been prospectively validated with mortality as the endpoint. The acceptance of endoscopy is significantly lower than that of non-invasive testing methods. Screening does not reduce overall mortality.

Risks of screening include stress and complications from endoscopy, especially during polypectomy, false-negative results of stool tests, and overdiagnosis in people with low disease risk.

Due to its high sensitivity and specificity, total colonoscopy is recommended as the standard procedure in Germany, Austria, and Switzerland. The recommendations are summarized in Table 1.

Table 1: Colorectal cancer screening

Procedure	Germany	Austria
Digital rectal examination	Annually from age 50	Annually from age 40
Test for occult blood in stool (immunochemical, iFOBT)	Every two years from age 50 as an alternative to colonoscopy	Annually from age 40
Total colonoscopy	Men and women from age 50 (repeat after 10 years if results are normal*)	From age 45, every 10 years if results are normal

Legend:
Key: ** Further individual guidelines for repeating the colonoscopy will be provided by the examiner.*

A more detailed description of the benefits and risks of early detection of colorectal cancer can be found in the knowledge database.

3.2.2 Risk groups

3.2.2.1 Relatives of patients with colorectal cancer

First-degree relatives should undergo colonoscopy at an age that is 10 years before the patient's diagnosis, but no later than age 50 [8, 9]. This recommendation also applies to first-degree relatives of patients who were diagnosed with colorectal adenomas before the age of

50. If the findings are normal, colonoscopy should be repeated in this risk group after 10 years at the latest.

3.2.2.2 Hereditary colorectal carcinomas

Diagnostics should be carried out in accordance with the guidelines for the diagnosis of genetic predisposition to cancer issued by the German Medical Association (Bundesärztekammer) in Germany, the Austrian Society for Gastroenterology and Hepatology (ÖGGH) in Austria, and the ESMO guidelines [2, 9]. The specific genetic aberration determines the risk of disease and forms the basis for the individualized early detection and prevention plan.

3.2.2.3 Ulcerative colitis

Aminosalicylate can be used for prophylaxis, but results from randomized studies with the primary endpoint of preventing colorectal cancer are not available. Recommendations for early detection depend on the extent of the colitis and the duration of the disease. Patients with pancolitis for more than 8 years or with left-sided colitis for more than 15 years should undergo a complete colonoscopy with staged biopsies annually. In patients with high-grade dysplasia, restorative proctocolectomy is an effective prophylactic measure.

3.2.2.4 Crohn's disease

No recommendations regarding prophylaxis and early detection can currently be given for these patients.

4 Clinical characteristics

4.1 Symptoms

There are no characteristic early symptoms. The symptoms can be classified as follows:

Local symptoms

- Blood in the stool
- Changes in bowel habits
- Abdominal pain, cramps
- Ileus

General symptoms

- Unintentional weight loss
- Loss of energy
- Symptoms of anemia: pallor, reduced exercise tolerance, tachycardia during light exercise
- Paraneoplastic syndromes

Further symptoms due to metastases include jaundice and liver failure in advanced liver metastases, cough and dyspnea in pulmonary and/or pleural metastases, and, less commonly, bone pain from skeletal metastases or neurological symptoms from cerebral metastases.

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis and recommended diagnostic procedures

The first step is to confirm the suspected diagnosis based on clinical and/or imaging findings, followed by staging once the diagnosis has been confirmed, see Table 2.

Table 2: Diagnostic procedures for newly emerged symptoms and for staging

Indication	Procedure	Note
New symptoms	Digital rectal examination	
	Complete colonoscopy with biopsy	Postoperatively at the latest, if not feasible preoperatively
	Rectoscopy/sigmoidoscopy with biopsy	If colonoscopy is not feasible
	Virtual colonoscopy	If colonoscopy is not feasible
Staging / treatment planning	Rigid rectoscopy	Gold standard for defining the distance of the tumor from the anus
	Quality-assured pelvic MRI	If necessary + EUS (endosonography)
	CT + EUS	If MRI is not feasible [9]
	Gynecological examination	If there is clinical or imaging suspicion of infiltration of the vagina or uterus
	Cystoscopy	If there is clinical or imaging suspicion of bladder infiltration
	Sphincter manometry	In cases of clinical suspicion of functional disorder
	Abdominal ultrasound	Recommendation S3 guideline
	CT scan of the abdomen (alternatively, MRI of the abdomen)	Additionally recommended, especially if sonography suggests liver metastases or if assessment by sonography is not optimal
	Chest X-ray in 2 planes	Recommendation S3 guideline [8]
	CT thorax	Additionally recommended
	CEA	
Tumor Biology	MSI (microsatellite instability)	Should be available when discussing treatment options in the tumor board

Quality-assured MRI examination is the diagnostic method of choice to determine the localization of the tumor (upper/middle/lower third) as well as its spread into the perirectal fat tissue and its relationship to the circumferential resection margin (CRM). It should also describe the following parameters: (i) extramural venous invasion (EMVI) as a relevant prognostic factor, (ii) lymph node involvement (criteria for lymphonodal positivity are short-axis diameter, which should be > 9 mm or, if this is not present, morphological criteria such as "round shape", irregular boundary and pathological internal reflex pattern, should be considered), (iii) relationship to adjacent organs (T4 tumor), (iv) suspected involvement of lateral lymph nodes (i.e., iliac-external and -internal lymph nodes and obturator lymph nodes, each scored as nodal-positive if short-axis diameter is > 7 mm) [52].

MRI is therefore the essential diagnostic component for staging of locally advanced rectal cancer and is crucial not only for treatment-planning but also for inclusion in clinical studies.

Positron emission tomography ± computed tomography (PET, PET/CT) and MRI of the liver are not standard in the primary diagnosis of rectal cancer.

5.3 Classification

The size of the primary tumor and the extent of metastasis are classified based on the TNM criteria. The Union Internationale Contre le Cancer (UICC) classification summarizes these criteria into stages, see Table 3.

Table 3: Classification of tumor stages (UICC) [1]

Stage	Primary tumor	Lymph node status	Distant metastases
0	Tis	N0	M0
I	T1, T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1 - 2	N1 (1-3 affected LK)	M0
	T1	N2a (4-6 affected LK)	M0
IIIB	T3 - 4	N1 (1-3 affected LK)	M0
	T2-3	N2a (4-6 affected LK)	M0
	T1-2	N2b (≥ 7 affected LK)	M0
IIIC	T4a	N2a (4-6 affected LK)	M0
	T3-T4a	N2b (≥ 7 affected LK)	M0
	T4b	N1-2	M0
IVA	Each T	Each N	M1a (distant metastases in one organ or localization without peritoneal involvement)
IVB	Each T	Each N	M1b (distant metastases in two or more organs or localizations without peritoneal involvement)
IVC	Each T	Each N	M1c (peritoneal involvement with or without distant metastases in other organs or localizations)

Rectal cancer is subdivided according to the distal end of the primary tumor relative to the anocutaneous line. The definitions of the distances between the primary tumor and the anocutaneous line are not completely identical in the various classifications; see Table 4.

Table 4: Classification of the location of rectal cancer according to the distance of the caudal end of the primary tumor to the anocutaneous line

Classification	UICC [1]	ESMO [2]
Lower third of the rectum	< 6 cm	< 5 cm
Middle third of the rectum	> 6-12 cm	> 5-10 cm
Upper third of the rectum	> 12-16 cm	> 10-15 cm

5.6 General condition and comorbidity

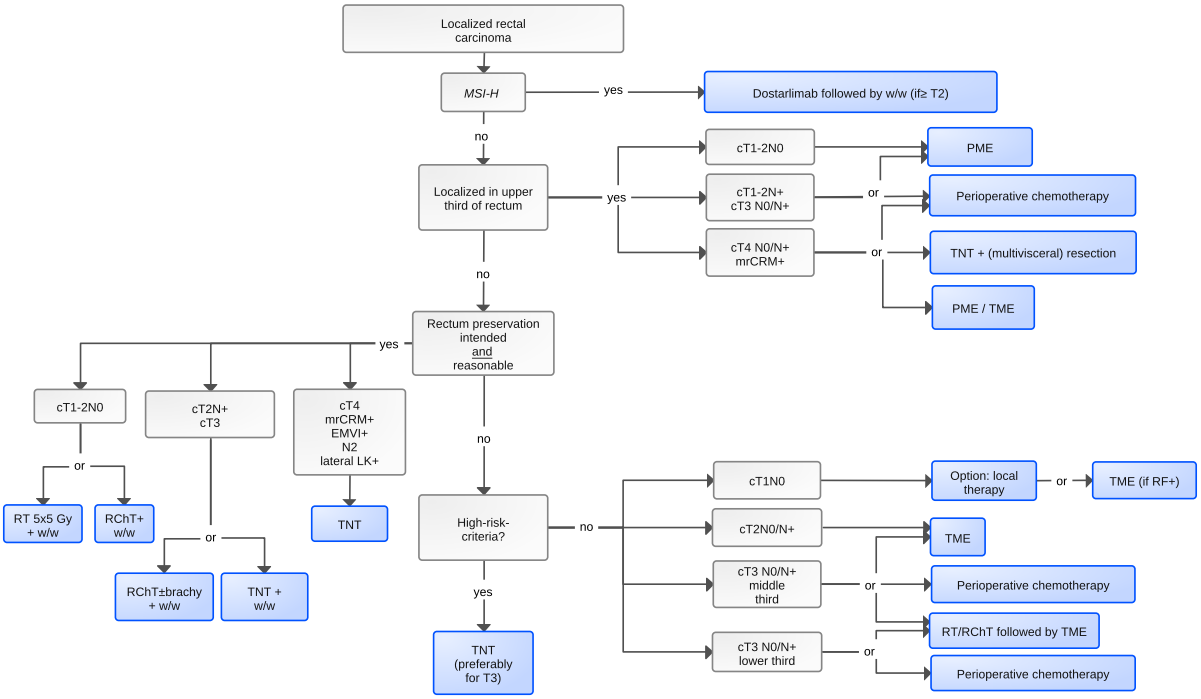
To objectively assess the general condition (performance), the use of geriatric assessment tools is recommended; see the Geriatric Assessment Knowledge Database. Tests for objectively examining mobility and comorbidity are particularly suitable. The indication for further tests is based on clinical impression and the planned treatment. Studies on the predictive value of geriatric assessment tools for specific treatment modalities are not yet available for colorectal cancer.

6 Therapy

6.1 Treatment structure

The treatment recommendation for patients is based on a quality-assured assessment of the relevant risk factors. Treatment algorithms are shown in Figures 5, 6 and 7.

