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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 in men in German-speaking countries. The average age at first diagnosis is 70-75 years, but individuals with a genetic or acquired predisposition can develop the disease at a younger age.

For early detection, non-invasive procedures for detecting occult blood in the stool triggering an endoscopic examination or the direct screening colonoscopy are used. Both procedures reduce cancer-specific mortality; in Germany, screening colonoscopy is preferentially recommended.

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

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 (inferior 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 frequent 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.

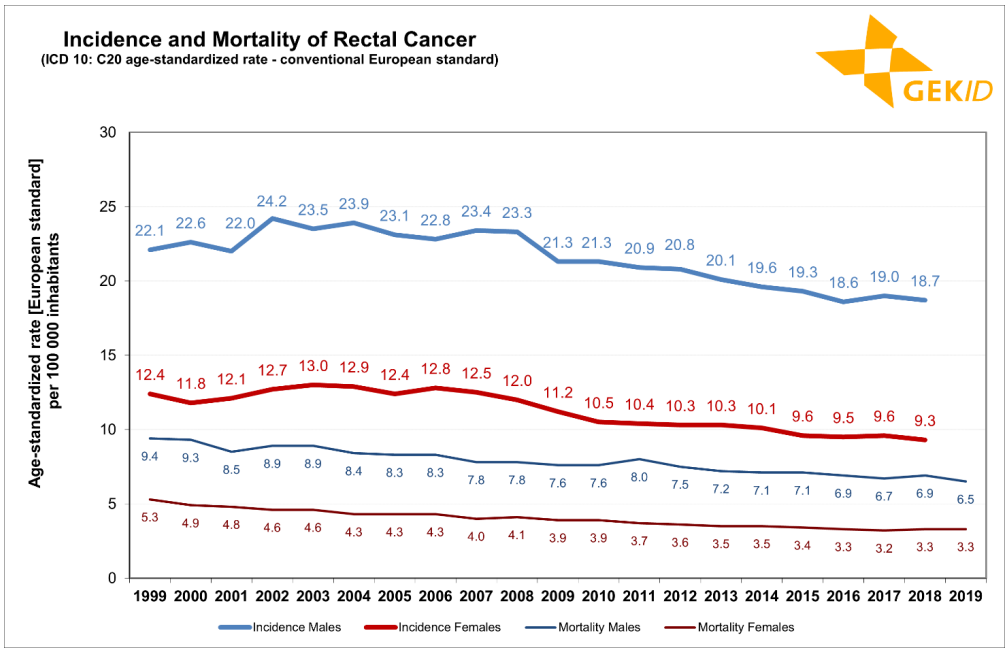
2.2 Epidemiology

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).

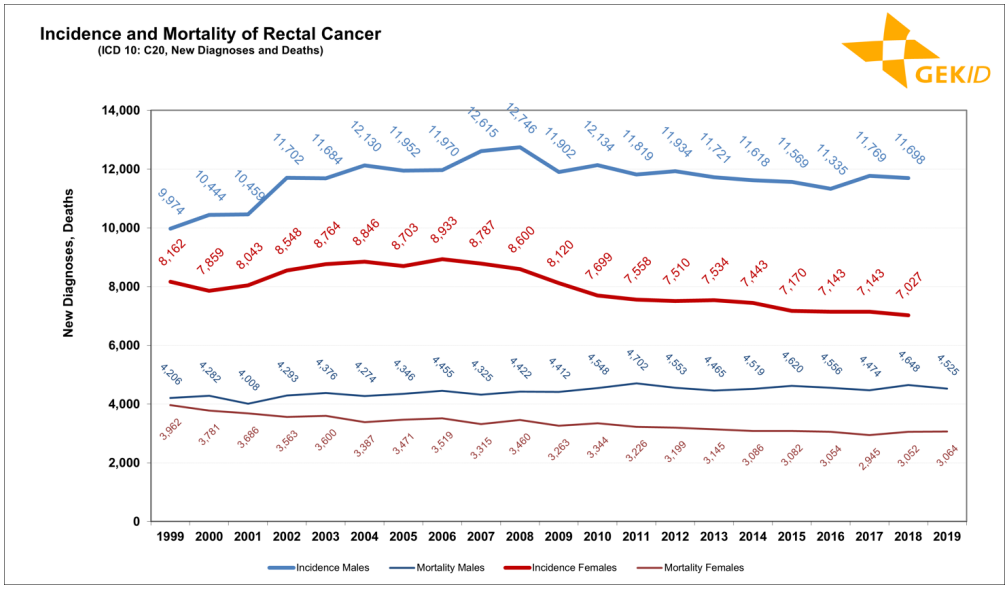
The age-standardized morbidity rates - i.e., the probabilities of developing the disease - as well as the age-standardized mortality rates - the probabilities of dying - show a decreasing trend over the past 15 years both for men and women, see Figure 1. This is also confirmed by a joinpoint analysis [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).

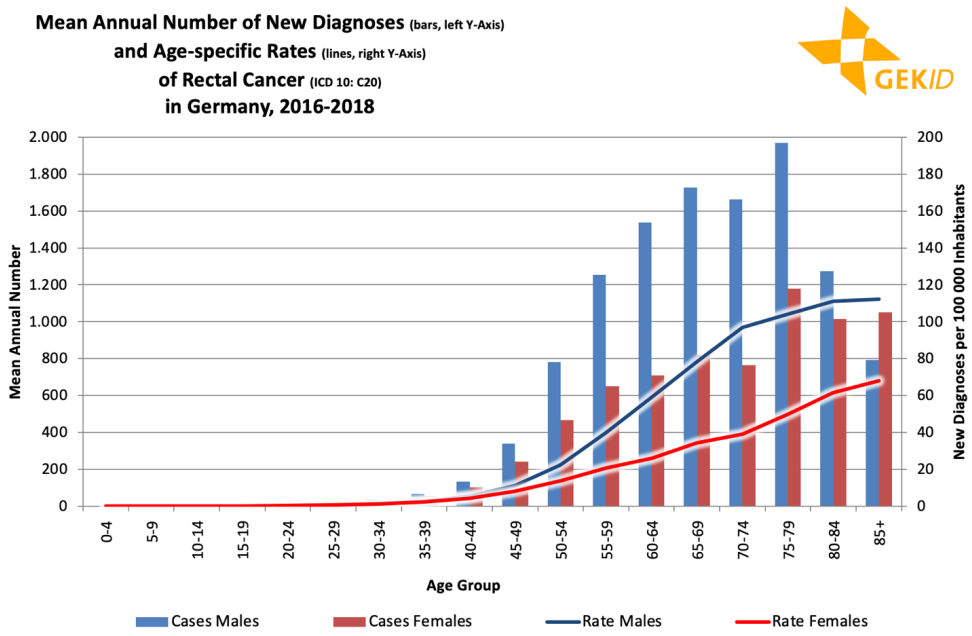
Figure 2: Estimated incidence and mortality of malignant neoplasms of the rectum (ICD 10: C20) in Germany - case numbers [3]



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

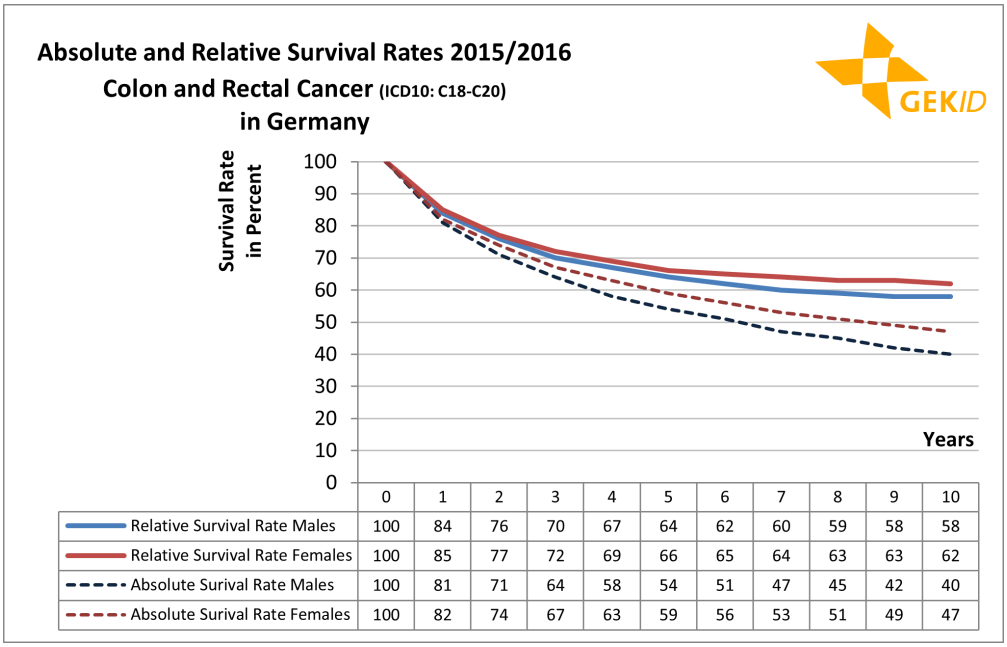
women. The number of cases is somewhat different due to the population distribution. The number of new cases increases in men up to the age group of 75-79 years (see Figure 3 [bars]). After that, the number of cases halves, which is due to the fact that the number of men declines due to their shorter 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 (around 3% of new cases)
  - Hereditary colorectal carcinoma 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
  - Rectal 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 diseases
  - Ulcerative colitis
  - Crohn's disease
- Toxic*
  - High alcohol consumption
  - Smoking
- Nutrition*
  - Low fiber intake
  - High fat consumption
  - High proportion of red meat and processed sausages
  - Low intake of vegetables
- Lifestyle*
  - Obesity
  - Lack of physical exercise

*Due to methodological limitations (study design, different cultures and lifestyles, self-assessment of participants, multifactorial events, etc.), the data on toxic, dietary and lifestyle-associated risk factors do not have the same impact as the data on the other risk factors listed above.

