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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 in men in German-speaking countries. The mean age at diagnosis is 70-75 years. Individuals with genetic predisposition may develop the disease in early adulthood.

For early detection, both screening for occult fecal blood triggering an endoscopic examination or 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. In stage I, surgery (possibly as a local excision) is the first priority. In stages II and III, preoperative radiochemotherapy or radiotherapy is recommended for tumors in the lower and middle thirds. Total neoadjuvant therapy (TNT) may be preferred if clinical risk factors are present. Upper third rectal cancers are usually resected primarily. In clearly defined exceptional cases, neoadjuvant radiation in the middle third may be omitted. A clear recommendation for or against adjuvant chemotherapy cannot be given; the implementation of adjuvant therapy should be discussed individually.

For the majority of patients in stage IV, treatment aims at palliation, with relief of symptoms and prolongation of survival time. In a subgroup of patients, a cure is also possible in this situation. For systemic cancer treatment in stage IV, different substances from the field of 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 data

The 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]. The more proximal carcinomas up to and including the ileocecal valve are defined as colon cancer. An ESMO Con-

sensus proposes a new definition taking into account the different measurement results from imaging procedures [2].

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

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

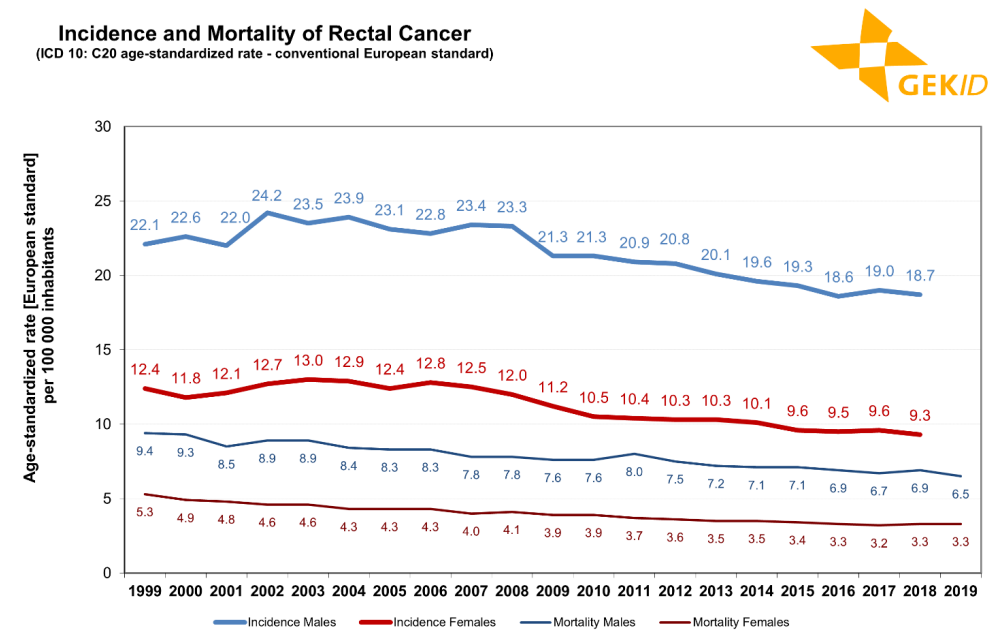
2.2 Epidemiology

Almost 20,000 new cases of rectal cancer are diagnosed in Germany every year. Almost 12,000 men and about 7,000 women are first diagnosed in Germany annually, corresponding to about 4.3% and 3.0%, respectively, of all malignant tumors. The prognosis of rectal cancer roughly corresponds to that of colon cancer and is in the middle range compared to other cancers. Annually, slightly less than half as many people die from rectal cancer than develop the disease (approximately 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 for cancer overall (75 years and 76 years, respectively).

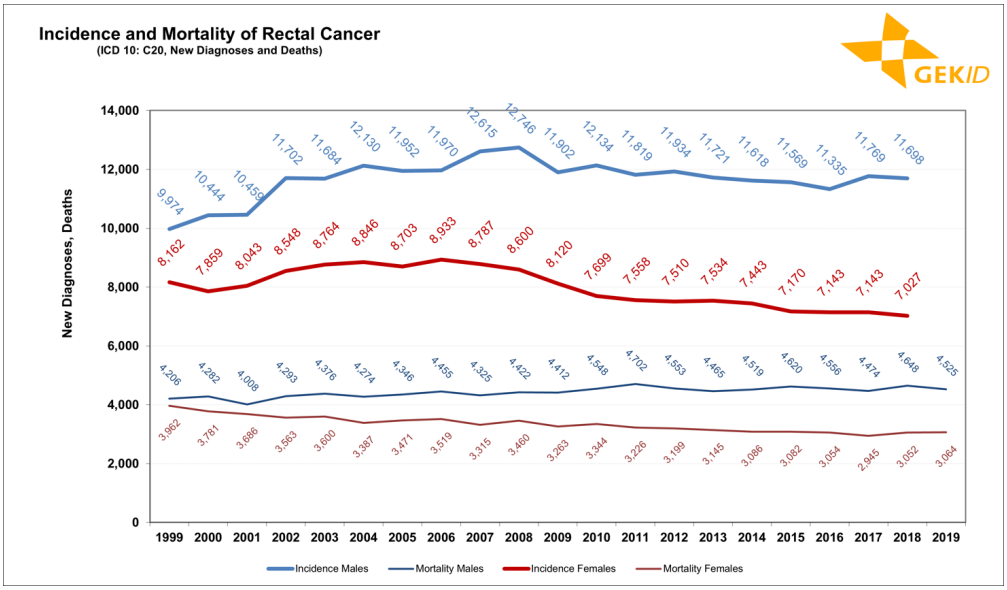
The age-standardized morbidity rates - i.e., the probability of disease - as well as the age-standardized mortality rates - i.e., the probability of death - show a decreasing trend over the past 15 years for both men and women, see Figure 1. This is also confirmed by a joinpoint analysis [4, 5], according to which the incidence rates in men decrease by an average of 1.8% per year, and those in women even by 2.1%. The declines in mortality rates are about the same, 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 (conventional European standard) [3]



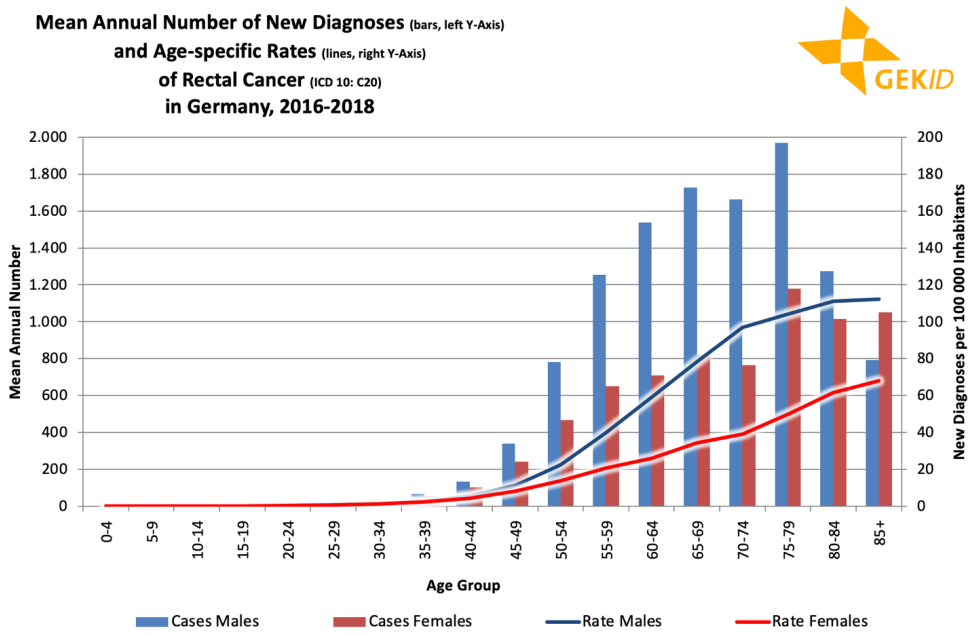
While the age-standardized rates of new cases are a measure of the probability of disease and are largely independent of the population structure, the number of new cases also depends on the age structure and population size. Due to the shift of the age structure towards an older society and the reaching of the age cohorts of the baby boomers who are likely to develop the disease, the courses of new cases and deaths differ from the courses of the rates. The higher the age at which the disease is first diagnosed, the stronger the effect. This effect is more pronounced for men than for women. Despite declining morbidity and mortality rates, the number of new cases in men and the number of deaths from colorectal cancer have remained almost constant since 2003. For women, as with the rates, decreasing numbers of cases are also observed for incidence and mortality, but the decrease 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 - number of cases [3]