Figure 5: Treatment algorithm for stage I-III rectal cancer



Legend:
curative therapy;
PME - partial mesorectal excision; TME - total mesorectal excision; w/w - watch & wait; TNT - total neoadjuvant therapy; RT - radiotherapy; RChT - radiochemotherapy; RF - risk factors; MSI-H – high microsatellite instability; EMVI+ - extramural vascular invasion; TNT – total neoadjuvant therapy; mrCRM+ - positive preoperative circumferential resection margin on MRI; LK+ - affected lymph nodes; Brachy – brachytherapy

Table 5: Treatment corridors for localized and locally advanced rectal cancer with microsatellite stability (MSS)/proficient MMR according to location, risk constellation, and treatment intention

Upper third of the rectum (12–16 cm from the anus)			
	cT1-2 N0	cT3 N0/+ cT1-2 N1-2	cT4; mrCRM+
	• PME/TME • Endoscopic resection (in low-risk cases)	• PME/TME • Neoadjuvant FOLFOX/ CapOx → PME/TME	• PME/TME • Neoadjuvant FOLFOX/ CapOx → PME/TME • TNT → PME/TME
Middle third of the rectum (6–12 cm from the anus)			
	cT1 N0	cT2 N0/1 cT3 N0/1	cT4, cN2, mrCRM+; EMVI+; lateral LK+
Planned surgery	• TME • Endoscopic resection (in low-risk cases)	• TME • Neoadj. FOLFOX/CapOx → TME • RChT / 5 x 5 Gy → TME	• TNT → TME
Intended organ preservation	• RChT / 5x5 Gy → WW/LE	• RChT (+/- brachytherapy) → WW/LE • TNT → WW/LE (for T3)	• TNT → WW/LE
Lower third of the rectum (0–6 cm from the anus)			
	cT1 N0	cT2 N0/1 cT3 N0/1	cT4, cN2, mrCRM+; EMVI+; lateral LK+
Planned surgery	• TME • Endoscopic resection (in low-risk cases)	• Neoadj. FOLFOX/CapOx → TME • RChT / 5x 5 Gy → TME	• TNT → TME
Intended organ preservation	• RChT / 5x5 Gy → WW/LE	• RChT (+/- brachytherapy) → WW/LE • TNT → WW/LE (T3)	• TNT → WW/LE

Legend:
5 x 5 Gy - Short-term radiotherapy with 5x5 Gy; LE - Local excision; mrCRM+ - Affected circumferential resection margin on MRI; PME - Partial mesorectal excision; RChT - Radiochemotherapy; TME - Total mesorectal excision; TNT - Total neoadjuvant therapy; WW - Watch and wait
Note (i): The order in which the options are listed does not imply any preference
Note (ii): The treatment recommendations in columns 2 and 3 are subject to negative mrCRM results and the exclusion of positive lateral lymph nodes and an N2 situation
Note (iii): Neoadjuvant FOLFOX/CapOx only if CRM > 3 mm, sphincter preservation possible in T2N1 and T3 N0/1.

6.1.1 Stage I

Stage I comprises T stages T1 and T2. A special form is stage T1 with a low risk of recurrence.

6.1.1.1 T1 (low risk of recurrence)

For carcinomas in stage pT1, local surgical tumor excision (full-wall excision) is sufficient as the sole therapeutic measure if the following conditions for classification as a low-risk situation are met:

- Diameter < 3 cm
- G1 / 2: good or moderate histological differentiation
- L0: no infiltration of lymph vessels
- V0: no infiltration of blood vessels

- R0: complete resection

Excision can be performed transanally as a microsurgical total wall excision or as a direct tumor excision.

At this stage, neither preoperative nor postoperative radiation therapy or systemic tumor therapy leads to a further reduction in the recurrence rate.

6.1.1.2 T1 (higher risk of recurrence)

cT1 carcinomas with grade G3-4 have a higher risk of recurrence. In this group and in all other T stages, mesorectal excision with removal of the regional lymphatic drainage area is considered standard, depending on the location of the carcinoma:

- Lower third of the rectum: total mesorectal excision (TME) with a minimum distal margin of ≥ 2 cm, measured from the macroscopic tumor margin
- Middle third of the rectum: total mesorectal excision (TME) with a minimum distal margin of ≥ 5 cm, measured from the macroscopic tumor margin
- Upper third of the rectum: partial mesorectal excision with a minimum distal margin of ≥ 5 cm, measured from the macroscopic tumor margin or TME.

In stage I, neither preoperative nor postoperative radiation therapy or systemic tumor therapy leads to a further reduction in the recurrence rate.

6.1.2 Stages II and III

6.1.2.1 Preliminary remarks

The aim of treatment in stages II and III is curative. Relapses may occur locally, but predominantly in the liver and/or lungs. The local relapse rate is 5-12% after TME, the systemic relapse rate is 35-45%, depending on the tumor stage at initial diagnosis and other biological and individual risk factors. Due to the anatomical conditions in the true pelvis, local recurrences of carcinomas in the lower and middle third of the rectum are particularly complicated. This justifies their prevention as a separate, important therapeutic goal. Preoperative radiochemotherapy (RChT) or radiotherapy (RT) and quality-assured surgery can reduce the local recurrence rate to around 5-6% when considering all patients in stages II and III [10]. Perioperative systemic therapy also contributes to reducing the local recurrence rate, but is primarily recommended with the aim of preventing distant metastases [11].

Preoperative RT or RChT has traditionally been recommended for carcinomas in the lower and middle third of the rectum. In carcinomas in the upper third of the rectum, the benefit of RT is very limited; in principle, an approach similar to that for colon cancer is preferred, i.e., primary resection of the tumor or neoadjuvant chemotherapy for locally advanced MSS tumors, see guideline on colon cancer.

Quality-assured imaging can identify patients with a very low risk of local recurrence, so that neoadjuvant RT, which has been uniformly recommended to date, may be omitted for these patients. The previously very conservative criteria for optional omission of radiation (T3 tumor with maximum infiltration of 5 mm into the perirectal fat without clearly affected lymph nodes) can be expanded, based on data from the OCUM and PROSPECT studies in particular [60, 61]. In the PROSPECT study, T3 tumors were included regardless of nodal involvement, provided that the distance to the circular resection margin (CRM) was at least 3 mm and continence-preserving surgery was possible [61]. In this study, neoadjuvant chemotherapy was compared with

neoadjuvant RChT. For the patient population described above, the non-inferiority of 3-month neoadjuvant FOLFOX therapy in terms of disease-free survival (DFS) was demonstrated. Local recurrence rates also did not differ between the two arms and were below 2%. In the OCUM study, a large phase II study with a prospectively defined treatment algorithm, only patients whose tumor (i) was located in the middle third of the rectum and had a critically small CRM (≤1 mm) or a T4 situation or (ii) was located in the lower third and had a T3 or T4 stage, received neoadjuvant RChT [60]. In both studies (PROSPECT and OCUM), the local recurrence rate in the defined groups was only 2-3%.

A single standard therapy in stages II and III can therefore no longer be defined. For certain subgroups (such as T3 N1 with free CRM in the middle third), several treatment options are available, so that treatment corridors are defined here (see Table 5).

Patients should be informed about these options. Figure 5 provides a treatment algorithm based on "key questions" and treatment goals, which takes into account various evidence-based treatment options depending on the tumor stage and treatment goal.

In the past, the option of organ preservation was often chosen after complete clinical remission, which was "incidentally" detected in the course of neoadjuvant RChT. In the meantime, however, it has been well demonstrated - not least by the data from the OPRA [57, 62] and OPERA studies [58] - that organ preservation after RChT can also be a *primary* treatment goal. This fact is also taken into account in the treatment algorithm; different and more or less intensive RChT regimens have been investigated for different tumor stages.

For the approximately 2-3% of patients with locally advanced, MSI-H / dMMR (highly microsatellite instable / mismatch-repair deficient) rectal cancer, the option of primary immune checkpoint inhibitor treatment without RT and / or surgery should be discussed. In an ongoing phase II study, complete clinical remissions were detectable after six months of primary dostarlimab therapy in all patients who were evaluable to date. After a short median follow-up, no case of "local regrowth", i.e., renewed growth of the primary tumor after an initial clinical complete remission (cCR), has occurred [13]. Immunotherapy for MSI-H/dMMR rectal cancer has not yet been approved. A handout from the German DGHO may be helpful when applying for this therapy as an off-label indication (https://www.dgho.de/publikationen/stellungnahmen/gute-aerztliche-praxis/immuncheckpoint-inhibitoren/immuncheckpointinhibitor-20230508).

In the following chapters (6.1.2.2. to 6.1.2.7), the individual treatment modalities and their possible indications are described in more detail in the context of the treatment corridor. Table 5 also provides a further overview of the treatment options according to localization and stage of the primary tumor.

6.1.2.2 Surgery - Stages II and III

Resection of the primary tumor is essential for curative therapy. The quality of the surgical procedure has a significant impact on prognosis. Oncological principles for surgery are

- Resection of the regional draining lymph node area with sampling and histological work-up of ≥ 12 lymph nodes
- Adequate safety distance to healthy tissue
- Respecting the integrity of the mesorectal fascia avoiding injuries during surgery
- En-bloc resection of tumor-adherent organs
- Protection of the autonomic pelvic nerves.

Standard for the middle and lower thirds of the rectum is TME. In the upper third of the rectum, PME is recommended; results of studies on TME for carcinomas in the upper third of the rectum are pending.

TME is the standard for the middle and lower third of the rectum. PME is recommended for the upper third of the rectum; results from studies on TME for carcinomas in the upper third of the rectum are pending.

Primary quality-assured surgery for rectal cancer in the middle third can also be performed without neoadjuvant RT/RChT if all criteria for a low risk of local recurrence are met on MRI scans. This applies in particular to tumors that have a reliably free CRM, no detectable EMVI and a tumor that is safely resectable with continence preservation [60]. Furthermore, an N2 situation and lateral lymph node metastases should be excluded. In the ongoing ACO/ARO/AIO 18.2 trial, primary surgery for tumors with a low risk of local recurrence (i.e., tumors in the upper third and tumors in the middle third with free CRM [> 2 mm] and an invasion into the perirectal fat limited to 10 mm, regardless of lymph node status) is compared with neoadjuvant 3-month oxaliplatin-based chemotherapy.

6.1.2.3 Radio(chemo)therapy - stages II and III

RT and RChT reduce the risk of locoregional recurrence. The target volume includes the region of the primary tumor as well as the mesorectal, presacral, and internal iliac lymphatic drainage pathways.

Due to the particular problem of local relapses in rectal cancer, radiation therapy has been intensively evaluated in preoperative study designs. Alternatives include short-term radiation therapy with high single doses (5 x 5 Gy) or conventionally dosed long-term radiation with single doses of 1.8-2.0 Gy up to a total dose of 45-50.4 Gy.