3 Prevention and early detection

3.1 Prevention

Recommendations for the prevention of colorectal cancer relate to the acquired risk factors identified to date:

- Ablation of adenomas
  - The ablation of adenomas is a preventive measure by removing the precursor stages of carcinoma. This procedure is carried out as part of the endoscopic screening/early detection procedures.
- Lifestyle habits
  - Weight reduction for overweight individuals
  - Regular physical exercise
  - Abstaining from excessive alcohol consumption
  - Abstaining from tobacco use
- Nutrition
  - High fiber intake (30 g/day)
  - Rich in folic acid, calcium and vitamin B6
  - Increased consumption of fruit and vegetables
  - Abstaining form daily intake of red or processed meat

The most extensive data for drug-based prevention are available for acetylsalicylic acid (ASA). Regular consumers of ASA at a dose of ≥ 75 mg/day have a colorectal cancer rate that is about half that of the comparator groups [7]. In HNPCC gene carriers, the 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 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 course between the detection of polyps and their malignant transformation offers the opportunity for early detection and prevention. Fecal 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 replaced the iFOBT in January 2017. A multi-test for DNA alterations and human hemoglobin leads to a further increase in sensitivity but also to a considerable rate of false positive results.

Sigmoidoscopy with prophylactic polypectomy reduces cancer-specific mortality [8]. The effect is stronger than the effect of fecal occult blood testing. Total colonoscopy increases the detection rate of cancer and precancerous lesions, but has not yet been prospectively validated using mortality as the primary endpoint. The acceptance of endoscopy is significantly lower than for non-invasive test procedures. Overall mortality is not reduced by screening.

Risks of screening include distress and complications caused by endoscopy, particularly when performing polypectomies, false-negative results of stool examinations and overdiagnosis in people with a low risk of colorectal cancer.

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

Table 1: Colorectal cancer screening

Investigation	Germany	Austria
Digital rectal examination	Annually from the age of 50 years	Annually from the age of 40.
Fecal occult blood test (immunochemical, iFOBT)	Annually between the ages of 50 and 54; every two years from the age of 55 as an alternative to colonoscopy	Annually from the age of 40.
Total colonoscopy	Men from the age of 50, women from the age of 55 Repeat after 10 years if findings are normal*	From the age of 45, every 10 years if the findings are normal*

Legend:
** Further individualized guidance on repeat colonoscopy may be provided by the investigator of screening.*

A more detailed discussion of the opportunities and risks of early detection of colorectal cancer can be found in the knowledge database (German language only).

3.2.2 Risk groups

3.2.2.1 Relatives of patients with colorectal cancer

First-degree relatives should be colonoscoped at an age 10 years prior to the patient's age at diagnosis, but at the latest at the age of 50 years [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 unremarkable, 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 of the German Medical Association, those of the Austrian Society for Gastroenterology & Hepatology (ÖGGH) in Austria and the ESMO guidelines [2, 9]. The specific genetic aberration determines the risk of disease and is the basis of the individualized early detection and prevention plan.

3.2.2.3 Ulcerative colitis

Aminosalicylate can be used for prophylaxis; results of randomized studies with the primary endpoint of preventing colorectal cancer are not available. Recommendations for screening/ 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 stepwise biopsies every year. In patients with high-grade dysplasia, restorative proctocolectomy is an effective prophylactic intervention.

3.2.2.4 Crohn's disease

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

4 Clinical characteristics

4.1 Symptoms

Characteristic early symptoms are absent. Possible symptoms can be depicted as follows:

Local symptoms

- Blood in the stool
- Changes in bowel habits
- Pain, cramps
- Ileus

General symptoms

- Unintended weight loss
- Loss of energy

- Symptoms from anemia: pallor, reduced exercise tolerance, tachycardia at low levels of exertion
- Paraneoplastic syndromes

Other symptoms due to metastases are jaundice and liver failure in advanced liver metastases, cough and dyspnea in pulmonary and / or pleural metastases, less commonly bone pain in skeletal metastases or neurological symptoms in case of cerebral metastases.

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis and recommended diagnostic procedures

The first step is to confirm the suspected clinical and/or imaging diagnosis, followed by staging if the diagnosis is confirmed, see Table 2.

Table 2: Diagnostic procedures for new onset of symptoms and for subsequent staging

Indication	Procedure	Note
New symptoms	Digital rectal examination	
	Complete colonoscopy with biopsies	Postoperatively at the latest, if not feasible preoperatively
	Rectoscopy / sigmoidoscopy with biopsies	If colonoscopy is not feasible
	Virtual colonoscopy	If colonoscopy is not feasible
Staging / Treatment planning	Rigid rectoscopy	Gold standard for defining the tumor distance from ano
	Quality-assured pelvic MRI	If applicable, combined with EUS (endosonography)
	CT + EUS	If MRI is not feasible [9]
	Gynecological examination	In case of clinical or imaging suspicion of infiltration of vagina or uterus
	Cystoscopy	In case of clinical or imaging suspicion of infiltration of the bladder
	Sphincter manometry	In case of clinical suspicion of dysfunction
	Abdominal ultrasound	Recommended by German S3 Guideline
	CT abdomen (alternatively MRI abdomen)	Additionally recommended, especially in case of suspected liver metastases or in case of non-optimal assessability in sonography
	Chest radiograph in 2 planes	Recommended by German S3 Guideline [8]
	CT Thorax	Additionally recommended
	Carcino-Embryonic Antigen (CEA)	
	MSI (microsatellite instability)	Should be available when discussing treatment options in the multidisciplinary 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 carcinomas 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

Definition of primary tumor size and metastasis is based on current TNM criteria. The classification of the Union Internationale Contre le Cancer (UICC) summarizes these criteria in 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
	T3a (< 1 mm)		
	T3b (1-5 mm)		
	T3c (5-15 mm)		
	T3d (> 15 mm)		
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-2	N1 (1-3 affected LN)	M0
IIIB	T3-4	N1 (1-3 affected LN)	M0
IIIC	All T	N2 (≥ 4 affected LN)	M0
IV	All T	All N	M1

Rectal carcinoma is subdivided according to the distal end of the primary tumor related to the anocutaneous line. The definitions of the distance from the primary tumor to the anocutaneous line are not completely identical in the various international classifications, see Table 4.

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

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

5.6 General condition and comorbidity

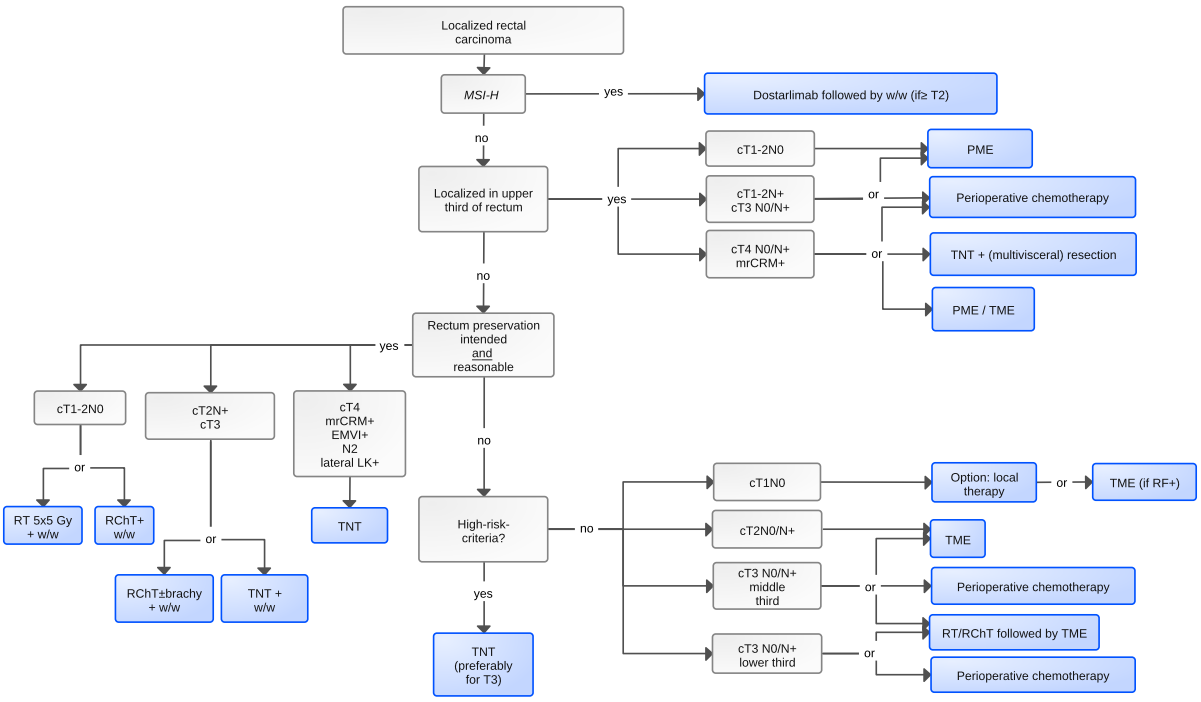
For objective assessment of the general condition, the use of geriatric assessment is recommended, see Geriatric Assessment Knowledge Base. Tests for objectifying mobility and comorbidity are particularly suitable. The indication to perform further tests is based on the clinical impression and the planned 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 basis of the treatment recommendation to the patient is the quality-assured survey of relevant risk factors. Therapeutic algorithms are depicted in Figures 4 and 5.