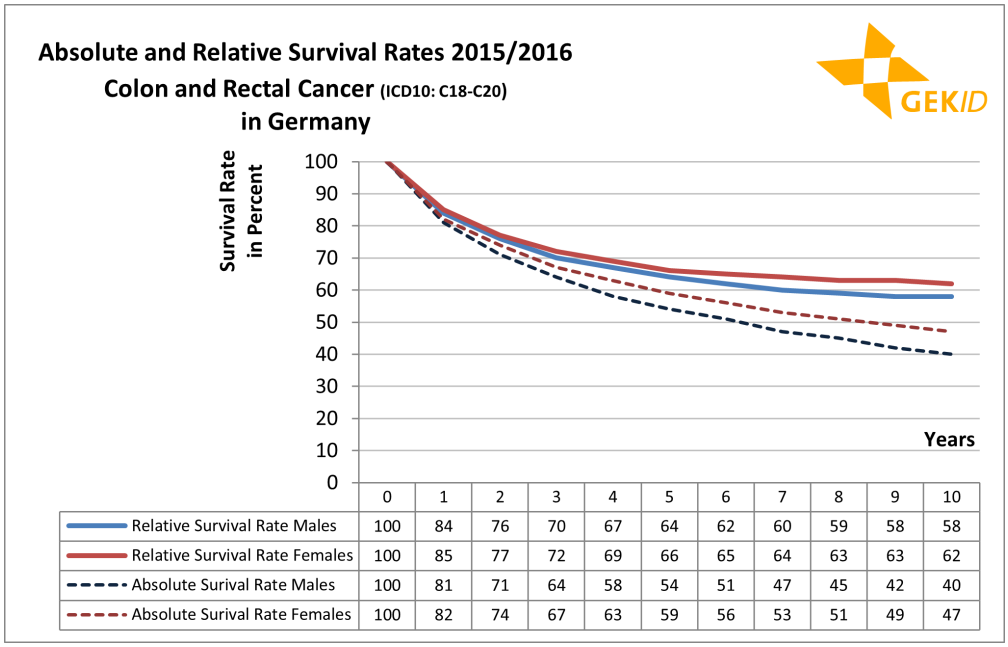
Up to the age of 40, rectal cancer is almost neglectable. From then on, the rates of disease increase steadily in both sexes and reach their peak in the highest age group (85 years and older) (see Figure 3 [lines]). From the beginning, the rate of men is always higher than that of women. The case rates are somewhat different due to the population distribution. The number of new cases increases in men up to the age group 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 becomes lower due to life expectancy. For women, a steady increase in the number of cases can be observed up to the age of 70. In the eighth decade of life, about 800 new cases are currently diagnosed. Thereafter, the number of cases increases by about 50% to 1,200 new cases and then remains stable at about this level.

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



The prognosis of colorectal cancer, as mentioned above, is in the middle range of all cancers. It is 54% of men and 59% of women who are alive five years after a diagnosis. Notably, in Figure 4, survival rates for colon (C18) and rectal (C19, C20) cancers are merged (Figure 4), as there is little difference between these entities. A difference between overall survival - the percentage of patients surviving for a given time - and relative survival - the ratio of absolute survival vs expected survival in the general population - is apparent. 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), because quite a few people have died in the general population during 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 disease and the 14th coordinated population projection of the Federal Statistical Office (G2L2W2, moderate development), an increase in the number of

cases by about 22% to almost 23,000 new cases (2050) can be expected for the next 30 years, solely due to the shift in age structures of the population.

2.3 Pathogenesis

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

2.4 Risk factors

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

- Defined genetic disease patterns (about 3% of new cases)
  - Hereditary colorectal carcinoma without polyposis (HNPCC, Lynch syndrome [OMIM ID # 120435] [6] with mutations in genes:
    - *MSH2* (HNPCC1): approximately 60% of patients
    - *MLH1* (HNPCC2): approximately 30% of patients
    - *PMS1* (HNPCC3), *PMS2* (HNPCC4), *MSH6* (HNPCC5), *TFGBR2 (*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 before the age of 50.
- 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 cultural and lifestyle groups, self-rating of participants, multifactorial events, and others), 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
  - Ablation of adenomas is a preventive measure by removing precursor stages of rectal cancer. This procedure is performed as part of the endoscopic screening procedures.
- Lifestyle habits
  - weight reduction for overweight people
  - 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 fruits and vegetables
  - abstaining from daily intake of red or processed meat

The most extensive data for drug prevention are available for acetylsalicylic acid (ASA). Regular consumers of ASA at a dose of ≥ 75 mg/day have a rate of colorectal cancer about half lower than comparator groups [7]. In HNPCC gene carriers, daily intake of 300-600 mg ASA reduces colorectal cancer risk by 37%.

These and numerous other studies on the association of colorectal cancer and certain forms or components of diet, micronutrients, electrolytes such as calcium or magnesium, or drugs 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 testing using the guaiac test (gFOBT) reduces cancer-specific mortality [8]. Immunochemical tests for occult blood (iFOBT) have a higher sensitivity. In Germany, the gFOBT has been replaced by the iFOBT since January 1, 2017. A multi-test for DNA alterations and for 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 carcinoma and precancerous changes, but has not been prospectively validated

using mortality as an endpoint. The uptake of endoscopy is significantly lower than the uptake of noninvasive testing methods. Overall mortality is not reduced by screening.

Risks of screening include distress and complications from endoscopy, particularly when performing polypectomies, false-negative results of stool examinations, and overdiagnosis in persons at low risk of disease.

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

Procedure	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; biennially 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 years Repetition after 10 years if findings are unremarkable*.	From the age of 50, every 10 years if the findings are unremarkable

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 in colorectal cancer can be found in the knowledge base.

3.2.2 Risk groups

3.2.2.1 Relatives of patients with colorectal cancer

First-degree relatives should undergo colonoscopy at an age 10 years prior to the patient's disease, but at the latest at the age of 50 years [8, 9]. This recommendation also applies to first-degree relatives of patients diagnosed with colorectal adenomas before the age of 50. If the findings are unremarkable, colonoscopy should be repeated in this risk group after a maximum of 10 years.

3.2.2.2 Hereditary colorectal carcinoma

Diagnostics should be performed according to the guidelines for the diagnosis of genetic predisposition to cancer of the German Medical Association, those of the Austrian Society of Gastroenterology & Hepatology (ÖGGH), and the ESMO guidelines [2, 9]. The specific genetic aberration determines the risk of disease and is the basis of the individualized screening and prevention plan.

3.2.2.3 Ulcerative colitis

Aminosalicylate can be used for prophylaxis; results of randomized trials with the primary endpoint of preventing colorectal cancer are not available. Recommendations for screening are based on the extent of colitis and the duration of disease. Patients with pancolitis for more than 8 years or with left-sided colitis for more than 15 years should have a complete colonoscopy with stepwise biopsies annually. In patients with high-grade dysplasia, restorative proctocolectomy is an effective prophylactic intervention.

3.2.2.4 Crohn's disease

For these patients, no recommendation regarding prophylaxis and early detection can be given at present.

4 Clinical characteristics

4.1 Symptoms

Characteristic early symptoms are absent. The symptoms can be classified 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
- Paraneoplastic syndromes

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

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis and recommended diagnostics

The first step is confirmation of the suspected clinical and / or imaging diagnosis, followed by staging after the diagnosis has been confirmed, see Table 2.

