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Colon Cancer

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

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

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AIO

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- Conflict of interests

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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 prognosis of patients with colon cancer depends on the stage of the disease at initial diagnosis and other biological risk factors. Therapy is determined by tumor stage. For locally confined colon cancer (stages I-III), surgery is the first line of treatment. In stage III and in subgroups of stage II, adjuvant chemotherapy reduces the risk of recurrence.

For the majority of patients in stage IV, the primary therapeutic goal is temporary tumor control, i.e., to alleviate or prevent symptoms and prolong survival. However, in a subgroup of patients, cure is also possible in this situation, especially through consequent surgery of metastatic lesions. For medical treatment in stage IV, different classes of agents (cytostatic drugs, monoclonal antibodies and molecular targeted drugs) are available. The optimal combination and sequence is the subject of current scientific efforts.

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

2 Basics

2.1 Definition and basic information

The 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 carcinoma. The ESMO Consensus proposes a new definition taking into account the different results from imaging diagnostic procedures [2]. Recommendations for the treatment of patients with localization of the carcinoma in the upper third of the rectum can be found in the Onkopedia guideline Rectal Cancer.

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

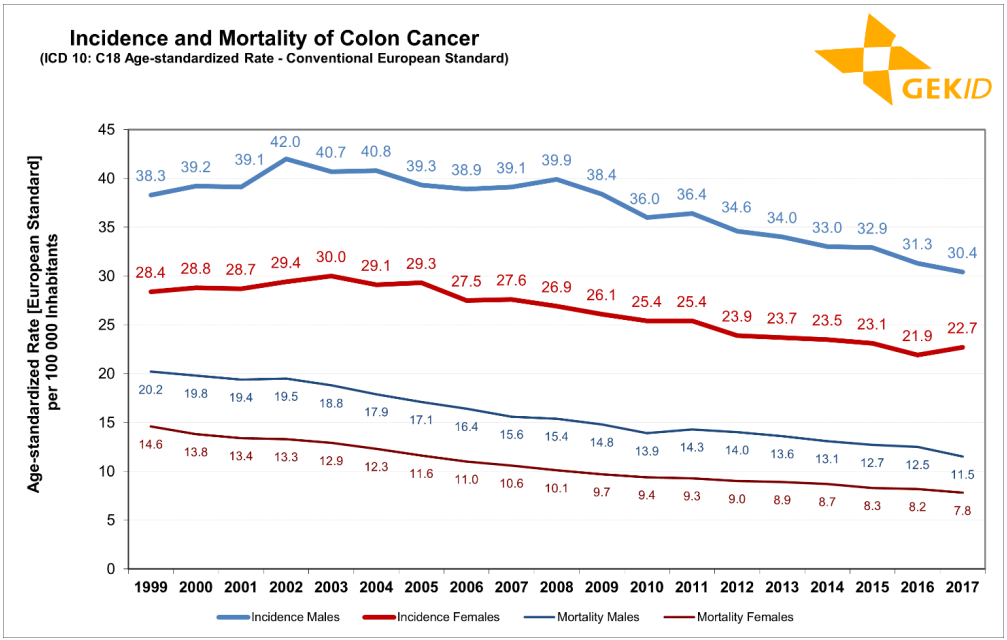
Colon and rectal cancer share many similarities in etiology and histology. However, they differ in the preoperative, surgical, and adjuvant treatment strategies. In the Onkopedia guidelines, they are handled separately. The topic of this guideline is adenocarcinoma of the colon. It accounts for 60-70% of all colorectal carcinomas in Germany.

2.2 Epidemiology

Nearly 40,000 new cases of malignant neoplasms of the colon are diagnosed annually in Germany (men: 20,000, women 18,500), and approximately 16,000 die of colorectal cancer each year [3]. The median age of onset is 74 years in men and 77 years in women.

The age-standardized disease rates - i.e., the probability of disease - as well as the age-standardized death rates - i.e., the probability of death - have been decreasing over the past 15 years in both men and women, see Figure 1. This is also confirmed by a joinpoint analysis [4, 5], according to which the rates in men decrease by an average of 2.0% per year, and those in women even by 2.2% (incidence).