Figure 5: Stage-adapted therapy algorithm for stages I-III



Legend:
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; LN+ - affected lymph nodes; Brachy - brachytherapy

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

Upper third of the rectum (12 - 16 cm from ano)			
	cT1-2 N0	cT3 N0/1 cT1-2 N1-2	cT4; mrCRM+
	• PME/TME • Endoscopic resection (for low-risk)	• 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 ano)			
	cT1 N0	cT2 N0/1 cT3 N0/1	cT4, cN2, mrCRM+; EMVI+; lateral LN+
Planned operation	• TME • Endoscopic resection (for low-risk)	• TME • Neoadjuvant FOLFOX/ CapOx → TME • RChT / 5 x 5 Gy → TME	• TNT → TME
Intended organ preservation	• RChT / 5x5 Gy → w/w / LE	• RChT (+/- brachy) → w/w / LE • TNT → w/w / LE (for T3)	• TNT → w/w - /LE
Lower third of the rectum (0 - 6 cm from ano)			
	cT1 N0	cT2 N0/1 cT3 N0/1	cT4, cN2, mrCRM+; EMVI+; lateral LN+
Planned operation	• TME • Endoscopic resection (for low-risk)	• Neoadjuvant FOLFOX/ CapOx → TME • RChT / 5x 5 Gy → TME	• TNT → TME
Intended organ preservation	• RChT / 5x5 Gy → w/w / LE	• RChT (+/- brachy) → w/w / LE • TNT → w/w / LE (T3)	• TNT → w/w / LE

Legend:
5 x 5 Gy - short-term radiotherapy with 5x5 Gy; Brachy – brachytherapy; LE - local excision; mrCRM+ - affected circumferential resection margin on MRI; PME - partial mesorectal excision; RChT - radiochemotherapy; TME - Total mesorectal excision; TNT - Total neoadjuvant therapy; w/w - watch and wait
Note (i): The order in which the options are named does not imply a preference
Note (ii): The treatment recommendations in columns 2 and 3 are subject to mrCRM negativity and the exclusion of positive lateral lymph nodes and an N2 situation
Note (iii): Neoadjuvant FOLFOX/CapOx only if CRM>3mm, sphincter preservation possible in T2N1 and T3 N0/1

6.1.1 Stage I

Stage I comprises the 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 stage pT1 carcinomas, 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 lymphatic vessels

- V0: no infiltration of blood vessels
- R0: complete resection

Excision can be performed transanal as a microsurgical full-wall excision or as a direct tumor excision.

At this stage, neither preoperative nor postoperative radiotherapy or systemic tumor therapy reduce the recurrence rate.

6.1.1.2 T1 (higher risk of recurrence) to T4

cT1 carcinomas with gradings G3-4 have a higher risk of recurrence. For this group and all other T stages, the standard procedure is mesorectal excision with removal of the regional lymphatic drainage area, technically depending on the localization of the carcinoma:

- Lower third of the rectum: total mesorectal excision (TME) with a minimum distal distance of ≥ 2 cm, measured from the macroscopic tumor margin
- Middle third of the rectum: total mesorectal excision (TME) with a minimum distal distance of ≥ 5 cm, measured from the macroscopic tumor margin
- Upper third of the rectum: partial mesorectal excision with a minimum distal distance ≥ 5 cm, measured from the macroscopic tumor margin, or TME.
- In stage I, neither preoperative nor postoperative radiotherapy or systemic cancer treatment further reduces the recurrence rate.

6.1.2 Stages II and III

6.1.2.1 Preliminary remarks

Treatment in stages II and III is curative. Relapse may occur locally, but predominantly in the liver and/or lungs. The local recurrence rate is 5-12% after TME, the systemic recurrence rate is 35-45%, depending on the tumor stage at initial diagnosis and other biological and individual risk factors. Due to the anatomy of the true pelvis, local recurrences of carcinomas in the lower and middle third of the rectum are particularly prone to complications. This justifies their prevention as an important therapeutic goal in its own right. Preoperative radiochemotherapy or radiotherapy and quality-assured surgery can reduce the local recurrence rate - considering all patients in stages II and III - to around 5-6% [10]. Systemic perioperative tumor treatment also contributes to reducing the local recurrence rate, but is primarily recommended with the aim of preventing distant metastases [11].

Preoperative radiotherapy or radiochemotherapy has traditionally been recommended for carcinomas in the lower and middle third of the rectum. For carcinomas in the upper third of the rectum, the benefit of radiotherapy is very limited; in principle, a procedure analogous to colon carcinoma is preferred here, i.e., primary resection of the tumor or neoadjuvant chemotherapy for locally advanced MSS tumors (see Onkopedia guideline Colon cancer).

Quality-assured imaging can identify patients with a very low risk of local recurrence, so that the previously uniformly recommended neoadjuvant radiotherapy can be waived for these patients. The previously very conservative criteria for the optional omission of radiotherapy (T3 tumor with maximum infiltration of 5 mm into the perirectal fat without clearly affected lymph nodes) can be expanded according to data from the OCUM and PROSPECT studies in particular. 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-pre-

serving surgery was possible [61]. In this study, neoadjuvant chemotherapy was compared with neoadjuvant radiochemotherapy. The non-inferiority of the 3-month neoadjuvant FOLFOX therapy with regard to DFS was demonstrated for the patient cohort described above. The 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 (≤ 1mm) or a T4 situation or (ii) was located in the lower third and had a T3 or T4 stage were treated with neoadjuvant radiochemotherapy [60]. In both studies (PROSPECT and OCUM), the rate of local recurrence in the defined groups was only 2-3%.

A single treatment standard 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 can be considered, 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" or treatment goals, which takes into account various evidence-based treatment options depending on tumor stage and treatment goal.

In the past, the option of organ preservation was often utilized after a complete clinical remission, which was "incidentally" detected in the course of neoadjuvant radiochemotherapy. 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 radiochemotherapy can also be a primary treatment goal. This fact is also taken into account in the treatment algorithm; different and more or less intensive radiochemotherapy 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 radiotherapy 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. During the (still 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 chapter 6.1.2.2. to chapter 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 a 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.

Primary quality-assured surgery for rectal cancer in the middle third can also be performed without neoadjuvant radiotherapy/radiochemotherapy 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 [> 2mm] and an invasion into the perirectal fat limited to 10mm, 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

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

Due to the particular problem of localized relapses in rectal cancer, radiotherapy has been intensively evaluated as part of preoperative study concepts. Available options are short-course radiotherapy with high single doses (5 x 5 Gy) or conventionally dosed long-course radiotherapy with single doses of 1.8-2.0 Gy up to a total dose of 45-50.4 Gy.

Preoperative, conventionally fractionated radiation can induce significant tumor shrinkage, reduces the local risk of recurrence, improves the disease-free survival rate and led to a significant increase in survival rates in some of the early randomized studies. With the exception of tumor reduction, this also applies to neoadjuvant short-term radiotherapy. In patients with large locally advanced tumors, where tumor shrinkage is the treatment goal, concurrent radiochemotherapy or TNT is therefore recommended due to its higher local efficacy. In about 10-15% of patients, pathohistologic complete remission is achieved after conventional neoadjuvant long-course radiochemotherapy.

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

Fluoropyrimidines are the most effective drugs for combined radiochemotherapy, with a low rate of side effects. The administration of 5-fluorouracil as a continuous infusion during radiotherapy is more effective than bolus therapy. Modulation of the 5-FU metabolism by folinic acid did not improve the long-term results. The perioperative administration of capecitabine is not inferior to 5-FU and led to an improvement in disease-free survival in one study. The results of randomized studies on the combination of 5-FU or capecitabine with oxaliplatin during radiotherapy can be summarized as follows according to the results of a meta-analysis: (i) gastrointestinal toxicity significantly increased, hematotoxicity comparable; (ii) DFS slightly but significantly improved (HR 0.90, 95% CI 0.81 - 0.99); (ii) lower rate of distant metastases. According to data from a meta-analysis, the clinically moderate benefit can be observed particularly in younger patients under 60 years of age. An increase in R0 resection rates or an increase in the chance of sphincter preservation was not found in any of the studies investigating the addition of oxaliplatin to neoadjuvant radiochemotherapy. A combination of fluoropyrimidines with oxali-

platin is therefore not recommended in principle for neoadjuvant radiochemotherapy, but can be considered in younger patients [10]. Details on dosage and application of chemotherapy are summarized in the German appendix Systemic tumor therapy - protocols.

Radiotherapy in rectal cancer of the middle third can be waived if defined criteria are met according to the PROSPECT and OCUM studies. These criteria are described in chapter 6.1.2.1. Stringent quality assurance of MRI imaging must be ensured if radiotherapy is waived.

Adjuvant (postoperative) radiotherapy alone has neither a significant impact on disease-free survival nor on overall survival, but leads to a reduction in local recurrence rates in previously non-irradiated patients. After incomplete anterior wall resection in stage I, radiotherapy is an experimental option in clinical trials. Data and recommendations on the procedure after successful primary radiochemotherapy are summarized in chapter 6.1.2.5.

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

With regard to perioperative chemotherapy in the context of radiotherapy, until recently a distinction was only made between the application of chemotherapy in the context of radiochemotherapy (primarily as a radiation sensitizer) and the administration of chemotherapy as adjuvant therapy after radiochemotherapy and TME surgery. "Total neoadjuvant therapy" (TNT) is now included as a further therapeutic principle, particularly for tumors with tumor-biologically unfavorable tumor stages and/or where organ preservation is intended. This refers to the supplementation of neoadjuvant therapy by chemotherapy, usually lasting 3 to 4.5 months. This can be administered after or before radio- or radiochemotherapy (as so-called induction or consolidation chemotherapy).