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

Indication	Procedure	Note
New-onset 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	
	Quality-assured pelvic MRI	If applicable, plus EUS (endosonography) in case of planned radiotherapy
	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	Recommendation by S3 Guideline
	CT abdomen (alternatively: MRI abdomen)	additionally recommended, especially in case of sonographic suspicion of liver metastases or in case of non-optimal assessability in sonography
	Thorax radiograph in 2 planes	Recommendation by S3 Guideline [9]
	CT Thorax	Additionally recommended
	CEA	

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

MRI is thus **the** essential diagnostic component for staging of locally advanced rectal cancer and is crucial for treatment-planning.

Positron emission tomography (PET) and MRI liver is not a standard part of the primary diagnosis of rectal cancer.

5.3 Classification

Classification 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

Additionally, rectal cancer is subdivided according to the distal end of the primary tumor to the anocutaneous line. The definitions of the distances of the primary tumor to the anocutaneous line are not completely identical in the different 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

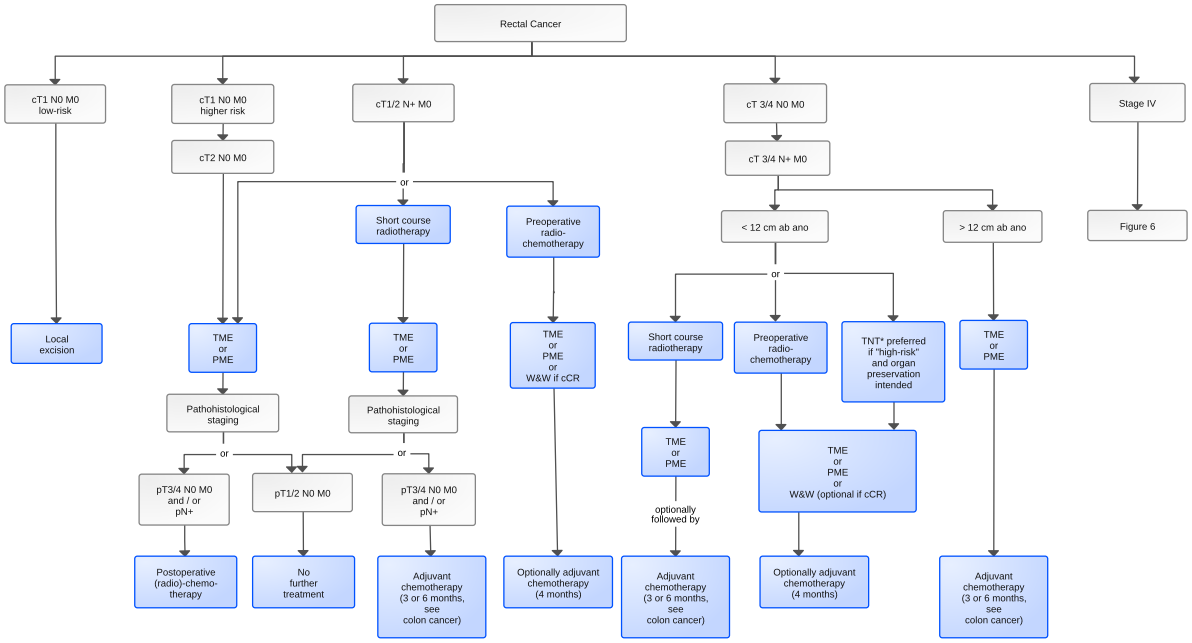
For objective assessment of the general condition, the use of geriatric assessment is recommended, see Geriatric Assessment Knowledge Base. Tests for objectifying mobility and comorbidity are particularly suitable. The indication to perform further tests is based on the clinical impression and the planned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

Figure 5: Stage-adapted treatment algorithm for rectal cancer



Legend:
TNT, total neoadjuvant therapy; cCR, clinical complete remission; TME - Total Mesorectal Excision, PME - Partial Mesorectal Excision; W&W, watch and wait
** Criteria for decision pro TNT, see chapter 6.1.2.2 and chapter 6.1.2.3*

6.1.1 Stage I

Stage I includes T stages T1 and T2. A special subtype 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 low-risk 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 transanally as a microsurgical full-wall excision or as a direct tumor excision.

At this stage, neither preoperative nor postoperative radiotherapy or systemic cancer treatment further reduces 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. In this group and in all other T stages, the treatment standard is mesorectal excision with resection of the regional lymphatic drainage area, technically depending on the location of the carcinoma:

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

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

The therapeutic goal in stages II and III is curative. Recurrences also occur locally, but mainly systemically 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 lower pelvis, local recurrences of carcinomas in the lower and middle thirds of the rectum are particularly prone to complications. This justifies their prevention as a separate, important therapeutic goal. Preoperative radiochemotherapy or radiotherapy and quality-assured surgery can reduce the local recurrence rate to 5-10% [10]. Systemic perioperative cancer therapy also contributes to the reduction of the local recurrence rate, but is recommended primarily with the goal of preventing distant metastases [11].

6.1.2.1 Surgery - Stages II and III

In stage II and III, the primary therapy depends on the tumor location, see Figure 5. For carcinomas in the lower and middle third of the rectum, preoperative radiation or radiochemotherapy is recommended. For carcinomas in the upper third of the rectum, the benefit of radiotherapy is controversially discussed and treatment in analogy to colon cancer preferred, i.e. primary resection of the tumor, see Guideline Colon Cancer.

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

- Removal of the regional lymphatic drainage area with sampling and histologic workup of ≥ 12 lymph nodes.
- Appropriate safety distance to healthy tissue
- Respecting the intactness of the fascia of the mesorectum avoiding injuries during surgery.
- En-bloc resection of tumor-adherent organs
- Protection of the autonomic pelvic nerves

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

6.1.2.2 Radiotherapy - Stages II and III

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

Radiotherapy in the middle third can be omitted if the following findings are present: (i) tumor penetration depth into perirectal fat of 5mm or less (mrT3a and b situation) and lack of contact

with circumferential resection margin; (ii) no confirmed extramural vein invasion (EMVI negative); (iii) no evidence of lymph node metastases (for definition see chapter 5.2.1)).

Because of the special problem of local recurrences in rectal cancer, radiotherapy has been intensively evaluated within the framework of preoperative study concepts. Alternatives are short-course radiotherapy with high single doses (5 x 5 Gy) or conventionally fractionated 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 irradiation can induce significant tumor shrinkage, reduce local recurrence risk, improve disease-free survival, and increases survival rates according to results from randomized trials. Apart from tumor shrinkage, this also holds true for neoadjuvant short-course radiotherapy. In patients with large locally advanced tumors where tumor shrinkage is the therapeutic goal, combined radiochemotherapy or TNT is therefore recommended because of its higher potential to shrink these tumors. In about 10-15% of patients, complete pathohistological remission is achieved after conventional long-course neoadjuvant radiochemotherapy.

Adjuvant (postoperative) radiotherapy alone has no significant impact on disease-free survival or 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 treatment approach after successful primary radiochemotherapy are summarized in chapter 6.1.2.4.

6.1.2.3 Radiochemotherapy and "total neoadjuvant therapy" - stages II and III

Compared to preoperative conventional fractionated radiotherapy alone, combined radiochemotherapy leads to higher pathohistological remission rates and improved locoregional control. It was also superior to postoperative radiochemotherapy in terms of local recurrence rates in the AIO/ARO/CAO-04 trial. 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 in combined radiochemotherapy, with a low rate of side effects. Administration of 5-fluorouracil as a continuous infusion during radiotherapy is more effective than bolus therapy. Modulation of 5-FU metabolism by folinic acid did not improve long-term outcomes. Perioperative administration of capecitabine is noninferior to 5-FU and resulted in a significant improvement in disease-free survival in one study. According to results of a meta-analysis, the results of randomized trials combining 5-FU or capecitabine with oxaliplatin during radiotherapy can be summarized as follows: (i) gastrointestinal toxicity significantly increased, hematotoxicity was comparable; (ii) DFS slightly but significantly improved (HR 0.90, 95% CI 0.81 - 0.99); (ii) a lower rate of distant metastases was reported. According to data from another meta-analysis, the clinically moderate benefit is particularly observed in younger patients < 60 years of age. There was no increase in R0 resection rates or chance of sphincter preservation in any of the trials on the addition of oxaliplatin to neoadjuvant radiochemotherapy. Therefore, a combination of fluoropyrimidines with oxaliplatin is not generally recommended for neoadjuvant radiochemotherapy, but may be considered in younger patents [10].