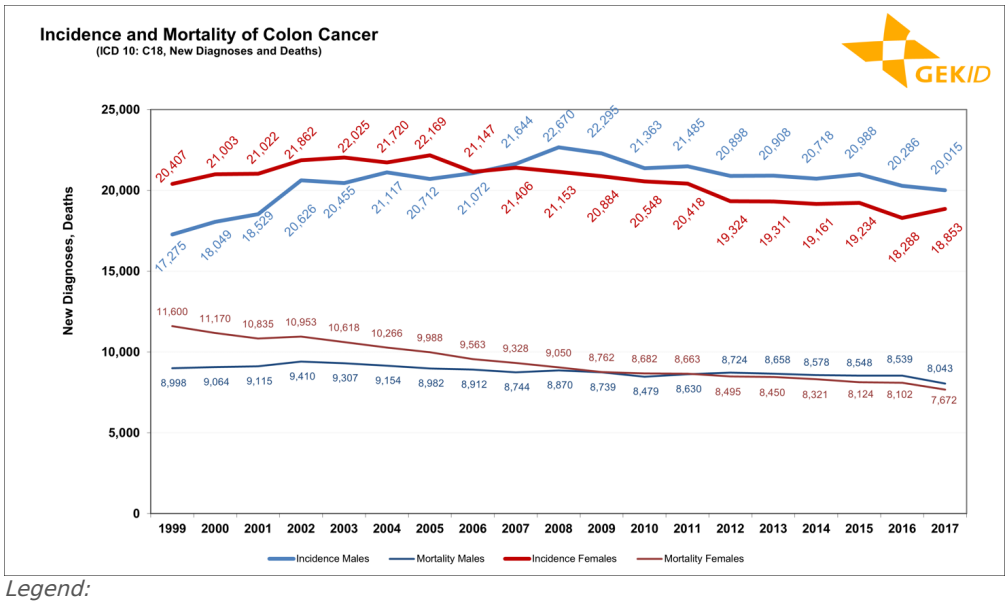
Figure 1: Estimated incidence and mortality of malignant neoplasms of the colon (ICD 10: C18) in Germany - age-standardized rates (old European standard).



Legend:
Source: Center for Cancer Registry Data, database query [3].

While age-standardized rates of first diagnoses are a measure of disease probability and largely independent of population structure, the number of new cases also depends on age structure and population size. Therefore, despite decreasing morbidity and mortality rates in an aging society, the number of new cases of colorectal cancer in men, as well as the number of deaths, has remained almost constant since 2003. For women, as for rates, decreasing numbers of cases are observed for incidence and mortality, but the decrease is smaller than for rates, at 1.3% per year (incidence) and 2.2% per year (mortality) (Figure 2). These epidemiologic data are consistent with those from Austria and Switzerland [7, 8]. In Austria, the age-standardized rate of new cases has decreased by 25% and the mortality rate even by nearly 30% in the past 10 years.

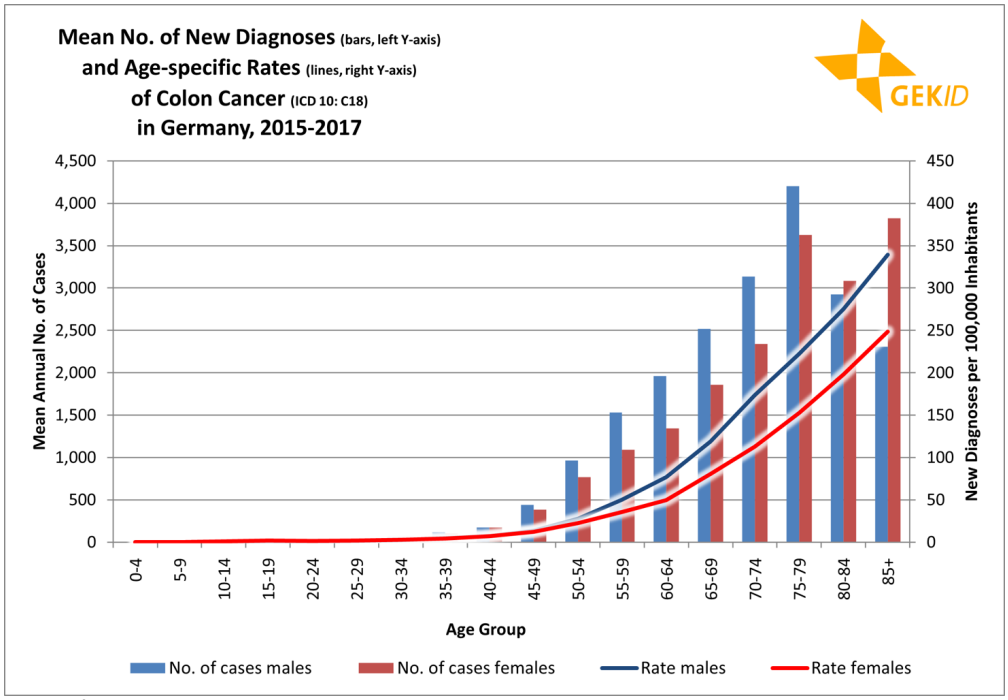
Figure 2: Estimated incidence and mortality of malignant neoplasms of the colon (ICD 10: C18) in Germany - number of cases



Legend:
Source: Center for Cancer Registry Data, database query [3].