In several randomized studies, TNT showed a significant benefit in disease-free survival, especially for patients whose tumors had defined "high-risk characteristics" (as used in the RAPIDO study): (i) T4 tumors, (ii) tumors with threatened/involved mesorectal resection margin, (iii) EMVI positivity, (iv) N2 status and (v) enlarged lateral lymph nodes [12, 53, 55].

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

According to multidisciplinary recommendations from working groups of the German Cancer Society, the following principles can be applied in treatment planning [51]: (i) Radiotherapy can be given as short-course radiotherapy (5x5 Gy) or long-course radiochemotherapy. (ii) Chemotherapy should be administered over 3 to 4.5 months, whereby according to data from the CAO/ARO/AIO-12 and OPRA trials, consolidation chemotherapy should be preferred if the treatment goal is to achieve the highest possible rate of clinical complete remissions (cCR). Chemotherapy should be carried out using FOLFOX or CapOx; the benefit of additional administration of irinotecan (e.g., in the FOLFIRINOX regimen) has not been proven.

6.1.2.5 Neoadjuvant chemotherapy

In the PROSPECT study, nodal-positive T2 tumors and T3 adenocarcinomas regardless of nodal involvement were included, provided that the distance to the circular resection margin (CRM) was at least 3 mm and continence-preserving surgery was possible [54]. Mainly tumors in the middle third were included. In this study, neoadjuvant chemotherapy with three months of FOLFOX was compared with neoadjuvant radiochemotherapy. In case of insufficient response to FOLFOX (defined as tumor shrinkage <20% or less than four administered FOLFOX cycles), additional RChT could be given. The non-inferiority of neoadjuvant chemotherapy with regard to DFS - the 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; test for non-inferiority: p=0.005).). There was also no difference in overall survival (HR 1.04; 95% CI 0.74-1.44; n.s.). Less than 2% local recurrences were diagnosed in both arms (HR 1.18; 95% CI 0.44-3.16; n.s.). The patient-reported outcomes (PRO) were reported separately [54]. Side effects and functionality differed between the arms in terms of frequencies and time of occurrence: during neoadjuvant therapy, patients on FOLFOX had less diarrhea and better bowel function, whereas patients in the RChT arm complained of less anxiety, loss of appetite, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea and vomiting, and neuropathy. After 12 months post surgery, however, FOLFOX patients had significantly less fatigue and neuropathy and better sexual function. There were no differences between the arms in terms of bladder function and health-related quality of life at any time point.

The results of the PROSPECT trial were confirmed by another randomized trial presented at the 2023 ESMO congress, which had a similar design and was conducted in Asia. This CONVERT trial compared neoadjuvant chemotherapy to RChT for patients with stage II/III tumors up to 12 cm ab ano that did not threaten the mesorectal fascia [56]. Between June 2014 and October 2020, patients were randomized to 4 cycles of CapOx or to 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. A 3-year locoregional recurrence-free survival of 93% was assumed in the standard arm; the non-inferiority margin was set at an HR of <1.6. A total of 663 patients were included, their 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%, lower third tumors accounted for 41% of patients, EMVI was positive in about 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 missed (3-year local recurrence rates 97.4% versus 96.3% to the disadvantage of chemotherapy; HR 1.08, 95% CI 0.46-2.54), the difference is not clinically relevant. DFS and overall survival - although 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, there were 29.2% grade 2-4 toxicities in the RChT arm compared to only 19% in the chemotherapy arm.

In summary, neoadjuvant chemotherapy was shown to be a valid alternative to neoadjuvant RChT in two randomized trials for patients who meet the inclusion criteria of PROSPECT.

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

While the value of adjuvant chemotherapy for rectal cancer after rectal resection without preoperative radiotherapy is certain (see Cochrane meta-analysis), adjuvant chemotherapy *par principe* after combined radiochemotherapy or short-term radiotherapy and TME surgery is controversial. In a meta-analysis, which primarily examined studies with bolus application of 5-FU, no advantage could be demonstrated in either disease-free or overall survival. However, while this meta-analysis is methodologically critical, at least it proves that bolus regimens should no longer be used. After neoadjuvant radiochemotherapy, adjuvant chemotherapy with optimal fluoropyrimidine regimens can therefore be offered. Capecitabine, for example, has a good data basis. The available study data do not allow us to make specific differential therapeutic recommendations based on the degree or extent of the tumor response to neoadjuvant radiochemotherapy. A general use of oxaliplatin in adjuvant chemotherapy cannot be justified on the basis of available study data. Younger patients with an increased risk of recurrence (yp stage III) should be informed about the option of additional oxaliplatin therapy (as investigated, for example, in the large randomized phase II ADORE study) [10]. The duration of perioperative

chemotherapy should be extended to a maximum of 6 months, e.g., with a further 5-6 cycles of adjuvant capecitabine or 8 cycles of FOLFOX. Patients after primary resection who have not undergone neoadjuvant radiochemotherapy can, according to data from the SCOT study, be treated in the adjuvant setting as for colon cancer (i.e., 3 or 6 months depending on the risk profile, see Onkopedia Colon cancer)

For patients with localization of the carcinoma in the upper third of the rectum, who have not received preoperative radiotherapy or radiochemotherapy, a procedure as for colon carcinoma is recommended in stages II and III. Criteria for adjuvant chemotherapy in stages II and III are compiled in the Onkopedia guideline on Colon cancer.

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 clinical complete remission with radiochemotherapy and immunotherapy

In the presence of a complete clinical remission (cCR) after radiochemotherapy or TNT, confirmed by quality-assured imaging procedures and experienced examiners, surgery can be omitted. The data basis for such a procedure is now also solid in the European patient population, but the follow-up period of the reported patients is generally still short. It is therefore recommended that these patients continue to be included in studies or registries in order to obtain better long-term data.

At present, waiving of surgery is only recommended for patients with good adherence to closely scheduled follow-up examinations if complete clinical remission is documented by experienced examiners (endoscopy, MRI, clinical digital rectal examination). A blind or staged biopsy of the rectal mucosa to document cCR is just as unnecessary as endosonography.

For patients with locally advanced, MSI-H / dMMR rectal cancer, the possibility of immune checkpoint inhibitor therapy *without* radiotherapy and / or surgery should be discussed. In an ongoing phase II study, cCR was detectable after six months of primary dostarlimab therapy in all patients who have been analyzed to date [13]. During the still short median follow-up, no case of local recurrence has occurred. Immune checkpoint inhibitors have not yet been approved for the treatment of locally advanced MSI-H rectal cancer. If such an organ preservation concept is used, clinical controls should be carried out after 3 and 6 months of therapy. The post-therapeutic watch-and-wait strategy should be carried out as depicted below.

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

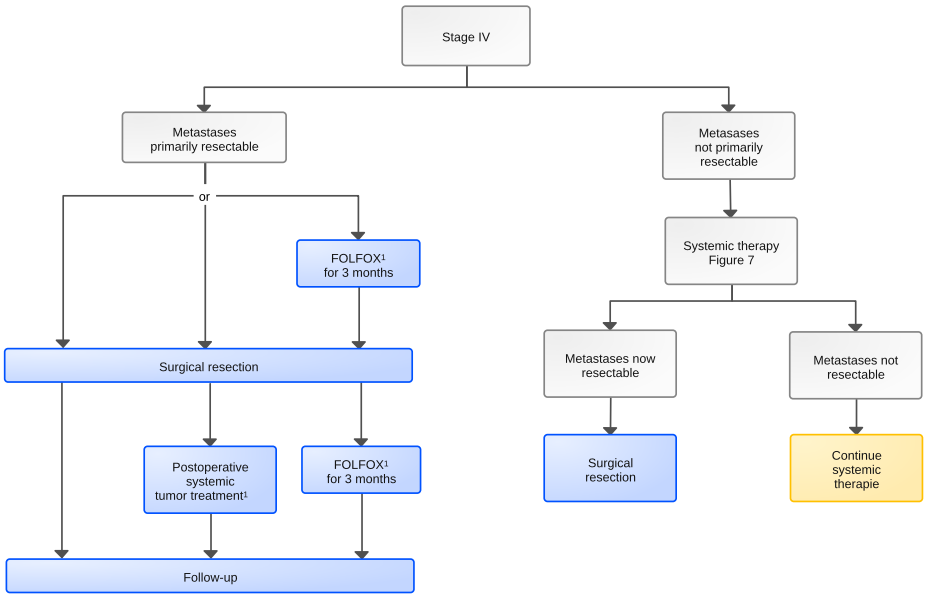
6.1.3 Stage IV

Preliminary remark:

This chapter deals with both metastatic rectal and colon cancer. The comments on right hemicolic tumors in the text and figures are therefore irrelevant for rectal cancer.

The therapeutic goal of stage IV patients used to be considered palliative. Over the past 20 years, it has become evident that up to 25% of patients with colorectal cancer and synchronous hepatic metastases have a curative potential [18, 19]. A curative potential also exists in patients with hepatic recurrence or isolated pulmonary metastasis (see chapter 6.1.3.1 and chapter 6.1.3.2), see Figure 6 and Figure 7.

Figure 6: Treatment structure for stage IV colon cancer



Legend:
curative intention; non-curative intention
[1]The significance of peri-/postoperative drug therapy has not been clearly clarified; ongoing studies should be supported. See also chapter 6.1.3.1.4

In previous versions of the German AWMF S3 and the EMSO guidelines, a classification of stage IV patients into subgroups was proposed [2], based on the primary goal of their therapy. In current guidelines, such a classification has been abandoned in favor of an algorithm that takes into account patient-specific characteristics, treatment goals, and molecular findings (MSI, *RAS* and *BRAF* mutations, etc.) in different hierarchical levels, as criteria for treatment selection [20]. These categories provide a pragmatic orientation, but their criteria have not been prospectively validated. In particular, the localization of the primary (so-called sidedness) should be considered 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 Resectability

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

In addition to the technical question of resectability of metastases, criteria of tumor biology have a significant impact on the recurrence rate. In patients with colorectal liver metastases, various models have been developed for the calculation and prognostic evaluation of risk factors. Widely used is the application of the Fong Score [21], see Table 6, which is based on data of primarily surgically treated patients without perioperative systemic cancer treatment. The risk score facilitates a benefit-risk assessment. It is not a static tool for determining contraindi-

cations. Recent retrospective analyses show that these criteria are also valid for resection after perioperative chemotherapy [22].