With regard to perioperative chemotherapy, until recently a distinction was only made between the application of chemotherapy in the context of radiochemotherapy (primarily as a radiosensitizer) and the administration of chemotherapy as adjuvant therapy after radiochemotherapy and TME surgery. As a further therapeutic principle, especially for tumors with stages unfavorable from a tumor biology point of view and/or if organ preservation is intended, the so-called "total neoadjuvant therapy" (TNT) should be considered. This means a prolongation of neoadju-

vant therapy by usually 3- to 4.5-months of chemotherapy. It can be administered after or before radio- or radiochemotherapy (as so-called induction or consolidation chemotherapy).

In several randomized trials, TNT showed a significant benefit for disease-free survival, especially for patients whose tumors had "high-risk characteristics" (RAPIDO trial criteria): (i) T4 tumors, (ii) tumors with / of mesorectal resection margin, (iii) EMVI positivity, (iv) N2 status, and (v) enlarged lateral lymph nodes [12].

The optimal design of a TNT is still subject to clinical studies. The question of which (radiotherapy) regimen should be used when organ preservation is intended is currently being investigated in the ACO/ARO/AIO-18-1 trial.

According to multidisciplinary recommendations of working groups of the German Cancer Society, the following principles can be applied in therapy planning: (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, with consolidation chemotherapy preferred according to data from the CAO/ARO/AIO-12 and OPRA trials if the therapeutic goal is to achieve the highest possible rate of clinical complete remission (cCR). Chemotherapy should be given using FOLFOX or CapOx; the benefit of adding irinotecan (such as in the FOLFIRINOX regimen) has not been proven.

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, complete clinical remissions were detectable in all 14 patients evaluable to date after six months of primary dostarlimab therapy. During the so far short median follow-up, no case of local recurrence had occurred. Imune checkpoint inhibitors have not yet been approved for the treatment of locally advanced MSI-H rectal cancer. If such an organ preservation approach is used, clinical controls should be scheduled after 3 and 6 months of therapy. The post-treatment watch-and-wait strategy should be performed as follows: 3-4 monthly sigmoidoscopy, digital-rectal examination and quality-assured rectal MRI for the first two years, then (years 3-5) every six months. Distant metastases should be excluded at least once per year by whole-body CT [13].

Data and recommendations on the approach after successful primary radiochemotherapy alone are summarized in chapter 6.1.2.4.

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

While the beneficial impact of adjuvant chemotherapy for rectal cancer after surgical resection without preoperative radiotherapy is verified (see Cochrane meta-analysis), adjuvant chemotherapy *par principe* after combined radiochemotherapy or short-term radiotherapy and TME surgery is controversial. A meta-analysis primarily examining trials with bolus application of 5-FU failed to demonstrate a benefit for disease-free or overall survival. While this meta-analysis is methodologically problematic, it provides further evidence that bolus regimens should no longer be used. Adjuvant chemotherapy with optimal fluoropyrimidine regimens should be offered after neoadjuvant radiochemotherapy. Capecitabine, for example, has a good data background in this setting. At present, available study results do not allow us to make firm differential therapeutic recommendations based on the degree or extent of tumor response to neoadjuvant radiochemotherapy. A general use of oxaliplatin in adjuvant chemotherapy cannot be justified from current trial data. Younger patients with an increased risk of recurrence (ypStage III) should be counseled about the possibility of additional oxaliplatin therapy [10]. The duration of perioperative chemotherapy should add up to about 6 months in total, e.g., by an additional 5-6 adjuvant cycles of capecitabine or 8 cycles of FOLFOX. Patients after primary

resection, who have not received neoadjuvant radiochemotherapy, can be given adjuvant chemotherapy (i.e., 3 or 6 months depending on the risk profile, see colon cancer) in analogy to colon carcinoma according to data from the SCOT study.

In patients with cancer localization in the upper third of the rectum, who have not received preoperative radiation or radiochemotherapy, a procedure analogous to that for colon carcinoma is recommended in stages II and III. Criteria for adjuvant chemotherapy in stage II and III are compiled in the guideline colon carcinoma.

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].

6.1.2.5 Non-surgical management after clinical complete remission

If a complete clinical remission (cCR), confirmed by quality-assured imaging procedures and experienced investigators, has been achieved after radiochemotherapy or TNT, surgery can be omitted. The database for this approach has been validated for a European patient population, but the follow-up of patients is relatively short. Therefore, the inclusion of these patients in studies or registries is still recommended in order to obtain better long-term data.

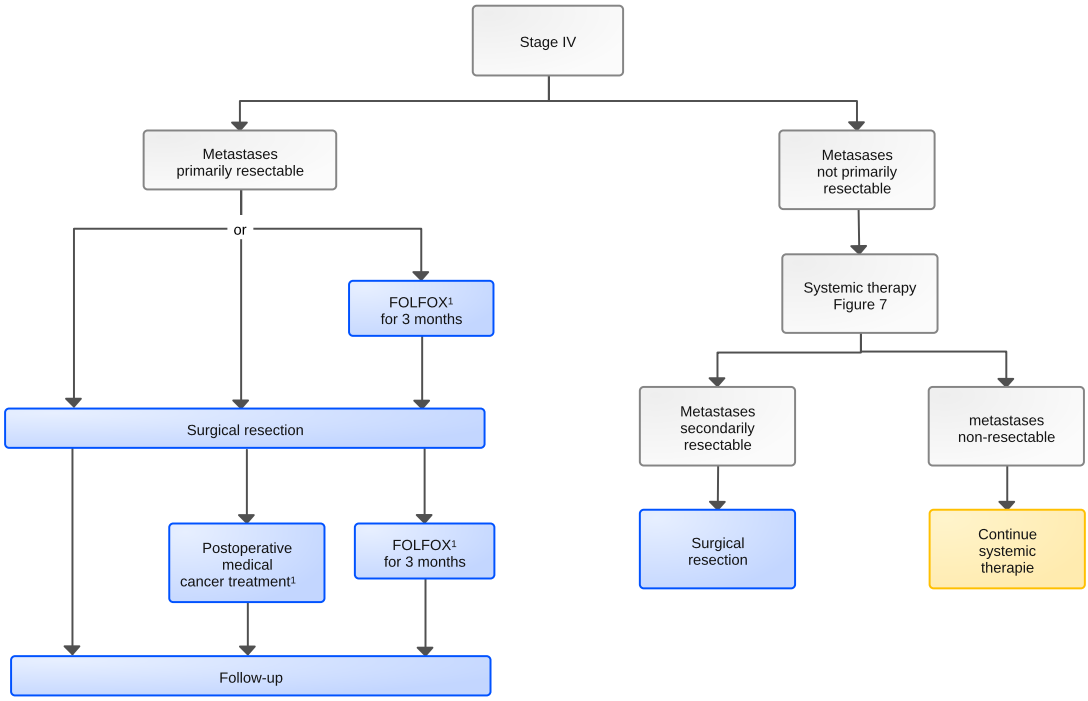
At this point in time, the waiver of surgical resection in case of cCR remission documented by experienced investigators (endoscopy, MRI, clinical digital-rectal examination) will be limited to patients with a reliable adherence to close follow-up examinations. A blind or step biopsy of the rectal mucosa to document a cCR is just as unnecessary as the performance of an endosonography.

Detailed patient information and adherence to stringent follow-up over at least 5 years is required. The optimal design of follow-up (or "watch & wait", respectively) is the subject of current studies; the following follow-up procedure can be recommended according to an international expert statement [17]: follow-up for 5 years after documentation of cCR; for three years, 3-monthly CEA, then six-monthly; for two years, 3-monthly digital-rectal examination, MRI, and endoscopy, then six-mothly; for 5 years, CT thorax/upper abdomen at months 6, 12, 24, 36, 48 and 60.