Up to the age of 45, colon cancers are almost neglectable. From then on, the disease rates increase steadily in both sexes and reach their peak in the highest age group (85 years and older) (see Figure 3 [lines]). The rate for men is always higher than that for women from the age of 35. The number of cases is somewhat different due to the distribution of the population. The number of new cases increases up to the age group of 75 - 79 years (see Figure 3 [bars]). The highest number of new cases is observed in men over 75 years and in women over 85 years.

Figure 3: Age distribution of the incidence of malignant neoplasms of the colon (ICD 10: C18) - age-specific case numbers and rates.

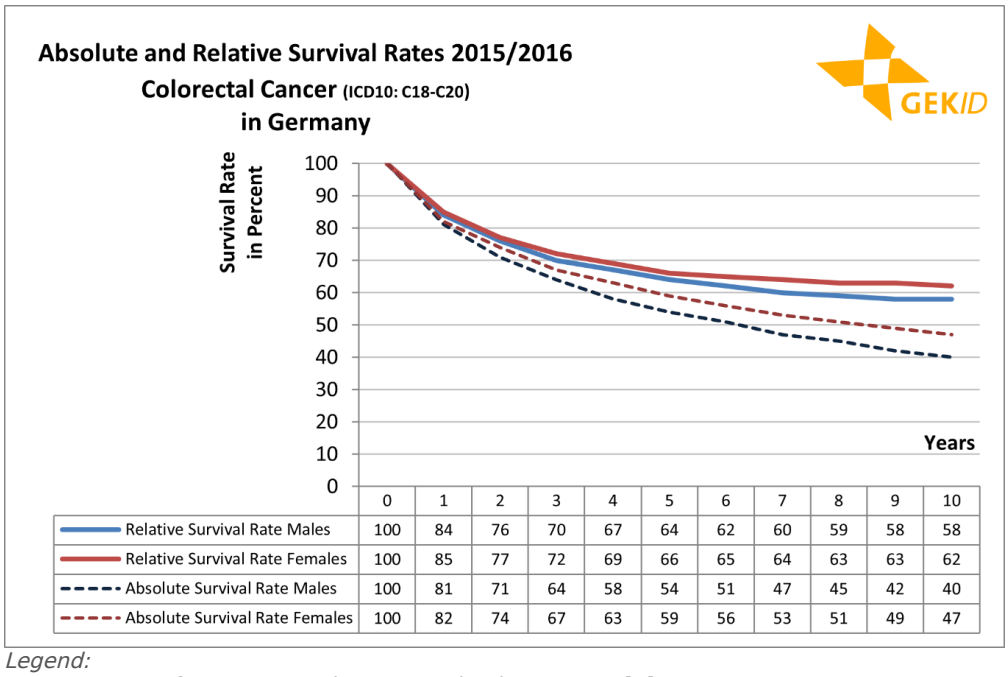


Legend:
Source: Center for Cancer Registry Data, database query [3].

The prognosis of colorectal cancer is in the middle range of all cancers: 54% of men and 59% of women are still alive five years after diagnosis. Due to the relatively high age of onset, there is a clear difference between absolute survival - i.e., the percentage of patients who survive a

certain time - and relative survival - i.e. the ratio of absolute survival to expected survival in the general population (Figure 4).

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



	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 Survival Rate Males	100	81	71	64	58	54	51	47	45	42	40
Absolute Survival Rate Females	100	82	74	67	63	59	56	53	51	49	47

Legend:
Source: Center for Cancer Registry Data, database query [3].

Based on the current incidence of the disease and the 14th coordinated population projection of the Federal Statistical Office (G2L2W2, moderate development), an increase in the number of cases by about 33% to more than 52,500 new cases (2050) can be expected in 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] [9] with mutations in genes:
    - *MSH2* (HNPCC1): about 60% of patients
    - *MLH1* (HNPCC2): about 30% of patients
    - *PMS1* (HNPCC3), *PMS2* (HNPCC4), *MSH6* (HNPCC5), *TFGBR2 (*HNPCC6), *MLH3* (HNPCC7)
  - Familial adenomatous polyposis (FAP) with germline mutations in the *APC* gene (1%) (OMIM ID #175100) [9].