Table 6: Risk score in patients with liver metastasis [22]

• Node-positive cancer at initial diagnosis • Disease-free interval between resection of the primary tumor and diagnosis of liver metastases < 12 months • More than one liver metastasis on preoperative imaging • CEA preoperative > 200 ng/ml • Largest metastasis diameter > 5 cm on preoperative imaging
Each risk factor is given a point and a score summarizes this:

Number of risk factors	Risk of recurrence	5-year survival rate in % [18, 63]
0	Low	60-75
1 - 2	Intermediate	40-45
3 - 5	High	15-30

Decisions on the resectability of liver and lung metastases should be made by multidisciplinary tumor boards. Details on resectability and surgical technique are discussed in chapter 6.2.1.2.

6.1.3.1.2 Resection of liver metastases

Resection of metastases is a key component of the curative concept. There is no uniform definition of criteria for resectability of liver metastases. The following conditions should be fulfilled:

- Exclusion of non-resectable extrahepatic metastases
- > 30% functional residual liver tissue postoperatively
- Sufficient safety margins to critical hepatic blood vessels
- No hepatic insufficiency, no liver cirrhosis Child B or C
- ECOG performance score 0 - 2
- No severe comorbidity
- Decisions regarding the resectability of liver metastases should be made by multidisciplinary tumor boards.

The standard for local treatment of liver metastases is surgical resection with or without perioperative systemic cancer treatment. Laparoscopic resection reduces morbidity without affecting 90-day mortality. Less invasive, ablative procedures include radiofrequency ablation, laser ablation or stereotactic radiotherapy. Very few overall survival data are available for these treatment modalities. Comparative randomized trials on the oncologic equivalence of these therapeutic approaches are not available. They are not recommended for curative approaches outside of clinical trials.

6.1.3.1.3 Resection of lung metastases

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

- Exclusion of non-resectable extrapulmonary metastases

- R0 resection possible
- Adequate residual pulmonary capacity postoperatively
- ECOG performance score 0-2
- No severe comorbidity

Decisions regarding the resectability of pulmonary metastases should be made by multidisciplinary tumor boards.

The standard of care for local therapy of pulmonary metastases has been open surgical resection. An alternative is minimally invasive resection using video-assisted thoracoscopy (although the intraoperative exclusion of occult lung metastases is critical here) or radiotherapeutic procedures (such as stereotactic radiotherapy).

6.1.3.1.4 Perioperative systemic cancer treatment in patients with primarily resectable metastases

Indication and optimal treatment regimens of perioperative medical tumor therapy are still subject to controversial debates and have to be discussed in the tumor board on a case-by-case basis, taking into account the tumor biology. Treatment options within clinical studies should be considered.

Based on data from the phase III EORTC 40983 intergroup study [64], perioperative therapy with FOLFOX, three months each pre- and postoperatively, can be used as systemic tumor therapy for resectable liver metastases. However, data justifying the use of molecularly targeted therapy in the setting of resectable metastases are not available. The use of cetuximab in this treatment setting has actually worsened therapeutic outcomes. FOLFOX perioperatively should rather be offered to patients with a higher risk or to patients in whom a "biological window" for the observation of the tumor biology seems reasonable after multidisciplinary counseling.

If preoperative chemotherapy has not been given, it can be given postoperatively, preferentially using a fluoropyrimidine plus oxaliplatin. Particularly in situations in which a low recurrence risk after metastasectomy is expected, additive or "secondary adjuvant" chemotherapy appears to be dispensable because of only small effects on survival parameters. Recent data from a randomized Japanese trial showed an improvement in progression-free survival from 6 months of FOLFOX chemotherapy, but no benefit in terms of overall survival [23]. Ongoing studies should therefore be supported.

6.1.3.2 Conversion therapy for potentially resectable metastases

The number of patients with potentially resectable metastases can be increased by means of so-called conversion therapy. The aim of this approach is to achieve technical resectability by downsizing the metastases. Accordingly, treatment protocols with high response rates and the chance of greater volumetric shrinkage of the metastases are recommended. In randomized and non-randomized phase II trials, doublet combinations plus antibodies (mAb) or triplet combinations ± mAb derived from the palliative setting were used, see chapter 6.2.3 and chapter 6.1.3.3. The PRODIGE-14 trial, which randomly tested doublet versus triplet, each + mAb (selected depending on *RAS* status), as conversion therapy, did not find a statistically significant improvement in R0/R1 resection rates, disease-free and overall survival [24]. However, in the smaller OLIVIA study (80 patients) [25] with more clearly defined and stricter inclusion criteria with regard to irresectability, a benefit was found for triplet therapy + bevacizumab versus FOLFOX + bevacizumab. In the randomized CAIRO-5 study, significantly more R0/R1 resections were also achieved with FOLFOXIRI + bevacizumab compared with FOLFOX + beva-

cizumab in patients with non-EGFR-sensitive tumors (i.e., primary in the right hemicolon, *BRAF V600E* MUT or *RAS* MUT) (51 versus 37%) [26]. In this respect, a triplet plus bevacizumab should be preferred in this patient group.

For *EGFR*-sensitive tumors in the VOLFI study (a randomized phase II study), the addition of panitumumab to a dose-reduced chemotherapy triplet led to high remission rates and consecutively improved resection rates in patients who tended to be younger. An improvement in overall survival was not shown [27]. However, the phase III TRIPLETE study [28] showed no benefit of a triple over a doublet therapy (each in combination with panitumumab) in terms of response and resection rates as well as PFS, so that a chemotherapy doublet should be chosen for patients who are to receive conversion therapy including an *EGFR*-mAb.

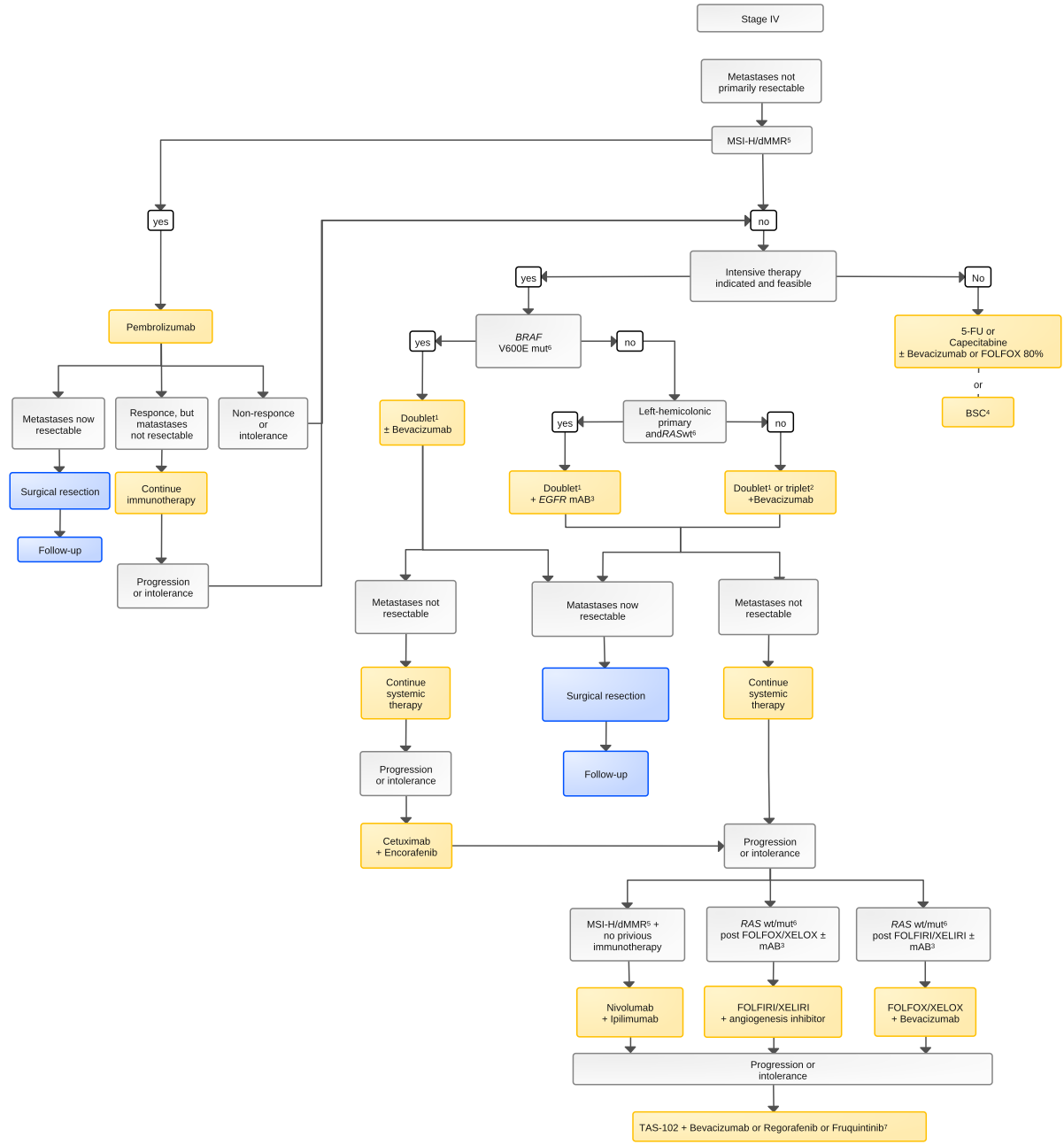
In studies with unselected patients, between 5 and 25% of initially non-resectable patients were subsequently resectable, up to 40% in the case of liver metastasis only. A treatment duration of 2 to 4, possibly up to 6 months is recommended, depending on clinical response. Once technical resectability has been achieved, surgery should be performed as soon as possible, and not deferred until maximum remission has been achieved. By this, increasing liver toxicity with a consecutive increase in surgical morbidity can be avoided. In the case of conversion therapy, restaging should be performed every 8-10 weeks with assessment of CT or MRI images by a multidisciplinary tumor board. Liver surgery expertise should be available on the tumor board or be consulted as part of a presentation at a liver surgery center. Surgery should be performed 4 weeks after the end of systemic tumor therapy, or after (4-) 6 weeks in the case of a therapy containing bevacizumab. The value of continuing chemotherapy after R0 or R1 resection, i.e., completing chemotherapy over a total of 6 months, is of unclear benefit and therefore the subject of clinical studies. Important factors to be considered in this setting are the toxicity of the previous therapy and comorbidity as well as the histopathological response. The added benefit of local treatment for R1 resection is also the subject of clinical studies.