6.1.4 Stage IV

The therapeutic goal of colorectal cancer stage IV patients used to be considered strictly palliative. In the past 20 years, it has become evident that up to 25% of patients with synchronous hepatic metastases may have a curative potential [18, 19]. A curative potential also exists in patients with hepatic recurrence or isolated pulmonary metastasis (see chapter 6.1.4.1 and chapter 6.1.4.2), see Figures 6 and 7.

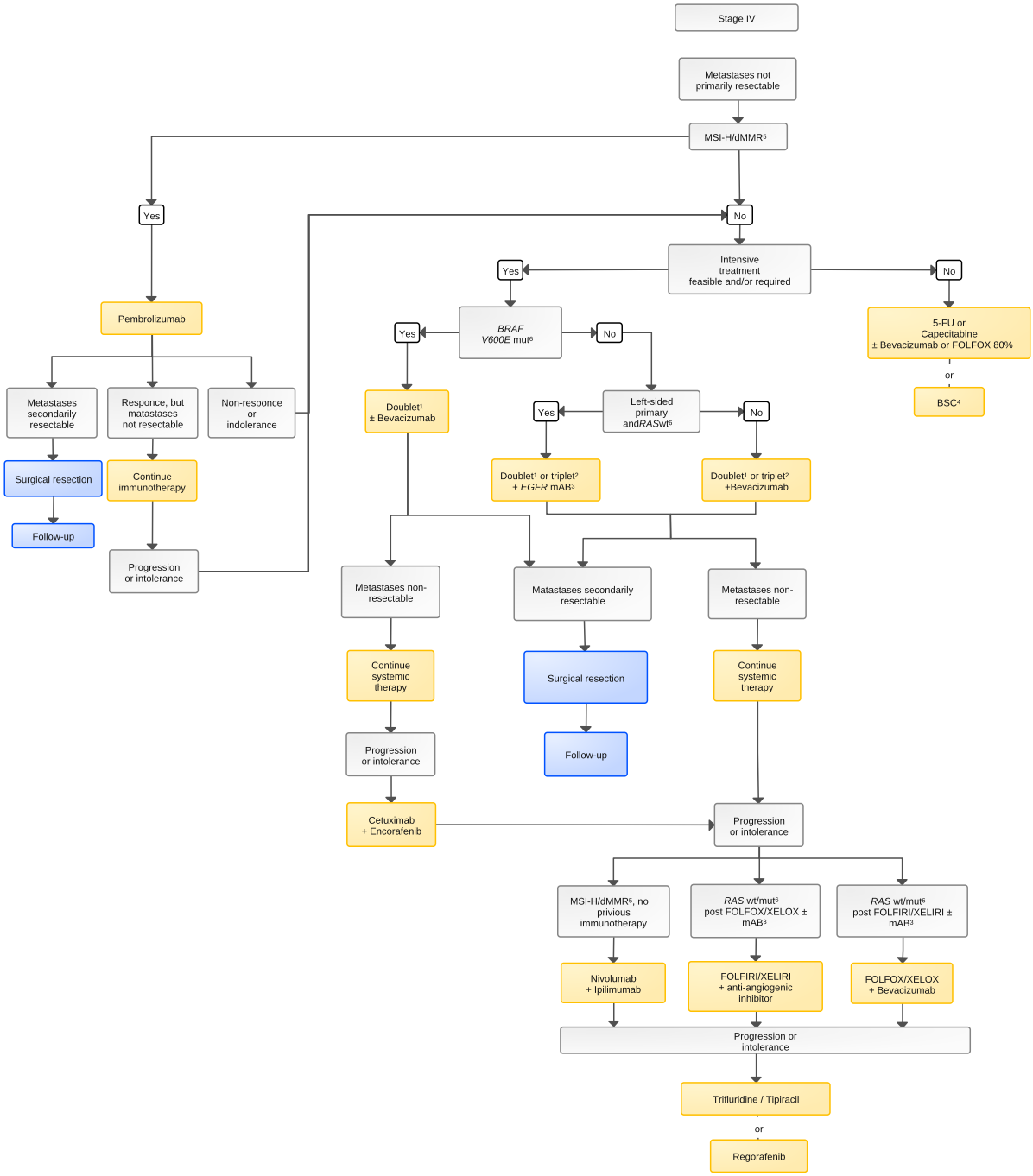
Figure 6: Treatment structure in patients with rectal cancer stage IV



Legend:
[1] the importance of perioperative systemic cancer treatment is still not clear, see also chapter 6.1.4.1.4.

In previous versions of the S3 and 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 is abandoned in favor of an algorithm that takes into account patient-individual characteristics, therapy goals, and molecular factors (MSI, RAS and BRAF mutations, etc.) in different hierarchical levels as criteria for treatment selection [20]. These classifications allow a pragmatic orientation, but their criteria have not been prospectively validated. In particular, the location of the primary (so-called sidedness) should be considered as an important predictive criterion for the use of anti-EGFR antibodies.

Figure 7: Treatment structure in stage IV rectal cancer with primary unresectable metastases



Legend:
[1] Doublet – combination of fluoropyrimidine plus either oxaliplatin or irinotecan;
[2] Triplet – combination of fluoropyrimidine plus oxaliplatin and irinotecan;
[3] EGFR mAB – anti-Epidermal Growth Factor Receptor monoclonal antibody;
[4] BSC – Best supportive care;
[5] MSI-H/dMMR – microsatellite instability-high/deficient DNA mismatch repair;
[6] mut – mutant; wt – wild-type

6.1.4.1 Stage IV with resectable metastases

6.1.4.1.1 Resectability

The 5-year-disease-free survival rate of patients with resectable liver or lung metastases may reach 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 liver metastases from colorectal carcinoma, 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 5, which is based on data from 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 contraindications. Recent retrospective analyses show that these criteria are also valid for resection after perioperative chemotherapy [22].

Table 5: Risk score in patients with liver metastasis [19].

• 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 %** [15, 16]
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 presented in chapter 6.2.1.2.

6.1.4.1.2 Resection of liver metastases

Resection of metastases is a central 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 vessels
- No hepatic insufficiency, no liver cirrhosis Child B or C
- ECOG perfomance score 0 - 2
- No severe comorbidity

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

The standard of care for local therapy of liver metastases is open 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 radiation. 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.

6.1.4.1.3 Resection of lung metastases

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

- Exclusion of unresectable extrapulmonary metastases
- R0 resection possible
- Adequate pulmonary residual volume 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 SBRT).

6.1.4.1.4 Perioperative drug therapy of primary 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. The possibility of treatment within the framework of a study should be reviewed.

Based on data from the phase III EORTC 40983 intergroup study perioperative therapy with FOLFOX, three months each pre- and postoperatively, can be used as drug-targeted 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 coordination.

If preoperative chemotherapy has not been given, it can be given postoperatively, preferentially using a fluoropyrimidine and 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 the overall small effects on survival parameters. Recent data from a randomized Japanese trial showed an improvement in progression-free survival with 6 months of chemotherapy with FOLFOX, but no benefit in terms of overall survival [23].

6.1.4.2 Conversion therapy in patients with potentially resectable metastases

The number of patients with potentially resectable metastases can be increased by a so-called conversion therapy. The aim of this therapy is to achieve technical resectability by downsizing the metastases. Accordingly, treatment protocols with high response rates and the chance of greater volumetric shrinkage of metastases are recommended. Two-drug combinations plus antibodies or three-drug combinations ± antibodies used in the palliative setting have been tested in randomized and non-randomized phase II studies, see chapter 6.2.3 and chapter 6.1.4.3. The UNICANCER PRODIGE 14 trial, which randomized doublet versus triplet, each + mAb (depending on *RAS* status) as conversion therapy, found no statistically significant

improvement of R0/R1 resection rates; disease-free and overall survival were also not significantly different [24] In the smaller OLIVIA trial (80 patients) [25] with more clearly defined and stricter inclusion criteria regarding irreversibility, there was a benefit for triplet therapy + bevacizumab versus FOLFOX + bevacizumab. These results were recently confirmed in a Dutch study presented at ASCO 2022 for the group of RAS or BRAF mutated or right-sided tumors [26]. In this respect, it should be decided on a case-by-case basis in the tumor board whether triplet + mAb or doublet + mAb should be used. In the randomized phase II VOLFI study, the addition of panitumumab to a dose-reduced chemotherapy triplet did lead to high remission rates and improved resection rates, mainly in younger patients [27]. However, the randomized phase III "Triplete" trial first presented at ASCO 2022 showed no benefit in terms of resection rates for FOLFOXIRI + panitumumab therapy compared with a doublet + panitumuab [28].