Preoperative, conventionally fractionated RT can lead to significant tumor reduction, reduces the risk of local recurrence, improves disease-free survival rates, and has led to a significant increase in survival rates in some early randomized studies. With the exception of tumor shrinkage, this also applies to short-term neoadjuvant radiation therapy. In patients with large locally advanced tumors, in whom tumor shrinkage is the treatment goal, combined RChT or TNT is therefore recommended due to its greater local efficacy. In approximately 10-15% of patients, complete remission is achieved after conventional neoadjuvant long-term RChT.

Compared to preoperative conventional fractionated RT alone, combined RChT leads to higher histopathological remission rates and improved locoregional control. In the AIO/ARO/CAO-04 study, it was also superior to postoperative RChT in terms of local recurrence rate. An increase in the rate of patients with disease-free survival or overall survival has not been achieved in the studies published to date.

Fluoropyrimidines are the most effective systemic drugs in combined RChT, with a low rate of side effects. The administration of 5-fluorouracil as a continuous infusion during radiation is more effective than bolus therapy. Modulation of 5-FU metabolism by folinic acid did not improve long-term results. The perioperative administration of capecitabine is not inferior to 5-FU and led to an improvement in disease-free survival in a study. The results of randomized studies on the combination of 5-FU or capecitabine with oxaliplatin during radiation therapy can be summarized as follows according to the results of a meta-analysis: (i) significantly increased gastrointestinal toxicity, comparable hematotoxicity; (ii) Disease-free survival (DFS) slightly but significantly improved (HR 0.90, 95% CI 0.81–0.99); (iii) lower rate of distant metastases. According to data from a meta-analysis, the clinically moderate benefit is particularly evident in younger patients under the age of 60. None of the studies investigating the addition of oxaliplatin to neoadjuvant RChT showed an increase in R0 resection rates or an increase in the

chance of sphincter preservation. A combination of fluoropyrimidines with oxaliplatin is therefore not recommended generally for neoadjuvant RChT, but may be considered in younger patients [10]. Details on the dosage and administration of chemotherapy are summarized in the appendix Systemic tumor therapy – protocols.

RT in the middle third can be omitted if defined criteria are met in accordance with the PROSPECT and OCUM studies. The criteria are described in chapter 6.1.2.1. Strict quality assurance of MRI imaging must be ensured if RT is not used.

Adjuvant (postoperative) rRT alone has no significant effect on disease-free survival or overall survival, but reduces local recurrence rates in patients who have not previously received RT. After incomplete anterior wall resection in stage I, RT is an experimental option in clinical trials. Data and recommendations on the procedure following successful primary RChT are summarized in chapter 6.1.2.5.

6.1.2.4 "Total neoadjuvant therapy" for high-risk tumors in stages II and III

Until recently, with regard to perioperative chemotherapy in the context of radiation therapy, a distinction was only made between the application of chemotherapy as part of RChT (primarily as a radiosensitizer) and the administration of chemotherapy as adjuvant therapy after RChT and TME surgery. As a further therapeutic principle, especially for tumors with unfavorable tumor stages and/or when organ preservation is intended, so-called "total neoadjuvant therapy" (TNT) should be considered. This refers to the extension of neoadjuvant therapy by chemotherapy, usually lasting 3 to 4.5 months. This can be administered after or before RT or RChT (as induction or consolidation chemotherapy).

In several randomized studies, "total neoadjuvant therapy" (TNT) showed a significant benefit in DFS, especially for patients whose tumors had the following "high-risk characteristics" (criteria from the RAPIDO study): (i) T4 tumors, (ii) tumors with threatened/involved mesorectal resection margins, (iii) EMVI positivity, (iv) N2 status, and (v) enlarged lateral lymph nodes [12, 53, 55].

The optimal design of TNT remains the subject of clinical studies. In particular, the question of which (radiation) regimen should be used when organ preservation is intended is currently being investigated in the ACO/ARO/AIO-18-1 study.

According to multidisciplinary recommendations from working groups of the German Cancer Society, the following principles can be applied in treatment planning [51]: (i) RT can be administered as short-term radiation (5x5 Gy) or long-term RChT. (ii) Chemotherapy should be administered over 3 to 4.5 months, with consolidation chemotherapy being preferred according to data from the CAO/ARO/AIO-12 and OPRA studies if the treatment goal is to achieve the highest possible rate of clinical complete remissions (cCR). FOLFOX or CapOx should be used for chemotherapy; the benefit of additional irinotecan (e.g., in the FOLFIRINOX regimen) has not been demonstrated.

6.1.2.5 Neoadjuvant chemotherapy

The PROSPECT study included patients with node-positive T2 and T3 adenocarcinomas of the rectum regardless of node involvement, provided that the distance to the circular resection margin (CRM) was at least 3 mm and continence-preserving surgery was possible [54]. Tumors in the middle third were predominantly included. In this study, neoadjuvant chemotherapy with three months of FOLFOX was compared with neoadjuvant RChT. In cases of inadequate response to FOLFOX (defined as tumor shrinkage <20% or < 4 FOLFOX cycles administered), additional RChT could be given. The non-inferiority of neoadjuvant chemotherapy in terms of

DFS (primary endpoint) was demonstrated: after a median follow-up of 58 months, the 5-year DFS rate was 80.8% in the FOLFOX arm and 78.6% in the RChT arm (HR 0.92; 90.2% CI 0.74-1.14; non-inferiority test: p=0.005). Overall survival also did not differ (HR 1.04; 95% CI 0.74-1.44; n.s.). Less than 2% of patients in both arms had local recurrence (HR 1.18; 95% CI 0.44-3.16; n.s.). Patient-reported outcomes (PRO) were reported separately in a detailed publication [54]. Side effects and functionality differed between the arms in terms of frequency and timing of onset: during neoadjuvant therapy, patients receiving FOLFOX experienced less diarrhea and better bowel function, whereas patients in the RCHT arm reported less anxiety, loss of appetite, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, and vomiting, as well as neuropathy. At twelve months postoperatively, however, FOLFOX patients had significantly less fatigue and neuropathy and better sexual function. At no point were there any differences between the arms in terms of bladder function and health-related quality of life.

The results of the PROSPECT study are confirmed by a second randomized study presented at the ESMO Congress in 2023, which was similarly designed and conducted in Asia. This CONVERT study compared neoadjuvant chemotherapy with RChT for patients whose tumors were stage II/III, up to 12 cm from the anus, and did not threaten the mesorectal fascia [56]. Between June 2014 and October 2020, patients were randomized to receive 4 cycles of CapOx or RChT with capecitabine (50Gy in 25 fractions). After surgery, completion with four or six cycles of CapOx was planned. The primary endpoint was locoregional recurrence-free survival. In the standard arm, a 3-year locoregional recurrence-free survival rate of 93% was assumed; the non-inferiority margin was set at an HR of <1.6. N=663 patients were included. The median age was 60 years. The patient population did not only include tumors with a low risk of local recurrence. The number of T4 tumors was 26%, tumors in the lower third accounted for 41% of patients, and EMVI was approximately 20% and lateral lymph nodes were positive in 10% of tumors. Thus, CONVERT included patients with significantly larger tumors, corresponding to a higher risk of recurrence. Although the primary endpoint was not met (3-year local recurrence rates 97.4% versus 96.3% in favor of chemotherapy; HR 1.08, 95% CI 0.46–2.54), the difference is not clinically relevant, especially as the disease-free and overall survival – albeit still preliminary – were almost identical (3-year DFS RChT 87.9% versus chemotherapy 89.2%; HR 0.88, 95% CI 0.54–1.44). Comparing long-term toxicities, 29.2% grade 2–4 toxicities were observed in the RChT arm compared with only 19% in the chemotherapy arm.

In summary, neoadjuvant chemotherapy is a proven alternative to neoadjuvant RChT in two randomized studies for patients who meet the PROSPECT inclusion criteria.

6.1.2.6 Adjuvant (postoperative) chemotherapy after conventional RChT – stages II and III

While the value of adjuvant chemotherapy in rectal cancer after rectal resection without preoperative radiation is well established (Cochrane meta-analysis), adjuvant chemotherapy after combined RChT or short-course radiation therapy and TME surgery is controversial. A meta-analysis primarily including studies with 5-FU bolus administration found no evidence of a DFS or overall survival (OS) benefit. However, this meta-analysis is methodologically problematic; at the very least, it demonstrates that bolus regimens should no longer be used. After neoadjuvant RChT, adjuvant chemotherapy with optimal fluoropyrimidine regimens can therefore be offered. Capecitabine, for example, has a good data base. The available study data do not allow definitive differential therapeutic recommendations to be made based on the degree or extent of tumor response to neoadjuvant RChT. Available study results do not justify the general use of oxaliplatin in adjuvant chemotherapy. Younger patients with an increased risk of recurrence (yp stage III) should be advised about the possibility of additional oxaliplatin therapy (as investigated, for example, in the large randomized phase II ADORE study) [10]. The total duration of perioperative chemotherapy should not exceed 6 months, e.g., 5-6 cycles of capecitabine adju-

vant or 8 cycles of FOLFOX. According to data from the SCOT study, patients who have undergone primary resection without neoadjuvant RChT can be treated adjuvantly in the same way as colon cancer (i.e., 3 or 6 months depending on the risk profile, see colon cancer).

For patients with carcinomas located in the upper third of the rectum who have not received preoperative radiation or RChT, a procedure analogous to colon cancer is recommended in stages II and III. Criteria for adjuvant chemotherapy in stages II and III are summarized in the colon cancer guideline.

A combination of proton pump inhibitors with capecitabine-containing therapy, e.g., in the CapOx or XELOX regimen, should be avoided, as several retrospective data sets suggest a possible negative effect on capecitabine efficacy [14, 15, 16].

6.1.2.7 Organ preservation, non-surgical management after complete clinical remission following RChT and immunotherapy

In case of complete clinical remission (cCR) after RChT or TNT, confirmed by quality-assured imaging procedures and experienced investigators, surgery can be avoided. The data basis for such an approach is now also good in European patients, although the observation period for the reported patients is generally still short. It is therefore still recommended that these patients be included in studies or registries in order to obtain better long-term data.

At this point in time, foregoing surgery in cases of complete clinical remission documented by experienced examiners (endoscopy, MRI, clinical digital rectal examination) is only recommended for patients who adhere well to closely scheduled follow-up examinations. A blind or staged biopsy of the rectal mucosa to document cCR is not necessary, nor is endosonography.

For patients with locally advanced MSI-H/dMMR rectal cancer, the possibility of immune checkpoint inhibitor therapy *without* RT and/or surgery should be discussed. In an ongoing phase II study, complete clinical remissions were observed in all evaluable patients after six months of primary dostarlimab therapy [13]. During the median follow-up period, which was short, no cases of local recurrence had occurred. Immune checkpoint inhibitors are not yet approved for the treatment of locally advanced MSI-H rectal cancer. If such an organ preservation concept is used, clinical checks should be performed after 3 and 6 months of therapy. The post-therapeutic watch-and-wait strategy should be carried out as described below.