Repeated liver metastasis resections should always be considered, if technically (R0 resection) and clinically feasible and appropriate.

6.1.3.3 Therapy of primarily non-resectable metastases

Despite effective primary therapy and progress in adjuvant treatment, distant metastases emerge in 35-45% of patients. The relapse rate is highest in the first two years after first diagnosis, while recurrence after more than 5 years is rare. In a subgroup of patients, a cure is also possible in this setting, see chapter 6.1.3.1 and chapter 6.1.3.2. For the treatment algorithm, see Figure 7.

Figure 7: Treatment structure in stage IV for primarily non-resectable metastases



Legend:
curative intention; non-curative intention
[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 (best supportive therapy)
[5] MSI-H/dMMR - microsatellite instability-high / deficient DNA mismatch repair
[6] mut - mutated; wt - wild type (unmutated)
[7] Fruquintinib is not yet approved (April 2024)

In the majority of patients in stage IV, the therapeutic goal is palliative and includes the treatment of physical and psychological complaints. It requires multidisciplinary cooperation. The necessity and the possibilities of supportive measures should be discussed early and comprehensively with all affected persons.

The selection of the therapeutic strategy and the most favorable drug combinations are determined by numerous factors. Aspects to be considered are:

- Treatment goals set with the patient (and his relatives, if applicable)

- Course of the disease so far
- Biology of the disease, e.g., *RAS* and *BRAF* mutation status and localization of the primary tumor
- Prior treatment, e.g., preoperative or adjuvant chemotherapy
- Therapy-related factors, i.e., toxicity, quality of life
- Disease-unrelated factors, such as biological age and comorbidity

Biological test methods for the selection of the optimal therapy, e.g., gene signatures or *in vitro* sensitivity testing, have not yet been sufficiently validated. Monitoring by serial measurement of 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 6.

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 combination): fluoropyrimidine (5-FU with folinic acid, or capecitabine) plus irinotecan and oxaliplatin.
- The addition of a monoclonal antibody to combination chemotherapy increased remission rates, progression-free survival, and in some cases overall survival in clinical studies. The combination of chemotherapy and antibodies result in a median progression-free survival of about 10 months and a median overall survival of about 30 months. Due to the mechanism of action of anti-*EGFR* antibodies, the choice of drugs is based on *RAS* and *BRAF* mutation status and the localization of the primary tumor.

Anti-*EGFR* antibodies were tested in combination with doublet chemotherapy, see chapter 6.1.3.3.1.1. In the TRIPLETE trial [28], triplet chemotherapy in combination with anti-*EGFR* antibodies showed no advantage in terms of response and resection rates or PFS and should therefore not be used. In combination with bevacizumab, triplet chemotherapy leads to longer progression-free survival (PFS) than doublet + bevacizumab [31]. Prolongation of the time to progression, thus possibly to symptomatic disease requiring renewed intensive therapy, is also a clinically relevant therapeutic goal for patients in a clearly palliative setting.

A better efficacy of triplet chemotherapy compared to doublet for patients with *BRAF V600E* mutated tumors has not been demonstrated [31]. Furthermore, in the FIRE 4.5 study, the addition of cetuximab to a chemotherapy triplet showed no benefit for patients whose tumor showed a *BRAF* mutation compared with a triplet plus bevacizumab [32]. Therefore, doublet chemotherapy with anti-angiogenic agents (e.g., FOLFOX/CAPOX + bevacizumab) currently appears to be a reasonable first-line therapy for these patients.

Withholding or "reserving" drugs for eventual second-line sequential 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 signaling 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 wild-type *RAS* was investigated in randomized studies. The sequence doublet + cetuximab versus doublet + bevacizumab was used first line, including a protocol-defined crossover to the other antibody in the event of relapse/refractory disease as provided for in the protocol. In the first study [32], a significantly longer survival time was found for the cetuximab sequence in the first line, followed by bevacizumab in the second line, with a hazard ratio of 0.7. In a second study [33], this difference could not be reproduced, see also the German AIO statement [34]. These data are now less relevant in light of the "sidedness" debate. In a pooled analysis of six prospective studies, the impact of primary tumor in the right hemicolon, i.e., proximal/oral to the Flexura coli sinistra, versus the left hemicolon, i.e., distal/aboral, on treatment outcomes in patients with a RASwt tumor was investigated [20]. On one hand, this showed a significantly worse overall survival for patients with a primary tumor in the right hemicolon. On the other hand, there was a clear benefit for patients with a primary tumor in the left hemicolon from treatment with anti-*EGFR* antibodies compared to the control arm with chemotherapy +/- bevacizumab (hazard ratio 0.75 for overall survival; 0.78 for progression-free survival). Patients with tumor site in the right hemicolon had no benefit from the administration of anti-*EGFR* antibodies in terms of progression-free and overall survival despite *RAS*wt. For the first-line treatment of patients with a *RAS*wt tumor and a primary tumor in the left-sided colon, the combination of anti-*EGFR* antibodies and combination chemotherapy is currently recommended. In patients with *RAS*wt and a right-sided location of the primary tumor, there is no benefit of an anti-*EGFR* antibody over chemotherapy or a bevacizumab combination in first-line therapy [34].

Data from the FIRE-4 and PARADIGM studies show that *RAS* mutations are detectable in the blood of around 10% of patients with a *RAS*wt status detected in the tumor tissue. Compared to patients without RAS mutations in tissue and blood, these patients show significantly poorer survival under a chemotherapy doublet with anti-*EGFR* antibodies. They should therefore not be treated with anti-*EGFR* antibodies. The prerequisite for this procedure is the use of certified and quality-assured 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 led to significant improvements in remission rates and progression-free survival compared to chemotherapy alone, and in some studies also in overall survival. The combination with a triplet (5-FU, folinic acid, irinotecan, oxaliplatin) leads to slightly higher remission rates and a significant extension of progression-free survival compared to a doublet (5-FU, folinic acid, irinotecan) [24].

6.1.3.3.1.3 MSI high/dMMR

For patients with microsatellite instability in their tumor tissue, pembrolizumab was compared with various "standard of care" regimens 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). Overall survival (as a secondary endpoint) was not statistically significantly prolonged (with a high rate of cross-over within and outside the study). Pembrolizumab has been approved by the EMA in February 2021 for the treatment of metastatic colorectal tumors with MSI. Analysis of MSI can be performed by immunohistochemistry [35].

6.1.3.3.2 Maintenance therapy

When deciding on maintenance therapy, the possible prolongation of progression-free and overall survival time, at the cost of side effects, is weighed against a therapy-free period under close monitoring and re-start of therapy in case of disease progression.

In randomized studies, post-doublet induction including oxaliplatin plus bevacizumab, maintenance therapy with a fluoropyrimidine + bevacizumab led to a statistically significant extension of the time to tumor progression compared to a watch-and-wait strategy. Bevacizumab monotherapy is not recommended. Patients who wish to interrupt therapy, or for whom this seems reasonable, can therefore be advised to take a break after 6 months of therapy without a significant worsening of the probability of survival. The significantly shorter progression-free survival time should be pointed out. Close follow-up is recommended in this situation. Immediate re-induction at first progression under maintenance therapy is only feasible in a minority of patients. Nevertheless, re-induction therapy should definitely be considered in the further course of treatment, 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 oxaliplatin-containing induction therapies, it is unclear whether the results described would be transferable to irinotecan-containing induction.

Regarding maintenance therapy with *EGFR* inhibitors, according to data from the PANAMA trial, continuation of 5-FU and the anti-*EGFR* antibody is recommended after 3 months of induction chemotherapy [37]. Non-inferiority of maintenance with panitumumab monotherapy versus panitumumab + 5-FU was not shown in an Italian randomized trial, so monotherapy with anti-*EGFR* antibody alone is not recommended for maintenance therapy [38]. However, based on the studies published to date, no statement can be made as to when and to what extent patients receiving anti-*EGFR* antibody therapy may take breaks from therapy, so that this decision must be 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 prior therapy, treatment goal, *BRAF* and *RAS* status, and *MSI* status. Second-, third-, or fourth-line therapy is individualized. The following principles should be considered:

- After treatment with an irinotecan-based first-line therapy, 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 in the first-line therapy, FOLFOX+ bevacizumab should be used in the second-line therapy.
- Continuation of bevacizumab beyond progression on first-line therapy significantly prolongs overall survival.
- For patients previously treated with oxaliplatin-based therapy, FOLFIRI chemotherapy can be combined with the anti-angiogenic agent aflibercept. This leads to a statistically significant increase in survival time.