In studies with non-selected patients, between 5 and 25%, and up to 40% in the case of exclusive liver metastasis, of initially unresectable patients subsequently underwent secondary resection. A preoperative systemic treatment duration of 2 to 4, possibly up to 6 months, depending on tumor response, is recommended. After achieving technical operability, surgery should be performed as soon as possible, not after maximum remission has been achieved. By this, increasing liver toxicity resulting in a higher surgical morbidity can be avoided. In patients undergoing conversion therapy, restaging should be performed every 8-10 weeks with discussion of CT or MRI images in the multidisciplinary tumor board. Surgery should be performed 4 weeks after the end of preoperative drug therapy, and after 6 weeks following bevacizumab-containing therapy. The value of continuing chemotherapy after R0 or R1 resection, in terms of completing chemotherapy for a total of 6 months, is not proven. Important factors also include toxicity of previous therapy and comorbidity, as well as histopathologic response. The additional value of locally effective therapy methods in R1 resection is the subject of clinical studies.

6.1.4.3 Therapy of primary non-resectable metastases

Despite effective primary therapy and progress in adjuvant treatment, distant metastases emerge in about 35-45% of patients. The relapse rate is highest in the first two years after initial diagnosis, while relapses after more than 5 years are rare. In a subgroup of patients, a cure is also possible in this situation, see Chapter 6.1.4.1 "Stage IV with resectable metastases" and chapter 6.1.4.2 "Stage IV with metastases after conversion therapy".

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.

6.1.4.3.1 Induction therapy

The goals of induction therapy depend on disease status (see chapter 6.1.4) 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 studies overall survival. The combination of chemotherapy and antibodies results in a median progression-free survival of about 10 months and a median overall survival of about 30 months [29, 30]. 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 have been tested in combination with doublet chemotherapy, see chapter 6.1.4.3.1.1. Data on triplet chemotherapy with cetuximab or panitumumab were available until recently from smaller randomized trials with selected patients. The Triplete trial has recently shown that the combination with a triplet is not superior to the combination with a doublet [28]. In combination with bevacizumab, triplet chemotherapy results in longer progression-free survival (PFS) than a doublet + bevacizumab [30]. Prolongation of the time to progression, thus possibly to symptoms and start of further intensive therapy, is also a clinically relevant therapeutic goal for patients in a clearly palliative setting.

A meta-analysis did not confirm a better efficacy of triplet chemotherapy compared to doublet for patients with *BRAF V600E* mutated tumors [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% patients per line of therapy.

6.1.4.3.1.1 RAS wild type (RASwt)

Intact signaling through the *RAS* signaling cascade is a prerequisite for the efficacy of the anti-EGFR antibodies cetuximab and panitumumab. Patients with tumors that have a mutation in one of the *RAS* genes (i.e., *KRAS* exon 2-4 and/or *NRAS* exon 2-4) should not be treated with an anti-EGFR antibodiy.

The question of whether an anti-EGFR antibody should be used primarily in patients with *RAS* wild-type was investigated in randomized trials. The sequence doublet + cetuximab versus doublet + bevacizumab was used first-line, including a protocol-defined crossover to the other antibody in case of relapse or refractory disease. The first study [29] found significantly longer survival for the sequence cetuximab in the first line followed by bevacizumab in the second

line, with a hazard ratio of 0.7. In a second study [33], this difference could not be confirmed, see also 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 the right-sided localization of the primary tumor, i.e., proximal/oral to the Flexura coli sinistra, versus the left-sided localization, i.e., distal/aboral, on treatment outcomes in patients with a RASwt tumor was analyzed [20]. On one hand, patients with a right-sided primary tumor had a significantly worse prognosis with regard to overall survival. On the other hand, patients with a left-sided primary showed a significant benefit from therapy 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 right-sided primary tumors did not benefit from the administration of anti-EGFR antibodies in terms of progression-free and overall survival despite *RAS*wt. *The* combination of anti-EGFR antibodies and combination chemotherapy is currently recommended for first-line treatment of patients with a *RAS*wt tumor and a primary tumor in the left-sided colon. In patients with *RAS*wt and a right-sided primary, there is no benefit of an anti-EGFR antibody over chemotherapy or bevacizumab combination in first-line therapy [34].

6.1.4.3.1.2 RAS mutations

In patients with *RAS* mutations, bevacizumab should be used as a monoclonal antibody in first-line therapy. Combination of chemotherapy with bevacizumab resulted in significant improvements in remission rates and progression-free survival compared with chemotherapy alone, and in some studies also in overall survival. Combination with a triplet (5-FU, folinic acid, irinotecan, oxaliplatin) results in slightly higher remission rates and significant prolongation of progression-free survival compared with a doublet (5-FU, folinic acid, irinotecan) [24].

6.1.4.3.1.3 MSI high/dMMR

For patients with microsatellite instable tumors, the KEYNOTE-177 study compared pembrolizumab to different "standard of care" regimens. A clinically meaningful and significant prolongation of PFS (hazard ratio 0.6 (0.45 - 0.80)) with significantly reduced treatment-related toxicity (22% instead of 6% grade 3-4 adverse events) was demonstrated. Overall survival (as a secondary endpoint) was prolonged clinically relevant, but not statistically significant (with high rates of cross-over to checkpoint inhibitors). Pembrolizumab has been approved by the EMA for the treatment of metastatic colorectal tumors harboring MSI-H since February 2021. Analysis of MSI can be performed by immunohistochemistry [35].

6.1.4.3.2 Maintenance therapy

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

In randomized trials, post-doublet induction (with oxaliplatin plus bevacizumab) maintenance therapy using a fluoropyrimidine + bevacizumab resulted in a statistically significant prolongation of time to tumor progression compared with 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 feasible only in a minority of patients. Nevertheless, re-induction therapy should be considered in the further course of therapy, see chapter 6.1.4.3.3.

A detailed discussion of the three large randomized trials on maintenance therapy with bevacizumab can be found in the AIO statement [36].

As all these studies used oxaliplatin-containing induction therapies, it is unclear whether the results described are 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.

6.1.4.3.3 Second-, third- and fourth-line therapy

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

- After therapy with first-line irinotecan-based 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 setting, FOLFOX+ bevacizumab should be used in the second-line setting.
- 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 results in a statistically significant prolongation of survival.
- In second-line therapy, the combination of the antiangiogenic antibody ramucirumab with FOLFIRI leads to prolonged survival in patients treated with first-line oxaliplatin- and bevacizumab-based therapy.
- Ramucirumab or aflibercept should be preferred in patients with only a short first-line PFS on bevacizumab-containing therapy.
- Patients with *RAS* wild-type, who have not received anti-EGFR antibody 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 Colon cancer treatment protocols. This includes switching cytostatic agents.
- Cetuximab and panitumumab should preferably be used in first-line therapy. When used for the first time in chemotherapy-refractory patients, both agents are equieffective. The use of panitumumab after failure of cetuximab-based regimens is no standard of care, and this also applies vice versa. Re-challenge of cetuximab or panitumumab should only be performed in patients with no detectable *RAS* and/or *BRAF* mutations on 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 results in a prolongation of progression-free and overall survival [49].