The patient must be given detailed information and must be willing to undergo close follow-up for at least 5 years. The optimal design of monitoring or the "watch & wait" approach is the subject of studies; the following follow-up procedure can be recommended in accordance with an international commission of experts [17] (see also Table 8): follow-up for 5 years after documentation of cCR; CEA every 3 months for three years, then every six months; digital rectal examination, MRI, and endoscopy every 3 months for two years, then every six months; CT scan of the chest/upper abdomen at months 6, 12, 24, 36, 48, and 60 for 5 years.

6.1.3 Stage IV

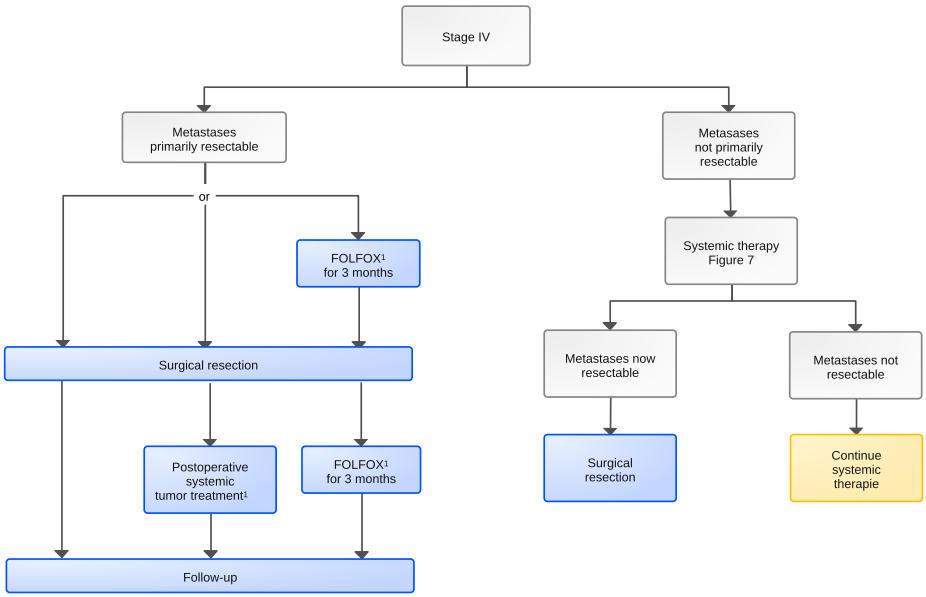
Preliminary remark:

This chapter addresses both metastatic rectal and colon cancer. The comments on right hemicolonic tumors in the text and illustrations are not relevant for rectal cancer.

The therapeutic goal for patients in stage IV used considered to be exclusively palliative. Over the last 20 years, it has become clear that up to 25% of patients with synchronous hepatic metastatic colorectal cancer have a curative potential [18, 63]. There is also curative potential

in patients with hepatic relapse or isolated pulmonary metastasis (see chapters 6.1.3.1 and 6.1.3.2), see Figures 6 and 7.

Figure 6: Treatment structure for stage IV rectal cancer



Legend:
[1] The significance of perioperative/postoperative drug therapy is not clear; ongoing studies should be supported. See also chapter 6.1.3.1.4

In previous versions of the AWMF-S3 and ESMO guidelines, a classification of stage IV patients into subgroups was proposed [2, 8], based on the primary objective of their treatment approach. Current guidelines have abandoned this classification in favor of an algorithm that takes into account patient-specific characteristics, treatment goals, and molecular factors (MSI, *RAS* and *BRAF* mutations, etc.) used as criteria for treatment selection at various hierarchical levels [19]. These strata provide pragmatic guidance, but their criteria have not been prospectively validated. In particular, the location of the primary tumor (known as "sidedness") must be taken into account as an important predictive criterion for the use of anti-EGFR antibodies [20].

6.1.3.1 Stage IV with resectable metastases

6.1.3.1.1 Surgical resectability

The disease-free survival rate of patients with resectable liver or lung metastases is up to 50% after 5 years. The criterion for the technical resectability of metastases is the documentation of an R0 situation.

In addition to the question of technical resectability of metastases, tumor biology criteria have a significant influence on the recurrence rate. Various models have been developed for calculating and prognostically evaluating risk factors in patients with liver metastases from colorectal cancer. The criteria according to Fong [21] are widely used (see Table 6). They are based on data from patients primarily treated surgically without perioperative systemic tumor therapy. The risk score supports a benefit-risk assessment. It is not a static instrument for determining contraindications. Recent retrospective analyses show that these criteria are also valid for resection after perioperative chemotherapy [22].

Table 6: Risk score [22]

• Nodal-positive cancer at first diagnosis • Disease-free interval between resection of the primary tumor and diagnosis of liver metastases < 12 months • > 1 liver metastasis in preoperative imaging • Carcinoembryonic antigen (CEA) preoperative > 200 ng/ml • Largest metastasis diameter > 5 cm in preoperative imaging
Each risk factor is assigned one point, and a score is calculated:

Number of risk factors	Risk of recurrence	5-year survival rate in % [18, 63]
0	Low	60
1-2	Intermediate	40–45
3-5	High	15–30

Decisions on the resectability of liver and lung metastases are made in multidisciplinary tumor conferences. Details on resectability and surgical techniques are provided in Chapter 6.2.1.2.

6.1.3.1.2 Resection of liver metastases

Resection of metastases is a central component of the curative concept. There are no uniform criteria for the resectability of liver metastases. The following conditions should be met:

- Exclusion of unresectable extrahepatic metastases
- > 30% functional residual liver tissue expected postoperatively
- Sufficient safety margin to critical liver vessels
- No hepatic insufficiency, no liver cirrhosis Child B or C
- ECOG Performance Score 0–2
- No severe comorbidity

Decisions on the resectability of liver metastases are made in multidisciplinary tumor conferences.

The standard local treatment for liver metastases is surgical resection with or without perioperative systemic tumor therapy. Laparoscopic resection reduces morbidity without affecting 90-day mortality. Less invasive, ablative procedures include radiofrequency ablation, laser therapy, and stereotactic radiotherapy (SBRT). Very little data on overall survival is available for these treatment modalities. There are no comparative, randomized studies on the oncological equivalence of these therapeutic approaches. They are not recommended for curative concepts outside of clinical trials.

6.1.3.1.3 Resection of lung metastases

Isolated lung metastases are less common. The criteria for the resectability of lung metastases are not clearly defined. The following conditions should be met:

- Exclusion of unresectable extrapulmonary metastases
- R0 resection possible
- Sufficient residual lung volume postoperatively

- ECOG PS 0–2
- No severe comorbidity

Decisions on the resectability of lung metastases are made in multidisciplinary tumor conferences.

Open surgical resection was the standard local treatment for lung metastases. Alternatives include minimally invasive resection using video-assisted thoracoscopy (where intraoperative exclusion of occult lung metastases must be critically evaluated) or RT (such as SBRT).

6.1.3.1.4 Perioperative systemic tumor therapy for primarily resectable metastases

The indication and optimal treatment regimens for perioperative systemic tumor therapy remain the subject of controversial discussions and study results and must be discussed on a case-by-case basis, taking into account the tumor biology in the tumor board. The possibility of treatment within the framework of a study should be evaluated.

Based on data from the phase III EORTC 40983 Intergroup study [63], perioperative therapy with FOLFOX, administered 3 months preoperatively and 3 months postoperatively, can be used as systemic tumor therapy for resectable liver metastases. However, there are no data to justify the use of molecularly targeted therapy in the setting of resectable metastases. The use of cetuximab in this treatment setting has even worsened the treatment outcomes. Perioperative FOLFOX may be offered to patients with a higher risk or to patients for whom, after multidisciplinary consultation, a "biological window" for observing tumor biology appears appropriate.

If perioperative chemotherapy has not been administered, postoperative chemotherapy, also preferably with a fluoropyrimidine and oxaliplatin, may be administered. Particularly in settings where a low risk of recurrence is expected after metastasis resection, additive or "secondary adjuvant" chemotherapy appears unnecessary due to its overall minimal effect on survival parameters. Although recent data from a randomized Japanese study showed an improvement in progression-free survival with 6 months of chemotherapy with FOLFOX, there was no advantage in terms of overall survival [23]. Ongoing studies should therefore be supported.

6.1.3.2 Conversion therapy for potentially resectable metastases

Conversion therapy can increase the group of patients with potentially resectable metastases. The aim of this therapy is to achieve technical resectability by downsizing the metastases. Accordingly, treatment protocols with high response rates and the chance of greater volumetric shrinkage of metastases are recommended. In randomized and non-randomized phase II studies, dual combinations plus monoclonal antibodies (mAb) or triple combinations ± mAb were used in palliative settings, see chapters 6.2.3 and 6.1.3.3. The PRODIGE-14 study, which randomly tested doublet versus triplet therapy, each + mAb (depending on *R*AS status), as conversion therapy, found no statistically significant improvement in R0/R1 resection rates; disease-free and overall survival were also not significantly different [52]. However, in the smaller OLIVIA study (80 patients) [24] with clearly defined and stricter inclusion criteria regarding non-resectability, a benefit was found for triple therapy + bevacizumab versus FOLFOX + bevacizumab. In the randomized CAIRO5 study, patients with tumors that were not sensitive to EGFR-directed therapy (i.e., right hemicolonic primary, *BRAF* V600E MUT or *RAS* MUT), significantly more R0/R1 resections were achieved with FOLFOXIRI + bevacizumab compared with FOLFOX + bevacizumab (51 versus 37%) [26, 69]. In this respect, a triplet with bevacizumab should be preferred in this patient group.

For EGFR-sensitive tumors, the VOLFI study, a randomized phase II study in younger patients, showed that the addition of panitumumab to a dose-reduced chemotherapy triplet led to high remission rates and consecutively improved resection rates. No improvement in overall survival was demonstrated [27]. However, the phase III TRIPLETE study [28] showed no benefit of triple therapy over doublet therapy (each in combination with panitumumab) in terms of response and resection rates and PFS, so that a chemotherapy doublet should be chosen for patients who are to receive conversion therapy with EGFR-mAb.