    - Attenuated Familial Adenomatous Polyposis (AAPC) with germline mutations in the 5' end of the *APC* gene and complete loss of function [OMIM ID # 175100] [9].
    - Peutz-Jeghers syndrome with germline mutations in the *STK11* gene
    - Cowden syndrome with germline mutations in *PTEN* genes
- History of familial predisposition
    - colon 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 exercise

Because of 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.

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 carcinoma. 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 25-50% lower rate of colorectal cancer than comparator groups [10]. The benefit of regular ASA use was also shown in a recently published cohort analysis after at least 6 years of use, although lower doses may be required for longer-term use (at least 10 years) [41, 42]. 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 specific forms or components of diet, micronutrients, electrolytes such as calcium or magnesium, or drugs such as COX-2 inhibitors have not yet been sufficiently validated for a specific positive recommendation for prevention [11].

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 Gujaktest (gFOBT) reduces cancer-specific mortality [11]. 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 [11]. 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 acceptance of endoscopy is significantly lower than the acceptance 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

Investigation	Germany	Austria
Digital rectal examination	Annually from the age of 50 years	Annually from the age of 40.
Fecal occult blood test (immunochemical, iFOBT)	Annually between the ages of 50 and 54; 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.*

For a more detailed discussion of the opportunities and risks of screening for colorectal cancer, see Knowledge Base.

3.2.2 Risk groups

3.2.2.1 Relatives of patients with colorectal cancer

First-degree relatives should undergo colonoscopy for the first time at an age 10 years prior to the patient's disease, but at the latest at the age of 50 years [11, 12]. 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) in Austria, and the ESMO guidelines [2, 12]. 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 specific 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

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: Diagnostics for new onset of symptoms and for staging

Setting	Investigation	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	Abdominal ultrasound	Recommendation by S3 Guideline
	CT or MRI abdomen	Additionally recommended in case of sonographic suspect of liver metastases or in case of suboptimal assessability in sonography
	Thoracic radiography in 2 planes	Recommended by S3 guideline [11].
	CT Thorax	Additionally recommended
	CEA	

Positron-emission tomography (PET) is not part of the standard of care in the primary diagnosis of colon cancer.

5.3 Classification

Classification of primary tumor size and metastasis is based on the TNM criteria. The classification of the Union Internationale Contre le Cancer (UICC) [1] 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
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1 - 2	N1 (1-3 affected LK)	M0
	T1	N2a (4-6 affected LK)	M0
IIIB	T3 - 4	N1 (1-3 affected LK)	M0
	T2-3	N2a (4-6 affected LK)	M0
	T1-2	N2b (≥ 7 affected LK).	M0
IIIC	T4a	N2a (4-6 affected LK)	M0
	T3-T4a	N2b (≥ 7 affected LK).	M0
	T4b	N1-2	M0
IVA	Each T	Each N	M1a (distant metastases in one organ or localization without peritoneal involvement).
IVB	Each T	Each N	M1b (distant metastases in two or more organs or localizations without peritoneal involvement).
IVC	Each T	Each N	M1c (peritoneal involvement with or without distant metastases to other organs or sites).

5.4 Prognostic factors

In addition to TNM stage, there are numerous biological factors that have an impact on prognosis but have not been predictive for the use of specific therapeutic measures. Data on the relevance of the location of the primary tumor are new. Patients with right-sided colon carcinoma, i.e., oral Flexura coli sinistra, have a less favorable prognosis in stages III and IV than patients with left-sided colon carcinoma. Right-sided carcinomas more often show hypermethylation with the CpG Island Methylator Phenotype (CIMP), hypermutations due to microsatellite instability (MSI), and *BRAF* mutations. In stages I and II, the prognostic differences are less clear.

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.