- After pretreatment with chemotherapy, the combination of nivolumab and ipilimumab can be used in patients with MSI-high tumors in accordance with current approval [39].
- When all established chemotherapies and monoclonal antibodies fail, the oral multikinase inhibitor regorafenib or trifluridine/tipiracil prolong overall survival.
- For patients with *HER2* positivity (especially after anti-EGFR therapy and in left-sided tumors), there is a treatment option with trastuzumab/lapatinib, trastuzumab/pertuzumab or trastuzumab-deruxtecan. However, approvals of these drugs for this treatment setting are pending.
- Patients whose tumor has an *NTRK* fusion can be treated with the tyrosine kinase inhibitors larotrectinib or entrectinib in accordance with their 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.

6.1.4.3.4 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. Among these, intra-arterial liver perfusion was compared with intravenous therapy with 5-FU/folinic acid. It led to higher remission rates, but no 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. However, 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 the multidisciplinary tumor board, taking into account the overall treatment plan and the potential, sometimes considerable, toxicity.

6.1.4.3.5 Peritoneal carcinomatosis

The median survival of patients with proven peritoneal carcinomatosis is significantly worse than for other metastatic manifestations. Nevertheless, in the PRODIGE-7 trial, the combination of systemic chemotherapy and cytoreductive surgery (CRS) showed a median overall survival of 41 months in patients with isolated peritoneal carcinomatosis. However, in this randomized trial (CRS +/- HIPEC), the added benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin could not be demonstrated [42]. In this respect, HIPEC with oxaliplatin after CRS currently cannot be recommended. Cytoreductive surgery alone is considered a standard treatment option at specialized centers. Criteria for decision-making are good general condition, localized and exclusively peritoneal metastasis (peritoneal carcinomatosis index PCI $\leq$ 15), and potential CC0 resectability. Regarding the indication for HIPEC, there is currently no consensus;

it should be performed either in the context of clinical trials or as an individual decision using mitomycin C over 60-90 minutes.

6.2 Treatment modalities

6.2.1 Surgery

6.2.1.1 Primary tumor

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

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

6.2.1.2 Surgical approach

The standard is the open surgical technique. An alternative is laparoscopic surgery. The advantage of open surgery is the shorter operating time and the shorter learning curve of surgeons. Significant advantages of laparoscopic surgery are better cosmetic outcome and earlier restorative diet. In the context of fast-track surgery applied to 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. For obstructive carcinomas, two-step surgery can be performed with creation of protective stoma or one-step subtotal colectomy is feasible. In patients with hereditary disease, the nature of the genetic burden, previous operations, and the overall treatment concept must be considered.

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

6.2.2 Radiotherapy

Radiotherapy leads to a significant reduction in local recurrence rates. Standard options are preoperative radiotherapy with 25 Gy over 5 days, or the combination of radiotherapy (50.4 Gy) with a fluoropyrimidine, see chapter 6.1.2.2.

Acute side effects of short-course, preoperative radiotherapy documented in larger randomized trials were diarrhea (20%), dermatitis (5%), cystitis (2%), and postoperative impairment of wound healing [44]. Long-term side effects included compromised anal sphincter function with increased stool frequency (20 vs 8%) and incontinence (50 vs 24%) [45]. In the randomized

Dutch trial, the rate of secondary neoplasias at 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 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.

6.2.3.2 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.

6.2.3.3 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].

6.2.3.4 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 oxali-

platin. 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. 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.

6.2.3.5 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].

6.2.3.6 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].

6.2.3.7 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%).

6.2.3.8 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.

6.2.3.9 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%).

6.2.3.10 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.

6.2.3.11 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.

6.2.3.12 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).

6.2.3.13 Ramucirumab

Ramucirumab is a human IgG1 antibody that specifically binds to vascular endothelial growth factor receptor-2 (VEGFR2). It is approved for second-line treatment of patients with adenocarcinoma of the stomach or gastroesophageal junction. In patients with metastatic colorectal can-

cer 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.

6.2.3.14 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.

6.2.3.15 S1 (Tegafur plus Gimeracil and Oteracil)

In 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.

6.2.3.16 TAS-102

TAS-102 is a new 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 taken 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.

7 Rehabilitation

Surgery, radiotherapy and systemic therapy of patients with colorectal carcinoma can lead to therapy sequelae of varying severity, which require targeted rehabilitative measures in the somatic and psychosocial areas. The goals of rehabilitation are training in stoma care, regaining continence, promoting regular physical activity, nutritional training, gaining information on non-drug therapy of chemotherapy-induced peripheral polyneuropathy, dealing with and overcoming fear of recurrence and other psycho-oncological impairments as well as professional reintegration.

Patients should be informed at an early stage about the possibilities of outpatient and inpatient rehabilitation measures as well as other claims arising from social law. With regard to the rehabilitation clinic, the patient's wishes should be taken into account (§9 SGB IX). Nevertheless, a recommendation for a clinic with an oncological focus should be made in order to ensure optimal rehabilitation success.

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8 Follow-up

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 colorectal carcinoma, intensive, structured follow-up can lead to prolonged survival [47].

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 6.

Table 6: Structured follow-up of patients with 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 ultrasound		X		X		X		X				X		X		X
CT Abdomen / Thorax				**X** X				**X** X				**X** X		X		X
Colonoscopy		X		X **X** X										**X** X		X

Legend:
X recommendations in Germany;
X recommendations in Austria;
X recommendations in Switzerland

9 References

1. Wittekind C, Meyer HJ. TNM Klassifikation maligner Tumoren, 7. Auflage. Wiley-VCH, Weinheim 2010

2. Schmoll HJ, Van Cutsem E, Stein A et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 2012;23:2479-2516. DOI:10.1093/annonc/mds236
3. Zentrum für Krebsregisterdaten im Robert Koch-Institut: Datenbankabfrage mit Schätzung der Inzidenz, Prävalenz und des Überlebens von Krebs in Deutschland auf Basis der epidemiologischen Landeskrebsregisterdaten. Mortalitätsdaten bereitgestellt vom Statistischen Bundesamt. www.krebsdaten.de/abfrage, Letzte Aktualisierung: 21.12.2021, Abrufdatum: 01.04.2022
4. Joinpoint Regression Program, Version 4.9.0.0 - March 2021; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.
5. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19:335-351
6. Lynch HA, Gatalica Z, Knezetic J. Molecular genetics and hereditary colorectal cancer: resolution of the diagnostic dilemma of hereditary polyposis colorectal cancer, Lynch syndrome, familial colorectal cancer type X and multiple polyposis syndromes. ASCO Educational Booklet, 2009. http://www.asco.org/ASCOv2/Education+%26+Training/Educational+Book?&vmview=edbk_detail_view&confID=65&abstractID=39
7. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomized trials. Lancet Oncol 2012;13:518-527. DOI:10.1016/S1470-2045(12)70112-2,
8. AWMF S3 - Leitlinie Kolorektales Karzinom 2019 https://www.awmf.org/uploads/tx_szleitlinien/021-007oll_s3_kolorektales-karzinom-krk_2019-01
9. Balmana J, Castells A, Cervantes A. Familial colorectal cancer risk: Rectal cancer. ESMO clinical practice guidelines. Ann Oncol 2010 Suppl 5;21:v78-v81. DOI:10.1093/annonc/mdq169
10. Ghadimi M, Rödel C, Hofheinz R et al. Multimodal treatment of rectal cancer. Dtsch Arztebl Int 2022 Aug 22
11. Hofheinz RD. Locally advanced rectal cancer - Standards and new multimodality treatment concepts. Dtsch Med Wochenschr 2021;146:1478-1487. DOI:10.1055/a-1391-5302
12. Bahadoer RR, Dijkstra EA, van Etten B et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29-42. DOI:10.1016/S1470-2045(20)30555-6
13. Cercek A, Lumish M, Sinopoli J et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022;386:2363-2376. DOI:10.1056/NEJMoa2201445
14. Wong GG, Ha V, Chu MP et al. Effects of proton pump inhibitors on FOLFOX and CapeOx regimens in colorectal cancer. Clin Colorectal Cancer 2019;18:72-79. DOI:10.1016/j.clcc.2018.11.001
15. Chu MP, Hecht JR, Slamon D et al. Association of proton pump inhibitors and capecitabine efficacy in advanced gastroesophageal cancer: secondary analysis of the TRIO-013/LOGiC randomized clinical trial. JAMA Oncol 2017;3:767-773. DOI:10.1001/jamaoncol.2016.3358
16. Sun J, Ilich AI, Kim CA et al. Concomitant administration of proton pump inhibitors and capecitabine is associated with increased recurrence risk in early stage colorectal cancer patients. Clin Colorectal Cancer 2016;15:257-263. DOI:10.1016/j.clcc.2015.12.008
17. Fokas E, Appelt A, Glynne-Jones R et al. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer. Nat Rev Clin Oncol 2021;18:805-816. DOI:10.1038/s41571-021-00538-5