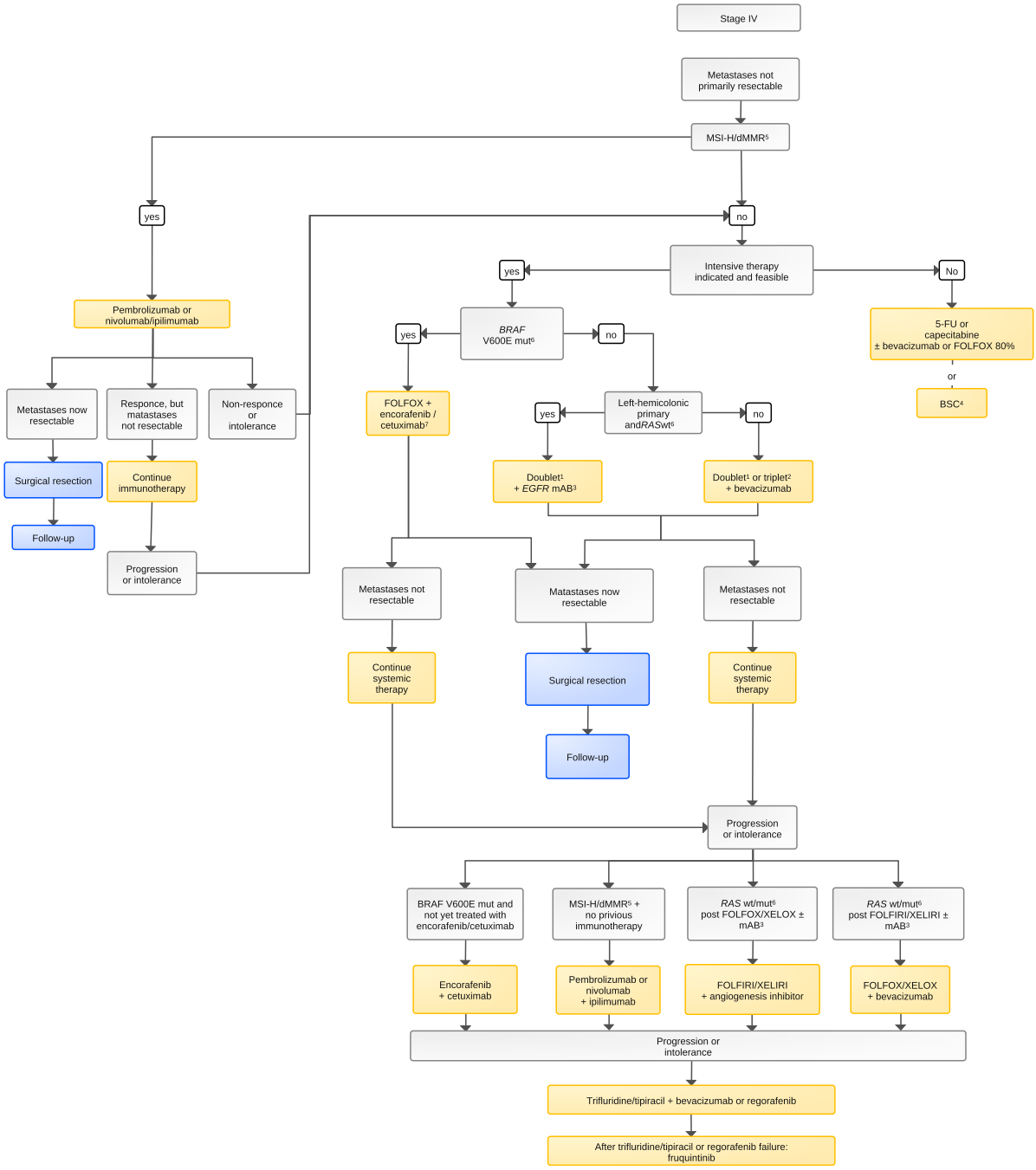
In studies with unselected patients, between 5 and 25% of initially unresectable patients were subsequently resectable, with up to 40% in cases of liver metastasis alone. A treatment duration of 2 to 4 months, or up to 6 months if necessary, is recommended depending on the response. Once technical operability has been achieved, surgery should be performed as soon as possible, not postponed after maximum remission has been achieved. This avoids an increase in liver toxicity with a consequent increase in surgical morbidity. In conversion therapy, restaging should be performed every 8–10 weeks with discussion of the CT or MRI images in a multidisciplinary tumor conference. Hepatic surgical expertise should be available in the tumor board or consulted during a referral to a center for hepatic surgery. Surgery should be performed 4 weeks after the end of systemic tumor therapy, or after (4-)6 weeks in the case of bevacizumab-containing therapy. The value of continuing chemotherapy after R0 or R1 resection, in terms of completing chemotherapy over a total treatment period of 6 months, is not established and is the subject of studies. Important factors also include the toxicity of previous therapy and comorbidity, as well as the histopathological response. The additional value of locally effective therapeutic procedures in R1 resection is the subject of clinical studies.

Repeated liver metastasis resections should always be considered if technically (R0 resection) and clinically possible and reasonable.

6.1.3.3 Treatment of primarily unresectable metastases

Despite effective primary therapy and advances in adjuvant treatment, distant metastases occur in approximately 35-45% of patients. The recurrence rate is highest in the first two years after initial diagnosis; after more than 5 years, recurrences are rare. In a subgroup of patients, a cure is possible even in this setting; see chapters 6.1.3.1 and 6.1.3.2. For the treatment algorithm, see Figure 7.

Figure 7: Treatment structure for stage IV rectal cancer with primarily unresectable metastases



Legend:
[1] Doublet – combination of fluoropyrimidine plus either oxaliplatin or irinotecan
[2] Triplet – combination of fluoropyrimidine plus oxaliplatin and irinotecan
[3] mAB – monoclonal antibody
[4] BSC – best supportive care
[5] MSI-H/dMMR – microsatellite instability-high/deficient DNA mismatch repair
[6] mut – mutated; wt – wild type (unmutated)
[7] Not yet approved in the EU (as of July 23, 2025)

For the majority of patients in stage IV, the therapeutic goal is palliative and includes the treatment of physical and psychological symptoms. Multidisciplinary cooperation is required. The necessity and the possibilities of supportive measures should be discussed early and comprehensively with all affected persons.

The choice of treatment strategy and the most suitable combination of systemic drugs is determined by numerous factors. The following are essential:

- Treatment goals agreed with the patient

- Previous course of the disease
- The biology of the disease, e.g., *RAS* and *BRAF* mutation status (in tumor tissue and, if available, in serum) and the location of the primary tumor
- Previous therapy, e.g., preoperative or adjuvant chemotherapy
- Therapy-related factors, i.e., toxicity, quality of life
- Disease-independent factors, such as biological age and comorbidity

Biological testing methods for selecting the optimal therapy, e.g., gene signatures or in vitro sensitivity, have not yet been sufficiently validated prospectively. Monitoring by determining circulating tumor cells or circulating DNA is also not a standard procedure.

6.1.3.3.1 Induction therapy

The goals of induction therapy depend on disease status (see chapter 6.1.3) and comorbidity. The treatment algorithm is shown in Figure 7.

For patients without severe comorbidities, who are expected to tolerate intensive chemotherapy, it can be administered as:

- Doublet (two-drug combination): fluoropyrimidine (5-FU with folinic acid or capecitabine) plus another cytostatic drug (irinotecan or oxaliplatin) or
- Triplet (triple-drug combination): fluoropyrimidine (5-FU with folinic acid or capecitabine) plus irinotecan and oxaliplatin.
- The addition of a monoclonal antibody to combination chemotherapy has been shown in many studies to increase remission rates, progression-free survival, and in some cases overall survival. The combination of chemotherapy and antibodies can achieve a median progression-free survival (PFS) of approximately 10 months and a median overall survival (OS) of approximately 30 months [20]. Due to the mechanism of action of anti-EGFR antibodies, the choice of drugs is based on the *RAS* and *BRAF* mutation status and the location of the primary tumor.
- In patients whose tumors had a *BRAF* V600E mutation, the BREAKWATER study [70, 71] showed that a combination of FOLFOX, encorafenib, and cetuximab significantly improved both the response rate and PFS (primary endpoints) as well as OS compared with the previous standard of care (see below).

Anti-EGFR antibodies have been tested in combination with doublet chemotherapy, see chapter 6.1.3.3.1.1. Triplet chemotherapy in combination with anti-EGFR antibodies did not show any advantage in terms of response and resection rates or PFS in the TRIPLETE study [28], while long-term survival was better in the triplet arm [27]. The value of triple therapy in combination with anti-EGFR antibodies cannot therefore be conclusively assessed. In combination with bevacizumab, triple chemotherapy leads to longer PFS than a doublet + bevacizumab [30]. Prolonging the time to progression, and thus to symptoms and renewed intensive therapy, is also a clinically relevant treatment goal for patients with a clearly palliative indication.

A meta-analysis did not confirm the superior efficacy of triple chemotherapy compared to double therapy in patients with *BRAF* V600E-mutated tumors [31]. In the FIRE 4.5 study, the addition of cetuximab to a triple chemotherapy regimen also showed no benefit compared to a triple regimen plus bevacizumab in patients whose tumors showed a *BRAF* mutation [32]. Until the publication of the BREAKWATER study, doublet chemotherapy with an angiogenesis inhibitor was therefore considered a reasonable primary therapy for these patients (e.g., FOLFOX/CAPOX + bevacizumab). In BREAKWATER, both the response rates (65.7% versus 37.4%),

PFS (12.8 vs. 7.1 months; HR 0.53; 95% CI 0.407-0.677; p<0.0001) and OS (30.3 vs. 15.1 months; HR 0.49; 95% CI 0.375–0.632; p<0.0001) were significantly and clinically highly relevant improved in the experimental arm. Therefore, patients with a *BRAF* V600E-mutated tumor should primarily be offered a therapy consisting of FOLFOX, encorafenib, and cetuximab. Approval has not yet been granted in the EMA area.

Withholding or "reserving" drugs for possible second-line sequence or escalation therapy is not recommended due to the loss of 25-30% of patients per line of therapy.

6.1.3.3.1.1 RAS wild type (RASwt)

Intact signal transmission via the *RAS* molecules is a prerequisite for the efficacy of the anti-EGFR antibodies cetuximab and panitumumab. Patients with tumors in which a mutation in one of the *RAS* genes has been detected (i.e., *KRAS* exon 2-4 and *NRAS* exon 2-4) should not be treated with any of the anti-EGFR antibodies.