- In second-line therapy, the combination of the anti-angiogenic antibody ramucirumab with FOLFIRI leads to prolonged survival in patients previously treated with oxaliplatin- and bevacizumab-based first-line therapy.
- Ramucirumab or aflibercept should be preferred in patients with only a short first-line PFS under bevacizumab-containing therapy.
- Patients with *RAS* wild-type who have not received anti-*EGFR* antibodies in first-line therapy and have a high remission pressure for second-line therapy, should be treated with a combination of an anti-*EGFR* antibody plus chemotherapy, see Systemic Tumor Treatment Protocols (in German only). This also includes a change of cytostatic drugs.
- Cetuximab and panitumumab should preferably be used in first-line therapy. When 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 a standard of care, and vice versa. A rechallenge of cetuximab or panitumumab should only be carried out in patients in whom no *RAS* and/or *BRAF* mutations are detectable in a liquid biopsy.
- In patients with *BRAF* V600E mutation, the use of a combination of encorafenib and cetuximab in second- and third-line therapy in accordance with current approval leads to an extension of progression-free and overall survival, see Colorectal Carcinoma approval (in German only).
- After pretreatment with chemotherapy, pembrolizumab or the combination of nivolumab and ipilimumab can be used in patients with MSI-H tumors in accordance with current approval [39].
- If established chemotherapeutic agents and monoclonal antibodies fail or are intolerable, trifluridine/tipiracil should be used in combination with bevacizumab [65].
- The oral multikinase inhibitors fruquintinib [66] and regorafenib have led to an increase in overall survival in heavily pretreated patients compared to placebo. However, fruquintinib is not yet approved (as of April 2024) and regorafenib is not available in Germany.
- For patients with *HER2* positivity (in particular, but not exclusively after anti-*EGFR* therapy and for 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, however, can also be used in patients whose tumors are *RAS*mut. Patients with *HER2* mutations showed responses with a combination of trastuzumab/tucatinib in the MOUNTAINEER study [67]. There is no approval for any of the drugs mentioned for this treatment setting; see Colorectal carcinoma approval (in German only).
- Patients with *KRAS* G12C mutations showed a significant benefit in response rate and PFS in the three-arm Phase III CodeBreaK-300 study from the combination of sotorasib (960mg) and panitumumab compared with trifluridine/tipiracil or regorafenib therapy or a combination of lower-dose sotorasib (240mg) and panitumumab [48]; sotorasib is not yet approved for the treatment of mCRC.
- Patients whose tumor shows an *NTRK* fusion can be treated with the tyrosine kinase inhibitors larotrectinib and entrectinib in accordance with current approval.

For all phases of drug-based tumor therapy, the occurrence of adverse effects should be monitored regularly, i.e., at each therapy cycle, by history, clinical examination, and laboratory analyses. The response to the systemic tumor therapy is monitored every 2 to 3 months by clinical examination and targeted, imaging diagnostics.

6.1.3.3.4 Local therapy for oligometastasis

Local therapy of metastases, especially liver metastases, may also be useful in the palliative situation. Decisions on systemic versus local measures and, if necessary, on sequential or combination therapies should be made by multidisciplinary tumor boards.

For local therapy of irresectable liver metastases, different procedures have been described, mainly in case series. The best evaluated is intra-arterial liver perfusion. Compared with intravenous therapy with 5-FU/folinic acid, it leads to higher remission rates, but not to a prolongation of survival. The effect of systemic chemotherapy is documented more clearly [40].

Other approaches include radiofrequency ablation, laser therapy, stereotactic radiotherapy, or SIRT (selective internal radiation therapy). Randomized clinical studies comparing these methods with systemic tumor therapy are sparse. As complementary measures to systemic chemotherapy, they should be evaluated on a case-by-case basis. The additional administration of selective internal radiotherapy (SIRT) in conjunction with first-line chemotherapy showed no benefit for either progression-free or overall survival in a large pooled ITT analysis, and is therefore not recommended [41]. The indication should be discussed in a multidisciplinary tumor board, taking into account the overall treatment plan and the potentially substantial toxicity.

6.1.3.3.5 Peritoneal carcinomatosis

The median survival time of patients with proven peritoneal carcinomatosis is significantly worse than for other metastatic manifestations. Nevertheless, the PRODIGE-7 trial showed a median overall survival of 41 months for the combination of systemic chemotherapy and cytoreductive surgical intervention (CRS) in patients with isolated peritoneal carcinomatosis. In this randomized study (CRS +/- HIPEC), however, the additional benefit of supplementary hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin could not be demonstrated [42]. In this respect, HIPEC with oxaliplatin after CRS cannot be recommended at the present time. Cytoreductive surgery alone can be regarded as a basic standard treatment option, carried out at specialized centers. Criteria for decision-making are good general condition, localized and exclusively peritoneal metastasis (peritoneal carcinomatosis index PCI max. 15), as well as potential CC0 resectability. There is currently no consensus regarding the indication for HIPEC; it should be carried out either as part of clinical trials or as an individual decision using mitomycin C infusion over 60-90 minutes. The use of mitomycin C rather than oxaliplatin is suggested in particular based on the data from the Spanish HIPECT4 trial, which was however conducted in a different treatment setting (tumors assessed preoperatively as T4) and showed an advantage in 3-year freedom from local recurrence [68].

6.2 Treatment modalities

6.2.1 Surgery

6.2.1.1 Primary tumor

The standard procedure is mesorectal excision with removal of the regional lymphatic drainage area, technically depending on the location of the carcinoma:

- Lower third of the rectum: total mesorectal excision (TME) with a minimum distal distance of ≥ 2 cm, measured from the macroscopic tumor margin;

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

6.2.1.2 Surgical access

Open surgery is standard, an alternative is laparoscopic surgery. The advantage of open surgery is the shorter operation time and the shorter learning curve for the surgeon. The main advantages of laparoscopic surgery are the better cosmetic result and the previous postoperative recovery. 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 stay, are hardly significant. Laparoscopic surgery can be performed in specialized centers, preferably under study conditions [43].

6.2.1.3 Special situations

Special local situations include ileus, tumor perforation, intestinal perforation or infiltration into adjacent organs. In these patients, the rectal carcinoma is usually locally advanced, so that resection is positioned as part of a multimodal treatment concept. In patients with hereditary disease, the type of genetic burden, previous operations and the overall concept of care must be taken into account.

The type and extent of the resection are determined by the localization, the supplying vessels and the lymph drainage area defined by these. The surgical technique depends on the location of the primary tumor, see Table 4.

6.2.2 Radiotherapy

Radiotherapy leads to a significant reduction in relapse for local recurrences. Options include preoperative irradiation with 25 Gy over 5 days, or the combination of irradiation with 50.4 Gy with a fluoropyrimidine, see chapter 6.1.2.2

Acute side effects of short-term, preoperative radiation documented in the larger, randomized studies were diarrhea (20%), dermatitis (5%), cystitis (2%) and postoperative wound healing disorders [44]. Long-term side effects were related to 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 neoplasia after 12 years was higher than in the control group (14 vs. 9%) [46].

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

6.2.3 Systemic tumor treatment agents

6.2.3.1 5-Fluorouracil

5-Fluorouracil is used in almost all forms of medical tumor therapy for patients with colorectal carcinoma. The best risk-benefit ratio is achieved with intravenous continuous infusion over 24-48 hours after previous administration of folinic acid. Remission rates are up to 30%. Severe side effects (grade 3-4) are 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 mucosites, and others. Mutations among the four major dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded prior to 5-FU- and capecitabine containing chemotherapy [48].

6.2.3.2 Aflibercept

Aflibercept is a recombinant fusion protein with anti-angiogenic activity. In the pivotal study, the addition of aflibercept to FOLFIRI significantly improved the hazard ratio in patients previously treated with oxaliplatin-based therapy. Overall survival was prolonged by 1.4 months. Progression-free survival and response rates were also better in the aflibercept arm. Drug-related adverse events in CTCAE grade 3/4 were consistent with other antiangiogenic agents: Hypertension (+17.8%), bleeding (+1.3%) (especially epistaxis), arterial (+1.3%) and venous thromboembolism (+1.6%), and proteinuria (+6.6%). Rare critical complications included arterial, thromboembolic events, and gastrointestinal tract perforations.

6.2.3.3 Bevacizumab

Bevacizumab is a monoclonal antibody with anti-angiogenic activity. In combination with 5-FU / folinic acid, capecitabine, irinotecan or oxaliplatin, remission rates of 50% and prolongation of progression-free survival are achieved. In combination with irinotecan and 5-FU bolus protocols, prolongation of overall survival has also been achieved. Bevacizumab is effective in both first-line and second-line therapy. Continuation of bevacizumab therapy beyond progression resulted in prolonged overall survival in two randomized clinical trials. In the larger trial, a significant improvement in hazard ratio to 0.81 was achieved. Median overall survival was prolonged by 1.4 months. Serious adverse events (grade 3/4) that occurred in more than 5% of patients in the pivotal studies were hypertension and proteinuria. Less common critical complications included arterial thromboembolic events and gastrointestinal tract perforations..

6.2.3.4 Capecitabine

The basic drug in the medical tumor therapy of patients with colorectal carcinoma is 5-fluorouracil. Capecitabine is an oral fluoropyrimidine that is enzymatically metabolized by the tumor to 5-FU. In comparative clinical trials, it was at least as effective as 5-FU bolus/folinic acid therapy. When used as monotherapy, remission rates are achieved in up to 25%, and in combination with irinotecan or oxaliplatin in up to 45% of patients. Serious adverse events (grade 3/4) occurring in more than 5% of patients in the pivotal trials were diarrhea and hand-foot syndrome. The combination of proton pump inhibitors with capecitabine-containing therapy should be avoided, as negative effects on capecitabine efficacy have been demonstrated in several retrospective studies. Mutations among the four major dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded prior to 5-FU- and capecitabine containing chemotherapy [48].