18. Alberts SR. Update on the optimal management of patients with colorectal liver metastases. Crit Rev Oncol Hematol 2012;8459-8470. DOI:10.1016/j.critrevonc.2012.02.007

19. van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-1422. DOI:10.1093/annonc/mdw235

20. Arnold D, Lueza B, Douillard JY et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomised trials. Ann Oncol 2017;28:1713-1729. DOI:10.1093/annonc/mdx175

21. Fong Y, Fortner J, Sun RL et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer, analysis of 1001 consecutive cases. Ann Surg 1999;230:309-318. DOI:10.1097/00000658-199909000-00004

22. Merkel S, Bialecki D, Meyer T et al. Comparison of clinical risk scores predicting prognosis after resection of colorectal liver metastases. J Surg Oncol 2009;100:349-357. DOI:10.1002/jso.21346

23. Kanemitsu Y, Shimizu Y, Mizusawa J et al. JCOG Colorectal Cancer Study Group. Hepatectomy followed by mFOLFOX6 versus hepatectomy alone for liver-only metastatic colorectal cancer (JCOG0603): a phase II or III randomized controlled trial. J Clin Oncol 2021;39:3789-3799. DOI:10.1200/JCO.21.01032

24. Ychou M, Rivoire M, Thezenas S et al. Chemotherapy (doublet or triplet) plus targeted therapy by RAS status as conversion therapy in colorectal cancer patients with initially unresectable liver-only metastases. The UNICANCER PRODIGE-14 randomised clinical trial. Br J Cancer 2022;126:1264-1270. DOI:10.1038/s41416-021-01644-y

25. Gruenberger T, Bridgewater J, Chau I et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann Oncol 2015;26:702-708. DOI:10.1093/annonc/mdu580

26. Punt CJA, Bond MJG, Bolhuis K et al. FOLFOXIRI + bevacizumab versus FOLFOX/FOLFIRI + bevacizumab in patients with initially unresectable colorectal liver metastases (CRLM) and right-sided and/or RAS/BRAFV600E-mutated primary tumor: Phase III CAIRO5 study of the Dutch Colorectal Cancer Group. J Clin Oncol 40, no. 17_suppl (June 10, 2022) LBA3506-LBA3506.

27. Modest DP, Martens UM, Riera-Knorrenschild J et al. FOLFOXIRI plus panitumumab as first-line treatment of RAS wild-type metastatic colorectal cancer: the randomized, open-label, phase II VOLFI Study (AIO KRK0109). J Clin Oncol 2019;37:3401-3411. DOI:10.1200/JCO.19.01340

28. Rossini D, Antoniotti C, Lonardi S et al. Upfront modified fluorouracil, leucovorin, oxaliplatin, and irinotecan plus panitumumab versus fluorouracil, leucovorin, and oxaliplatin plus panitumumab for patients with RAS/BRAF wild-type metastatic colorectal cancer: the phase III TRIPLETE study by GONO. J Clin Oncol 2022 Jun 6:JCO2200839. DOI:10.1200/JCO.22.00839

29. Heinemann V, von Weikersthal LF, Decker T et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-1075. DOI:10.1016/S1470-2045(14)70330-4

30. Cremolini C, Loupakis F, Antoniotti C et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015;16:1306-1315. DOI:10.1016/S1470-2045(15)00122-9

31. Cremolini C, Antoniotti C, Stein A et al. Individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublets plus bevacizumab as initial therapy of unresectable metastatic colorectal cancer. J Clin Oncol 2020;38: 3314-3324. DOI:10.1200/JCO.20.01225

32. Stintzing S, Heinrich K, Tougeron D, et al.: Randomized study to investigate FOLFOXIRI plus either bevacizumab or cetuximab as first-line treatment of BRAF V600E-mutant mCRC: The phase-II FIRE-4.5 study (AIO KRK-0116). J Clin Oncol 2021 39:15_suppl, 3502-3502. DOI:10.1200/JCO.2021.39.15_suppl.3502

33. Venook AP, Niedzwiecki D, Lenz HJ et al.: Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA 2017;317:2392-2401. DOI:10.1001/jama.2017.7105

34. Statement der AIO-KRK-Leitgruppe zur Wahl der Erstlinientherapie bei Pat. mit RAS Wildtyp: AIO-KRK-0306/FIRE-3-Studie und andere (aktuell: CALGB 80405, PEAK) https://www.aio-portal.de/stellungnahmen.html

35. André T, Shiu KK, Kim TW et al. KEYNOTE-177 investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med 2020;383:2207-2218. DOI:10.1056/NEJMoa2017699

36. Statement der AIO-KRK-Leitgruppe zur Bedeutung der „Maintenance“-Therapie (Erhaltungstherapie nach Induktion): AIO-KRK-0207-Studie und andere (SAKK 41-06, CAIRO-3) 30.06.2013. https://www.aio-portal.de/stellungnahmen.html

37. Modest DP, Karthaus M, Fruehauf S et al. Panitumumab plus fluorouracil and folinic acid versus fluorouracil and folinic acid alone as maintenance therapy in RAS wild-type metastatic colorectal cancer: the randomized PANAMA trial (AIO KRK 0212). J Clin Oncol 2022;40:72-82. DOI:10.1200/JCO.21.01332

38. Pietrantonio F, Morano F, Corallo S et al. Maintenance therapy with panitumumab alone vs panitumumab plus fluorouracil-leucovorin in patients with RAS wild-type metastatic colorectal cancer: a phase 2 randomized clinical trial. JAMA Oncol 2019;5:1268-1275. DOI:10.1001/jamaoncol.2019.1467

39. Overman MJ, Lonardi S, Wong KYM et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018;36:773-779. DOI:10.1200/JCO.2017.76.9901

40. Mocellin S, Pasquali S, Nitti D. Fluoropyrimidine-HAI (hepatic arterial infusion) versus systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer. Cochrane Database of Systemic Reviews 2009, CD007823, Issue 3. DOI:10.1002/14651858.CD007823.pub2

41. Wasan HS, Gibbs P, Sharma NK et al. FOXFIRE trial investigators; SIRFLOX trial investigators; FOXFIRE-Global trial investigators, van Hazel G, Sharma RA. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol 2017;18:1159-1171. DOI:10.1016/S1470-2045(17)30457-6

42. Quénet F, Elias D, Roca L et al. UNICANCER-GI Group and BIG Renape Group. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:256-266. DOI:10.1016/S1470-2045(20)30599-4

43. Bonjer HJ, Deijen CL, Abis GA et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372:1324-1332. DOI:10.1056/NEJMoa1414882

44. Wong RKS, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD002102. DOI:10.1002/14651858.CD002102.pub2
45. Folkesson J, Birgisson H, Pahlman L et al. Swedish Rectal Cancer Trial: Long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-5650. DOI:10.1200/JCO.2005.08.144
46. Van Gijn W, Marijnen CAM, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575-582. DOI:10.1016/S1470-2045(11)70097-3
47. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database of Systemic Reviews 2007, CD002200, Issue 1. DOI:10.1002/14651858.CD002200.pub2
48. Wörmann B, Bokemeyer C, Burmeister T et al. Dihydropyrimidine dehydrogenase testing prior to treatment with 5-fluorouracil, capecitabine, and tegafur: a consensus paper. Oncol Res Treat 2020;43:628-636. DOI:10.1159/000510258
49. Tabernero J, Grothey A, Van Cutsem E et al. Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. J Clin Oncol 2021;39:273-284. DOI:10.1200/JCO.20.02088

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.