The question of whether an anti-EGFR antibody should be used primarily in patients with *RAS* wild type has been investigated in randomized studies. The sequence of primary doublet + cetuximab versus doublet + bevacizumab was used first-line, including a protocol-specified crossover to the other antibody in case of relapse/refractoriness. In the first study [29], significantly longer survival was found for the sequence cetuximab in the first line, followed by bevacizumab in the second line, with a hazard ratio of 0.7. In a second study [30], this difference could not be reproduced; see also the statement by the AIO [31]. These data are now less relevant in light of the "sidedness" debate. A pooled analysis of six prospective studies investigated the influence of the right-sided location of the primary tumor, i.e., proximal/oral to the Flexura coli sinistra, versus the left-sided location, i.e., distal/aboral, on treatment outcomes in patients with a *RAS*wt tumor [20]. On the one hand, this showed a significantly poorer prognosis for patients with a right hemicolonic primary tumor in terms of OS. On the other hand, patients with a left hemicolonic primary tumor showed a clear benefit from therapy with anti-EGFR antibodies compared to the control arm with chemotherapy +/- bevacizumab (hazard ratio 0.75 for OS; 0.78 for PFS). Patients with tumors located in the right hemicolon did not benefit from the administration of anti-EGFR antibodies in terms of progression-free and overall survival despite *RAS*wt. For first-line therapy of patients with a *RAS*wt tumor and a primary tumor in the left colon, the combination of anti-EGFR antibodies and combination chemotherapy is currently recommended. In patients with *RAS*wt and a right-sided primary tumor, there is no benefit of anti-EGFR antibodies over chemotherapy or a bevacizumab combination in first-line therapy [31].

Data from the FIRE-4 and PARADIGM studies show that *RAS* mutations are detectable in the blood of approximately 10% of patients with *RAS*wt status in tumor tissue. Compared to patients without *RAS* mutations in tissue and blood, these patients show significantly poorer survival with a chemotherapy doublet with anti-EGFR antibodies. They should therefore not be treated with anti-EGFR antibodies [72]. This approach requires the use of certified and quality-assured liquid biopsy-based circulating tumor DNA (ctDNA) analysis.

6.1.3.3.1.2 RAS mutations

In patients with defined *RAS* mutations (in tissue and/or blood), bevacizumab should be used as a monoclonal antibody in first-line therapy. A combination of chemotherapy with bevacizumab leads to significant improvements in remission rates and PFS compared to chemotherapy alone, and in some studies also in OS. Combination with a triplet (5-FU, folinic acid, irinotecan, oxaliplatin) results in slightly higher remission rates and a significant prolongation of PFS compared to a doublet (5-FU, folinic acid, irinotecan) [30].

6.1.3.3.1.3 MSI-high/dMMR

For patients with high microsatellite instability in their tumor tissue, the monoclonal PD1-directed immune checkpoint inhibitor pembrolizumab was compared with various standard of care regimens (chemotherapy +/- EGFR/VEGF antibodies) in the KEYNOTE-177 study. This showed a clinically meaningful and significant prolongation of PFS (hazard ratio 0.6 (0.45–0.80)) with significantly reduced toxicity (22% instead of 6% grade 3/4 side effects). OS (as a secondary endpoint) was clinically meaningfully, but not statistically significantly prolonged (with a high crossover rate within and outside the study) [73].

The combination of the immune checkpoint inhibitors nivolumab (anti-PD1) and ipilimumab (anti-CTLA4) was compared with nivolumab monotherapy and standard-of-care chemotherapy in the 3-arm CheckMate 8HW study [74]. Survival data are still pending. PFS was significantly and clinically meaningfully better with ipilimumab/nivolumab than with both chemotherapy and nivolumab monotherapy (HR versus nivolumab: 0.62, 95% CI 0.48-0.81; p=0.0003). In this respect, dual checkpoint inhibition with nivolumab/ipilimumab is preferable to monotherapy with PD1/PD-L1 inhibitors. Ipilimumab/nivolumab and pembrolizumab are approved for the treatment of metastatic colorectal tumors that are MSI-H. MSI can be assessed by immunohistochemistry.

6.1.3.3.2 Maintenance therapy

When deciding on maintenance therapy, the possible prolongation of PFS and OS, accepting side effects, is weighed against a therapy-free period under close observation and second-line therapy in the event of disease progression.

In randomized studies following doublet induction with fluoropyrimidine/oxaliplatin plus bevacizumab, maintenance therapy with a fluoropyrimidine + bevacizumab resulted in a statistically significant prolongation of time to tumor progression compared with a watch-and-wait strategy. Monotherapy with bevacizumab is not recommended. Patients who wish to interrupt therapy or for whom this appears appropriate can therefore be advised to take a break after 6 months of therapy without a significant deterioration of OS. The significantly shorter PFS time should be pointed out. Close follow-up is recommended in this setting. Immediate re-induction after progression under maintenance therapy is only feasible in a minority of patients. Nevertheless, re-induction therapy should definitely be considered in the further treatment course, see chapter 6.1.3.3.3.

A detailed description of the three large randomized studies on maintenance therapy with bevacizumab can be found in the AIO statement [36]. Since all studies investigated induction therapies containing oxaliplatin, it is unclear whether the results described would be transferable to induction therapy containing irinotecan.

With regard to maintenance therapy with EGFR inhibitors, the PANAMA study recommends continuing 5-FU and the anti-EGFR antibody after 3 months of induction chemotherapy [37]. The non-inferiority of maintenance with panitumumab monotherapy versus panitumumab + 5-FU was not demonstrated in an Italian randomized study, so that monotherapy with anti-EGFR antibodies alone is not recommended as maintenance therapy [38]. However, based on the studies published to date, no statement can be made as to when and to what extent treatment breaks can be taken in patients receiving anti-EGFR antibody therapy, so that decisions must be made on a case-by-case basis.

6.1.3.3.3 Second-, third- and fourth-line therapy

For patients whose tumor disease progresses after first-line therapy, further treatment is determined by the previous therapy, the treatment goal, the *BRAF* and *RAS* status, and the MSI status. Second-, third-, and fourth-line therapy is individualized. The following principles should be observed:

- After first-line therapy with irinotecan, oxaliplatin should be used in combination with a fluoropyrimidine.
- After prior therapy with oxaliplatin, irinotecan should be combined with a fluoropyrimidine.
- If a bevacizumab-free irinotecan-based therapy was chosen as first-line therapy, FOLFOX + bevacizumab should be used as second-line therapy.
- Continuing bevacizumab beyond the progress in first-line therapy leads to a significant prolongation of overall survival.
- For patients who have previously been treated with oxaliplatin-based therapy, FOLFIRI chemotherapy can be combined with the antiangiogenic agent aflibercept. This results in a statistically significant prolongation of survival.
- In second-line therapy, the combination of the antiangiogenic antibody ramucirumab with FOLFIRI in patients who have been treated with oxaliplatin- and bevacizumab-based first-line therapy leads to a prolongation of survival.
- Ramucirumab or aflibercept should be preferred in patients with a short PFS under first-line bevacizumab-containing therapy.
- Patients with *RAS* wild type who have not received anti-EGFR antibodies in first-line therapy and who show remission pressure for second-line therapy should be treated with a combination of anti-EGFR antibodies plus chemotherapy, see Systemic tumor therapy - Protocols. This also includes a change of cytostatic drugs.
- Cetuximab and panitumumab should be used in first-line therapy. If used for the first time in chemotherapy-refractory patients, both substances are equally effective. The use of panitumumab after failure of cetuximab-based regimens is not standard therapy, and vice versa. Re-challenge with cetuximab or panitumumab should only be considered in patients in whom no *RAS* and/or *BRAF* mutations are detectable by liquid biopsy.
- In patients with *BRAF* V600E mutation who have not yet been treated with FOLFOX/encorafenib/cetuximab in first-line therapy, the combination of encorafenib and cetuximab in second- and third-line therapy leads to a prolongation of PFS and OS (see approval for colorectal cancer [49]).
- After prior treatment with chemotherapy, pembrolizumab or the combination of nivolumab and ipilimumab can be used in accordance with the approval for patients with MSI-H tumors [39].
- In cases of failure of or intolerance to established chemotherapeutic agents and monoclonal antibodies, trifluridine/tipiracil should be used in combination with bevacizumab [65].
- The oral multikinase inhibitors fruquintinib [66] and regorafenib have led to a prolongation of OSin heavily pretreated patients, when compared to placebo. Fruquintinib is approved for monotherapy after failure of all established standard therapies including trifluridine/tipiracil; regorafenib is not available on the market in Germany.
- For patients with *HER2* positivity (especially, but not exclusively, after anti-EGFR therapy and in left-sided tumors), data from various phase II studies indicate that trastuzumab/lapatinib, trastuzumab/pertuzumab, trastuzumab/tucatinib, or trastuzumab-deruxtecan

are treatment options. Most study data are available for *RAS*wt tumors. Trastuzumab deruxtecan can also be used in patients whose tumors are *RAS*mut. Patients with a *HER2* mutation showed a response with a combination of trastuzumab/tucatinib in the MOUNTAINEER study [49]. None of the drugs mentioned are approved for this treatment setting; see approval for colorectal cancer.

- Patients with *KRAS* G12C mutations showed a significant advantage in terms of response rate and PFS in the three-arm phase III CodeBreaK-300 study with the combination of sotorasib (960 mg) and panitumumab showed a significant advantage in terms of response rate and PFS compared with trifluridine/tipiracil or regorafenib therapy or a combination of lower-dose sotorasib (240 mg) and panitumumab [48]; sotorasib has not yet been approved for mCRC.
- Patients whose tumors have an *NTRK* fusion can be treated with the tyrosine kinase inhibitors larotrectinib and entrectinib in accordance with their approval.

For all phases of systemic tumor therapy, the occurrence of adverse effects should be monitored regularly, i.e., during each treatment cycle, by taking a medical history, performing clinical examinations, and conducting laboratory analyses. The response to systemic tumor therapy is monitored every 2 to 3 months by means of clinical examination and targeted imaging diagnostics.

6.1.3.3.4 Surgical resection of an asymptomatic primary tumor of the colon

In a definitely palliative setting, an asymptomatic primary tumor should not be resected. Two randomized studies showed no survival benefit from resection of an asymptomatic primary tumor of the colon. After a randomized study from Japan had already shown no survival benefit [23], the Synchronous study [75], conducted primarily in Germany, also showed that primary tumor resection did not provide a survival advantage in primarily metastatic disease (median survival without surgery 18.6 versus 16.7 months with surgery). Patients in the surgery arm received systemic palliative chemotherapy significantly less often (24% versus 6.4%). However, SAEs related to the gastrointestinal tract were slightly more common in the chemotherapy arm (10.7% versus 4.8%).

Based on this study, primary tumor resection cannot be recommended for asymptomatic primary tumors.

6.1.3.3.5 Local therapy for oligometastasis

Even in palliative settings, local therapy of metastases, especially liver metastases, may be useful. Decisions about systemic versus local measures and, if necessary, about sequence or combination therapies are the task of multidisciplinary tumor conferences.

Various procedures for the local treatment of unresectable liver metastases have been described, primarily in case series. Intra-arterial liver perfusion is the best evaluated method. Compared to intravenous therapy with 5-FU/folinic acid, it leads to higher remission rates but does not prolong survival. The effect of systemic chemotherapy is better documented [40].