6.2.3.5 Cetuximab

Cetuximab is a monoclonal antibody against the EGF receptor. The remission rate after monotherapy in second-line is 8%. In first-line therapy in patients with *KRAS* wild-type, remission rates of 55-65% are achieved in combination with 5-FU / folinic acid and irinotecan or oxaliplatin. Progression-free survival is prolonged. Overall survival data are inconsistent. Patients with defined *RAS* mutations (*KRAS* genes exon 2-4, *NRAS* genes exon 2-4) have no benefit from cetuximab therapy, and in some chemotherapy combinations even a trend towards shorter survival was observed. Because there is evidence 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, see also Approval Status Colorectal Cancer for the German speaking countries. Serious adverse events (grade 3/4) that occurred in more than 5% of patients in the pivotal studies were acneiform dermatitis and infusion reactions. Prophylactic therapy for acneiform dermatitis should be given with doxycyline or minocycline. Additional prophylactic local therapy with vitamin K1 cream (Reconval K1) may be considered in women. Medications for prophylaxis of infusion reactions are corticosteroids and H1 blockers. Biweekly administration (500 mg/m²) was equivalent to weekly cetuximab administration (400 / 250 mg/m²) in a randomized trial.

6.2.3.6 Dostarlimab

Dostarlimab is a humanized anti-PD-1 monoclonal 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 has progressed 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. At a follow-up period of up to 25 months, no relapse had occurred [13]. In 363 patients in the GARNET study, the main side effects observed were hypothyroidism (7%), liver enzyme elevations (6%) and arthralgias (5%) [50].

6.2.3.7 Encorafenib

Encorafenib is an oral highly selective *RAF* kinase inhibitor. In combination with cetuximab, it resulted in prolonged survival in patients with *BRAF V600E*-mutated CRC after first-line therapy compared with chemotherapy plus cetuximab. The most common adverse events in the pivotal study were diarrhea, nausea, vomiting, and acneiform dermatitis, of which severe (≥ grade 3) were fatigue (4%), anemia (4%), and diarrhea (2%). Another typical side effect is palmar-plantar erythrodysesthesia syndrome (PPES) 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 increase in median survival time from 4.8 to 7.4 months was achieved compared to placebo in 691 patients with refractory metastatic colorectal cancer. The most common adverse events observed in the study were arterial hypertension (14%), weakness (8%) and hand-foot syndrome (6%). The marketing authorization application to the EMA was accepted for review in June 2023 and FDA approval was granted in November 2023.

6.2.3.9 Ipilimumab

Ipilimumab is a drug from the group of monoclonal antibodies named immune checkpoint inhibitors. It blocks the inhibitory T-cell regulator CTLA-4 and thereby enhances the autologous immune response. It is approved in combination with nivolumab after pretreatment and treatment failure with/under fluoropyrimidine-containing combination chemotherapy for stage IV patients with MSI-H/dMMR. The overall response rate (ORR) for this combination was 55% in the pivotal Checkmate-142 trial, with survival rates at 9 and 12 months of 87% and 85%, respectively. 32% of patients experienced grade 3-4 toxicities associated with therapy: elevation of AST and/or ALT (11%), elevation of lipase (4%), anemia (3%), 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%. Progression-free survival and overall survival are significantly prolonged compared to fluoropyrimidine therapy. Serious adverse events (grade 3/4) that occurred in more than 5% of patients in the pivotal studies were diarrhea, nausea / vomiting, neutropenia and neutropenic fever. This drug can be applied weekly, bi-weekly or tri-weekly.

6.2.3.11 Nivolumab

Nivolumab is an anti-PD-1 monoclonal antibody of the immune checkpoint inhibitor class. It is approved in combination with ipilimumab after pretreatment and treatment failure with/under chemotherapy for stage IV patients with MSI-H/dMMR, after pretreatment with fluoropyrimidines. The overall response rate (ORR) for this combination in the pivotal Checkmate-142 trial was 55%, with survival rates at 9 and 12 months of 87% and 85%, respectively. 32% of patients experienced grade 3-4 toxicities associated with therapy: elevation of AST and/or ALT (11%), elevation of lipase (4%), anemia (3%), colitis (3%).

6.2.3.12 Oxaliplatin

Oxaliplatin is a platinum derivative. It is highly effective in combination with fluoropyrimidines (5-FU/folinic acid (FS), capecitabine). In first-line therapy, it increases remission rates to 40-60% and prolongs progression-free survival compared to 5-FU/FS. Serious adverse events (grade 3/4) occurring in more than 5% of patients in pivotal trials were nausea/vomiting, diarrhea, mucositis, and polyneuropathy. Intravenous administration of calcium and magnesium do 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. Response to panitumumab is dependent on mutations in the *RAS* genes. In the pivotal study, patients with *RAS*wt showed statistically significantly longer survival for the panitumumab/chemotherapy combination versus the chemotherapy-only arm. Progression-free and overall survival were worse in patients treated with panitumumab in the presence of a mutation in one of the *RAS* genes. Serious adverse event (grade 3/4) occurring in more than 5% of patients in the pivotal studies was acneiform dermatitis. Prophylactic therapy for acneiform dermatitis should be given with doxycyline or minocycline. Additional prophylactic topical therapy with vitamin K1 cream (Reconval K1) may be considered in women.

6.2.3.14 Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody from the class of immune checkpoint inhibitors. In patients with dMMR/MSI-H CRC, pembrolizumab improved survival in first-line therapy and was better tolerated than doublet chemotherapy with or without *VEGFR* or *EGFR* antibodies. Toxicities ≥ grade 3 occurred in 56% of patients receiving pembrolizumab and 78% in the chemotherapy group. More severe (≥ 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 humanized IgG1 antibody that specifically binds to vascular endothelial growth factor receptor-2 (VEGFR2). It is approved for second-line treatment of patients with adenocarcinoma of the stomach or gastroesophageal junction. In patients with metastatic colorectal cancer recurrent or refractory after therapy with a fluoropyrimidine, oxaliplatin and bevacizumab, it was tested in a phase III trial in combination with FOLFIRI. The addition of ramucirumab resulted in a statistically significant prolongation of progression-free survival from 4.7 to 5.7 months with a hazard ratio of 0.77 and prolongation of overall survival from 11.7 to 13.3 months with a hazard ratio of 0.84. Adverse events CTCAE grade 3/4 that occurred in more than 5% of patients treated with ramucirumab in the combination therapy in the pivotal study, and more frequently than in the control group, were neutropenia (28%) and hypertension (11%). Fatigue (12%) and diarrhea (10%) were not significantly more common than in the chemotherapy control arm. Information on approval status is summarized in Colorectal Cancer Approval for Germany, Austria and Switzerland.

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 after failure of all established chemotherapies, regorafenib monotherapy has been shown in two phase III studies to significantly improve overall survival compared to best supportive care in a meta-analysis with a hazard ratio of 0.76. Regorafenib causes symptomatic toxicity in many patients. CTCAE grade 3/4 adverse events that occurred in more than 5% of regorafenib-treated patients in the pivotal 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 dose reduction if necessary. Information on approval status is summarized in Colorectal carcinoma approval for Germany, Austria and Switzerland .

6.2.3.17 S1 (Tegafur plus Gimeracil and Oteracil)

For the case of intolerance of 5-fluorouracil, S1 has been approved by EMA in 2022. This approval is based on several studies showing that S1 is non-inferior to capecitabine or 5-FU in terms of efficacy, and that switching from fluoropyrimidines to S-1 due to cardiotoxicity or pronounced hand-foot syndrome is safely feasible. 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 hand-foot syndrome or cardiovascular toxicity has developed in an adjuvant or metastatic setting.

6.2.3.18 Trifluridine/Tipiracil (TAS-102)

TAS-102 is a newer oral cytostatic drug. It consists of trifluridine, a thymidine analog, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor. The cytotoxic component is trifluridine while tipiracil inhibits its rapid degradation. In a phase III study in relapsed or refractory patients with metastatic colorectal cancer after at least two standard chemotherapies, TAS-102 resulted in a statistically significant prolongation of progression-free survival (HR 0.48; median 0.3 months) and overall survival (HR 0.68, median 1.7 months). The remission rate was 1.6%. TAS-102 is given for 5 days in each of two consecutive weeks, followed by a 2-week treatment break. Adverse events CTCAE grade 3/4 that occurred in more than 5% of patients treated with

TAS-102 in the pivotal study were neutropenia (38%), leukocytopenia (21%), anemia (18%), and thrombocytopenia (5%). Febrile neutropenia was observed in 4% of patients. These complications require close monitoring of blood counts and dose reduction if necessary. Information on approval status is summarized in Colorectal carcinoma approval for Germany, Austria and Switzerland .

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.

8 Follow-up and monitoring, including patients with a watch-and-wait approach

The 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 col-

orectal 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 of rectal cancer

Investigation	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** 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** X		X **X** X		X **X** X
Abdominal sonography		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:
X recommendations in Germany;
X recommendations in Austria;
X Recommendations in Switzerland

Patients who have achieved a complete clinical remission after radio/radiochemotherapy and are taking a watch-and-wait approach in response should be monitored by experienced investigators according to the following Table 8 (after: [17]).

Table 8: Tests and time intervals for watch-and-wait procedure (after: [17])

Year	CEA	DRU	Endoscopy	MRI pelvis	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:
CEA - carcinoembryonic antigen in serum; DRU - 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.