Other approaches include radiofrequency ablation, laser therapy, SBRT and SIRT (selective internal radiation therapy). Randomized clinical trials comparing these methods with systemic tumor therapy are currently lacking. They should be considered as complementary measures to systemic chemotherapy on a case-by-case basis. The additional use of SIRT in combination with first-line chemotherapy showed no PFS or OS benefit in a large pooled ITT analysis and is there-

fore not recommended [41]. The indication should be discussed in a multidisciplinary tumor conference, taking into account the overall treatment concept and the potential, sometimes considerable, toxicity.

6.1.3.3.6 Peritoneal carcinomatosis

The median survival time of patients with proven peritoneal carcinomatosis is significantly shorter than that of patients with other manifestations of metastasis. Nevertheless, the PRODIGE-7 study showed a median OS of 41 months for patients with isolated peritoneal carcinomatosis who received a combination of systemic chemotherapy and cytoreductive surgery (CRS). However, in this randomized study, an additional benefit of supplementary hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin in addition to CRS could not be demonstrated [42]. At this point in time, HIPEC with oxaliplatin after CRS can therefore no longer be recommended. Cytoreductive surgery alone can be considered a basic standard treatment option at specialized centers. The prerequisits are good patient condition, localized and exclusively peritoneal metastasis (Peritoneal Carcinomatosis Index max. 15), and potential CC0 resectability („Complete Cytoreduction“). There is currently no consensus on the indication for HIPEC; it should either be performed in clinical trials or as an individual decision using mitomycin C over 60-90 minutes. The use of mitomycin C instead of oxaliplatin is particularly supported by data from the Spanish HIPECT4 study, which, however, was conducted in a different treatment setting (tumors classified as T4 preoperatively) and showed an advantage in 3-year local recurrence-free survival [68].

6.2 Treatment modalities

6.2.1 Surgery

6.2.1.1 Primary tumor

The standard treatment is mesorectal excision with removal of the regional lymphatic drainage area. The technique depends on the location of the carcinoma:

- Lower third of the rectum: total mesorectal excision (TME) with a minimum distal margin of ≥ 2 cm, measured from the macroscopic tumor margin;
- Middle third of the rectum: total mesorectal excision (TME) with a minimum distal margin of ≥ 5 cm, measured from the macroscopic tumor margin;
- Upper third of the rectum: partial mesorectal excision (PME) with a minimum distal margin of ≥ 5 cm, measured from the macroscopic tumor margin.

6.2.1.2 Surgical access

The standard technique is open surgery. Laparoscopic surgery is an alternative. The advantage of open surgery is the shorter operating time and the shorter learning curve for the surgeon. The main advantages of laparoscopic surgery are the better cosmetic result and the earlier postoperative oral nutrition. In the context of fast-track surgery, which is used for open and laparoscopic rectal surgery, the advantages of laparoscopic surgery, such as faster mobilization and shorter hospital stays, are hardly significant. Laparoscopic surgery can be performed in specialized centers, preferably under study conditions [43].

6.2.1.3 Special settings

Special local settings include ileus, tumor perforation, intestinal perforation, or tumor invasion into adjacent organs. In these patients, rectal cancer is usually locally advanced, so resection is part of a multimodal treatment plan. In patients with hereditary disease, the type of genetic predisposition, previous operations, and the overall treatment plan must be taken into account. The type and extent of resection are determined by the location, the supplying vessels, and the lymph drainage area defined by these factors. The surgical technique depends on the location of the primary tumor; see Table 4.

6.2.2 Radiotherapy

Radiotherapy (RT) leads to a significant reduction in local relapse. Options include preoperative radiation with 25 Gy over 5 days or a combination of radiation with 50.4 Gy and a fluoropyrimidine, see chapter 6.1.2.2.

In larger, randomized studies, acute side effects of short-term preoperative RT were diarrhea (20%), dermatitis (5%), cystitis (2%), and postoperative anal sphincter dysfunction [44]. Long-term side effects affected anal sphincter function with increased stool frequency (20% vs. 8%) and incontinence (50% vs. 24%) [45]. In the randomized Dutch study, the rate of secondary neoplasms after 12 years was higher than in the control group (14% vs. 9%) [46].

Side effects of combined RChT (50.4 Gy, infusional 5-FU) in CTCAE grade 3 or 4 were diarrhea (15%), dermatitis (13%), and hematotoxicity (7%).

6.2.3 Drugs for systemic tumor therapy

6.2.3.1 5-fluorouracil

5-Fluorouracil is used in almost all forms of drug therapy for patients with colorectal cancer. The best risk-benefit ratio is achieved with continuous intravenous infusion over 24–48 hours after prior administration of folinic acid. Remission rates are up to 30%. Severe side effects (grade 3 or 4) include diarrhea and stomatitis. Patients with functionally relevant polymorphisms of the 5-FU degradation genes have an increased risk of severe side effects, including neutropenia, neutropenic fever, severe ulcerative mucositis, and others. Before chemotherapy containing 5-FU, a mutation in the four most important dihydropyrimidine dehydrogenase (DPD) gene loci must be ruled out [48].

6.2.3.2 Aflibercept

Aflibercept is a recombinant fusion protein with antiangiogenic activity. In the registration study, the hazard ratio was significantly improved in patients who had previously been treated with oxaliplatin-based therapy by adding aflibercept to FOLFIRI. OS was prolonged by 1.4 months. PFS and response rate were also better in the aflibercept arm. Substance-specific side effects in CTCAE grade 3 or 4 correspond to those of antiangiogenic substances: hypertension (+17.8%), bleeding (+1.3%) (especially epistaxis), arterial (+1.3%) and venous thromboembolism (+1.6%), and proteinuria (+6.6%). Rare critical complications include arterial thromboembolic events and perforations in the gastrointestinal tract.

6.2.3.3 Bevacizumab

Bevacizumab is a monoclonal antibody with antiangiogenic activity. In combination with 5-FU/folinic acid, capecitabine, irinotecan, or oxaliplatin, remission rates of around 50% and prolonged PFS are achieved. In combination with irinotecan and 5-FU bolus protocols, an extension of OS was also achieved. Bevacizumab is effective in both first-line and second-line therapy. Continuation of bevacizumab therapy beyond progression resulted in prolonged OS in two randomized clinical trials. In the larger study, a significant improvement in the hazard ratio to 0.81 was achieved. Median OS was prolonged by 1.4 months. Severe side effects (grade 3 or 4) that occurred in more than 5% of patients in the approval studies were hypertension and proteinuria. Less common critical complications include arterial thromboembolic events and perforations in the gastrointestinal tract.

6.2.3.4 Capecitabine

The basic drug in systemic tumor therapy for patients with colorectal cancer is 5-fluorouracil. Capecitabine is an oral fluoropyrimidine that is metabolized enzymatically by the tumor to 5-FU. In comparative clinical studies, it was at least as effective as 5-FU bolus/folinic acid therapy. In monotherapy, remission rates of up to 25% are achieved, and in combination with irinotecan or oxaliplatin, up to 45% of patients. Severe side effects (grade 3 or 4) that occurred in more than 5% of patients in the approval studies were diarrhea and hand-foot syndrome. The combination of proton pump inhibitors with capecitabine-containing therapy should be avoided, as several retrospective studies have shown negative effects on the efficacy of capecitabine. Before starting chemotherapy containing 5-FU, a mutation in the four most important dihydropyrimidine dehydrogenase (DPD) gene loci must be ruled out [48].

6.2.3.5 Cetuximab

Cetuximab is a monoclonal antibody directed against the EGF receptor. The remission rate as monotherapy in second-line treatment is 8%. In first-line therapy in patients with *KRAS* wild type, remission rates of 55-65% are achieved, each in combination with 5-FU/folinic acid and irinotecan or oxaliplatin. PFS is prolonged. Data on OS are inconsistent. Patients with defined *RAS* mutations (*KRAS* gene exons 2-4, *NRAS* gene exons 2-4) do not benefit from cetuximab therapy and even show a trend toward shorter survival in some chemotherapy combinations. Since there are indications of a negative interaction with capecitabine and bolus 5-FU protocols that is not yet understood, the combination of cetuximab with oral fluoropyrimidines and bolus 5-FU protocols is not recommended. Severe side effects (grade 3 or 4) that occurred in more than 5% of patients in the approval studies were acneiform dermatitis and infusion reactions. Prophylactic therapy for acneiform dermatitis should be given with doxycycline or minocycline. Additional prophylactic local therapy with vitamin K1 cream (Reconval K1) may be considered in women. Medications for the prophylaxis of infusion reactions include corticosteroids and H1 blockers. Biweekly cetuximab administration (500 mg/m2) was equivalent to weekly administration (400/250 mg/m2) in a randomized study.

6.2.3.6 Dostarlimab

Dostarlimab is a humanized monoclonal anti-PD1 antibody (IgG4) approved as monotherapy for the treatment of adult patients with recurrent or advanced endometrial cancer with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H) that is progressive during or after prior treatment with platinum-based therapy. In the primary treatment of patients with rectal cancer and dMMR, a clinical CR rate of 100% was achieved in 12 published cases. No relapse had occurred after a follow-up period of up to 25 months [13]. In 363 patients in the

GARNET study, the most common side effects were hypothyroidism (7%), elevated liver enzymes (6%), and arthralgia (5%) [50].

6.2.3.7 Encorafenib

Encorafenib is an oral, highly selective RAF kinase inhibitor. In combination with cetuximab, it prolongs survival in patients with *BRAF* V600E-mutated CRC after first-line therapy compared to chemotherapy plus cetuximab. The most common side effects in the approval study were diarrhea, nausea, vomiting, and acneiform dermatitis, including severe (≥ grade 3) fatigue (4%), anemia (4%), and diarrhea (2%). Another typical side effect is palmar-plantar erythrodysesthesia syndrome (PPES; hand-foot syndrome) in 4% of patients (severe in <1%) [49].

6.2.3.8 Fruquintinib

Fruquintinib is an oral, selective inhibitor of VEGF receptors 1, 2, and 3. In the FRESCO-2 study [66], a significant prolongation of median survival from 4.8 to 7.4 months was achieved in 691 patients with refractory metastatic colorectal cancer, when compared to placebo. The most common side effects observed in the study were arterial hypertension (14%), weakness (8%), and hand-foot syndrome (6%). Fruquintinib is approved for use after treatment with available standard therapies, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF and anti-EGFR mAbs, and after progression or intolerance to TAS-102 or regorafenib.

6.2.3.9 Ipilimumab

Ipilimumab, an immune checkpoint inhibitor, is a monoclonal antibody directed against the inhibitory T-cell regulator CTLA-4, thereby enhancing the autologous immune response. It is approved in combination with nivolumab for patients with stage IV MSI-H/dMMR. The overall response rate (ORR) for this combination was 55% in the Checkmate-142 registration study, with survival rates of 87% and 85% after 9 and 12 months. In 32% of patients, treatment-related grade 3 or 4 toxicities occurred: increased liver enzymes AST and/or ALT (11%), increased lipase (4%), anemia (3%) and autoimmune colitis (3%).

6.2.3.10 Irinotecan

Irinotecan is a topoisomerase I inhibitor. In combination with 5-FU/folinic acid, remission rates are 40-50%. PFS and OS are significantly prolonged compared to fluoropyrimidine therapy. Severe side effects (grade 3 or 4) that occurred in more than 5% of patients in the approval studies were diarrhea, nausea/vomiting, neutropenia, and neutropenic fever. The substance can be administered weekly, biweekly, or every three weeks.

6.2.3.11 Nivolumab

Nivolumab is a monoclonal anti-PD1 antibody and belongs to the class of immune checkpoint inhibitors. It is approved in combination with ipilimumab for patients with stage IV MSI-H/dMMR, first-line or after prior treatment with fluoropyrimidines. The overall response rate (ORR) for this combination was 55% in the Checkmate-142 approval study, with survival rates after 9 and 12 months at 87% and 85%. Therapy-related grade 3 or 4 toxicities occurred in 32% of patients: increased AST and/or ALT (11%), increased lipase (4%), anemia (3%) and autoimmune colitis (3%).

6.2.3.12 Oxaliplatin

Oxaliplatin is a platinum derivative. In colorectal cancer treatment, it is highly effective in combination with fluoropyrimidines (5-FU/folinic acid, capecitabine). In first-line therapy, it increases remission rates to 40-60% and prolongs PFS compared to 5-FU/FA. Severe side effects (grade 3/4) that occurred in more than 5% of patients in the approval studies were nausea/vomiting, diarrhea, mucositis, and polyneuropathy. Intravenous administration of calcium and magnesium does not reduce the risk of polyneuropathy.

6.2.3.13 Panitumumab

Panitumumab is a monoclonal antibody directed against the EGF receptor. In patients with *KRAS*wt tumors, the remission rate in second-line therapy was 10% for monotherapy and 35% for combination with FOLFIRI after failure of oxaliplatin ± bevacizumab. The response to panitumumab depends on mutations in the *RAS* genes. In the approval study, patients with *RAS*wt showed a statistically significant longer survival time for the combination of panitumumab and chemotherapy compared to the chemotherapy alone arm. In patients who had been treated with panitumumab in the presence of a mutation in one of the *RAS* genes, PFS and OS were poorer. A severe side effect (grade 3 or 4) that occurred in more than 5% of patients in the approval studies was acneiform dermatitis. Prophylactic treatment of acneiform dermatitis should be given with doxycycline or minocycline. Additional prophylactic local treatment with vitamin K1 cream (Reconval K1) may be considered in women.

6.2.3.14 Pembrolizumab

Pembrolizumab is a monoclonal anti-PD1 antibody and belongs to the class of immune checkpoint inhibitors. In patients with dMMR/MSI-H CRC, pembrolizumab in first-line therapy led to improved survival with better tolerability compared to doublet chemotherapy with or without anti-VEGFR or -EGFR antibodies. Grade ≥ 3 toxicities occurred in 56% of patients receiving pembrolizumab and 78% in the chemotherapy group. Clinically relevant (≥ grade 3) were diarrhea (6%) and hypertension (7%), immune-mediated hepatitis (3%), colitis (3%), skin toxicity, and adrenal insufficiency (1% each).

6.2.3.15 Ramucirumab

Ramucirumab is a human IgG1 antibody that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR2). It is approved for second-line treatment in patients with adenocarcinoma of the stomach or gastroesophageal junction. In patients with metastatic colorectal cancer in relapse or refractory to therapy with a fluoropyrimidine, oxaliplatin, and bevacizumab, it was tested in combination with FOLFIRI in a phase III study. The addition of ramucirumab resulted in a statistically significant prolongation of PFS from 4.7 to 5.7 months with a hazard ratio of 0.77 and a prolongation of OS from 11.7 to 13.3 months with a hazard ratio of 0.84. CTCAE grade 3 or 4 adverse events that occurred in more than 5% of patients treated with ramucirumab in combination therapy in the registration study and more frequently than in the control group were neutropenia (28%) and hypertension (11%). Fatigue (12%) and diarrhea (10%) were not significantly more frequent than in the chemotherapy control group. Information on approval status is summarized in Colorectal Cancer Approval.

6.2.3.16 Regorafenib

Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases, including those involved in the regulation of tumor angiogenesis, oncogenesis, and the microenvironment. In patients who had failed all established chemotherapy regimens, two phase III studies showed that regorafenib monotherapy significantly improved OS compared with best supportive care in a meta-analysis with a hazard ratio of 0.76. Regorafenib causes symptomatic toxicity in many patients at the start of treatment. CTCAE grade 3 or 4 side effects that occurred in more than 5% of patients treated with regorafenib in the approval study and significantly more frequently in the treatment arm than in the placebo arm were fatigue (+6%), diarrhea (+4%), hand-foot syndrome (+17%), and hypertension (+6%). Side effects occur after a median of 14 days and therefore require close monitoring (e.g., weekly) at the start of therapy and, if necessary, a consistent dose reduction. Information on the approval status is summarized in Colorectal cancer approval.

6.2.3.17 S1 (Tegafur plus gimeracil and oteracil)

For cases of intolerance to 5-fluorouracil, the substance S1 has been approved by the EMA since 2022. This approval is based on several studies showing that S1 is not inferior to capecitabine or 5-FU in terms of efficacy and that switching from fluoropyrimidines to S1 because of cardiotoxicity or pronounced hand-foot syndrome is safe. S1 is approved as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer who cannot continue treatment with another fluoropyrimidine because of hand-foot syndrome or cardiovascular toxicity in an adjuvant or metastatic setting.

6.2.3.18 Trifluridine/Tipiracil (TAS-102)

TAS-102 is an oral cytostatic drug consisting of trifluridine, a thymidine analogue, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor. The cytotoxic component is trifluridine; tipiracil inhibits its rapid degradation. In a phase III study in patients with recurrent or refractory metastatic colorectal cancer after at least two standard chemotherapy regimens, TAS-102 resulted in a statistically significant prolongation of PFS (HR 0.48; median 0.3 months) and prolonged OS (HR 0.68, median 1.7 months). The remission rate was 1.6%. TAS-102 is taken for 5 days in two consecutive weeks, followed by a 2-week break. CTCAE grade 3 or 4 side effects that occurred in more than 5% of patients treated with TAS-102 in the approval study were neutropenia (38%), leukocytopenia (21%), anemia (18%), and thrombocytopenia (5%). Febrile neutropenia occurred in 4% of patients. These complications require close monitoring of blood counts and dose reduction if required. Information on the approval status is summarized in Colorectal Cancer Approval.

7 Rehabilitation

Surgery, radiotherapy and systemic therapy of patients with colorectal carcinoma can result in treatment-related disorders of various types and degrees of severity and thus significantly impair quality of life, independence and possibly also work and performance. Patients should therefore be informed about the possibilities of outpatient and inpatient rehabilitation measures. Planned surgical and radiotherapeutic measures should be completed before starting rehabilitation.

The rehabilitation facility should be able to continue systemic tumor therapies, including immunotherapies/monoclonal antibodies, in accordance with the instructions of the primary

tumor center during rehab in order to avoid interruptions or delays in therapy. During their stay, patients should be informed in detail about their underlying disease and all diagnostic and therapeutic options, taking into account their individual disease status.

The aims of rehabilitation also include training in stoma care or regaining continence, promoting regular physical activity, nutritional training, gaining information on non-pharmacological therapy and dealing with the fear of recurrence and other psycho-oncological impairments. An initial psychological examination is required in order to identify deficits in coping with the disease or reactive moods, and to initiate further measures.

Comprehensive training therapies are designed to help patients regain muscular strength and endurance and motivate them to remain physically active after rehabilitation. Patients of working age must be informed and supported about the possibilities of returning to work (gradual reintegration, internal redeployment, placement in a job suitable for the patient's condition, retraining). Furthermore, if necessary, support must be organized at home for activities of daily live or nursing care. The rehabilitation facility should also organize the patient’s further medical care if this has not been arranged. Patients should be informed about the possibilities of joining a patient advocate (self-help) group (e.g., https://www.ilco.de/).

In principle, the patient's right to choose should be respected when selecting a rehabilitation facility. However, particular consideration should be given to facilities that are able to provide professional care for patients with colorectal cancer, i.e., clinics with a gastroenterological or oncological focus that are regularly certified and participate in standardized quality assurance programs.

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8 Follow-up and monitoring in a watch-and-wait approach

Follow-up of patients with colorectal carcinoma is structured. The goals of follow-up are the early diagnosis of a recurrence with the aim of prolonging the survival time / increasing the chance of cure, the detection of side effects of the therapy and prevention. In patients with colorectal carcinoma, intensive, structured follow-up can lead to prolonged survival [47], see Study Results Colorectal Carcinoma.

In addition, colonoscopy is required after completion of primary therapy if it was not performed preoperatively.

Follow-up is stage- and risk-adapted, see Table 7.

Table 7: Structured follow-up for rectal cancer

Procedure	**Months** **3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**42**	**48**	**54**	**60**
Medical history, physical examination	**X** X	X **X** X	**X** X	X **X** X	**X**	X **X** X	**X**	X **X** X		**X** X		X **X** X		X **X** X		X **X** X
CEA	**X** X	X **X** X	**X** X	X **X** X	**X**	X **X** X	**X**	X **X** X		**X** X		X **X** X		X **X** X		X **X** X
Abdominal ultrasound		X		X		X		X				X		X		X
CT abdomen/thorax				**X** X				**X** X				**X** X		X		X
Colonoscopy		X		X **X** X										**X** X		X

Legend:
Key: *X Recommendations in Germany;*
X Recommendations in Austria;
X Recommendations in Switzerland

Patients who have achieved complete clinical remission after radiation/radiation chemotherapy and are undergoing a watch-and-wait approach should be monitored by experienced investigators in accordance with Table 8 (according to: [17]).

Table 8: Restaging procedures and time intervals for watch-and-wait approach (according to: [17])

Year	CEA	DRE	Endoscopy	Pelvic MRI	CT thorax and/or abdomen
1	Every 3 months	Every 3-4 months	Every 3-4 months	Every 3-4 months	Every 6-12 months
2	Every 3 months	Every 3-4 months	Every 3-4 months	Every 3-4 months	Annually
3	Every 3 months	Every 6 months	Every 6 months	Every 6 months	Annually
4	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Annually
5	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Annually

Legend:
Key: *CEA – carcinoembryonic antigen in serum; DRE – digital rectal examination; MRI – magnetic resonance imaging; CT – computed tomography*

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.