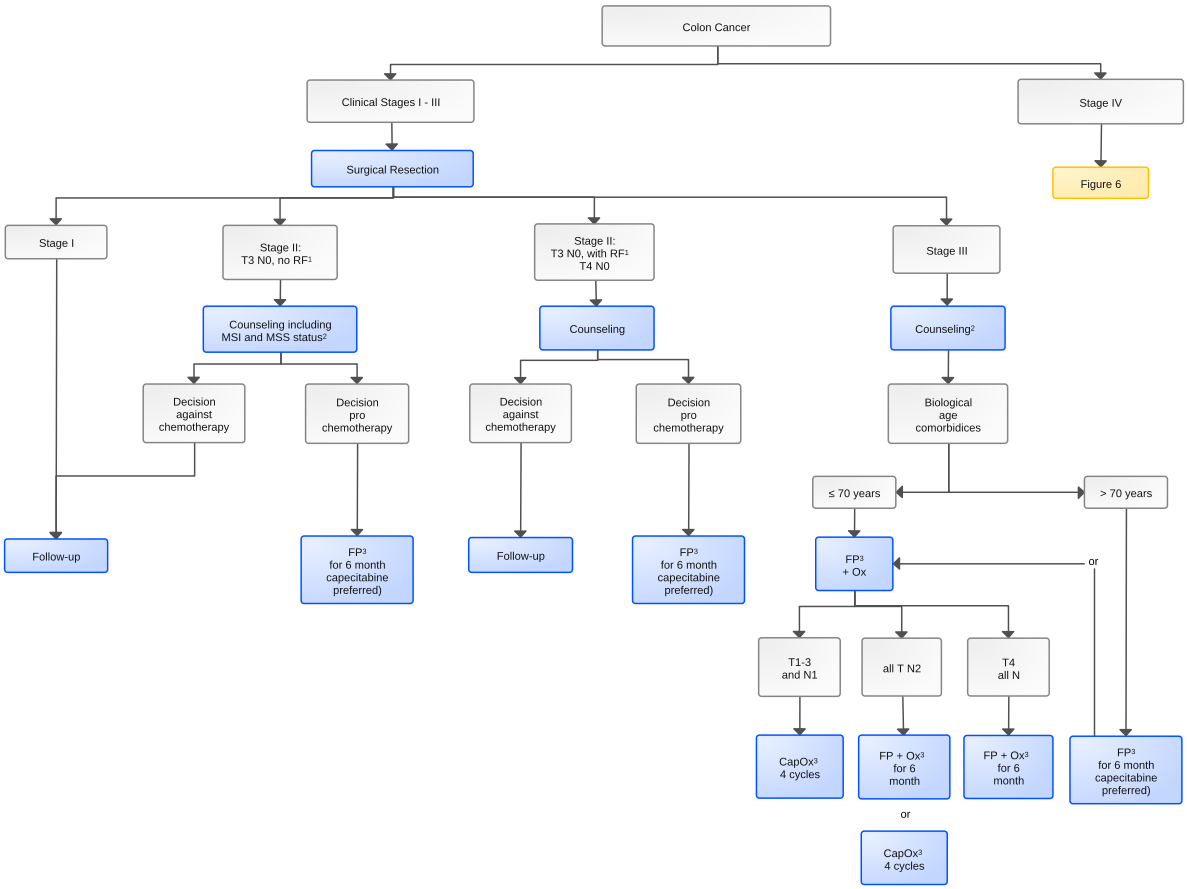
6 Therapy

6.1 Treatment structure

The basis of the treatment recommendation for the patient is the quality-assured survey of the relevant risk factors [2, 11]. Therapeutic algorithms are shown in Figure 5 and Figure 6 and Figure 7.

In Germany and Austria, a mutation among the four major dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded prior to 5-flurouracil (5-FU)-containing chemotherapy. Recommendations for the approach resulting from this mutation analysis, i.e., the extent of dose reduction of 5-FU in the case of heterozygous DPD mutations and the omission of 5-FU in the case of homozygous DPD mutations, have been presented in a consensus paper involving a large number of professional societies and working groups. This publication, available online, is referred here due to its complexity [39].

Figure 5: Treatment structure in colon cancer



Legend:

[1] RF – risk factors, see chapter 6.1.2;
[2] Counseling on potential benefit, including MSI status (if applicable): patients with microsatellite stable (MSS) tumors have an unfavorable prognosis und may benefit from adjuvant chemotherapy; patienten mit microsatellite-instable (MSI) tumors have a more favorable prognosis and may achieve only marginal benefit from adjuvant chemotherapy;
[3] Cap – capecitabine, FP – fluoropyrimidine: infusional 5-fluoro-uracil/folinic acid or capecitabine; Ox – oxaliplatin
[4] The benefit from oxaliplatin in elederly patients is questionable. The use of this agent in patients of higher biological age should be critically considered on a case-by-case basis. A definite age cut-off is not established.

6.1.1 Stage I

The therapeutic goal in stage I is curative. The essential procedure is complete surgical resection of the primary tumor. The individual variations of radical surgical resection for colon cancer have not been proven by randomized clinical trials. They are based on large retrospective analyses and international consensus building [11, 13].

Oncological principles are:

- Resection of the regional lymphatic drainage area with removal of at least 12 lymph nodes (total mesocolic excision).
- Appropriate safety margins to healthy tissue
- En-bloc resection of tumor-adherent organs

The rule for resection is a distance of at least 10 cm from the microscopic tumor margin, whereby the extent of bowel resection is essentially determined by the lymphadenectomy with core resection of the arterial vessels. The aim of lymph node dissection is the avoidance of lymphatic local recurrences and the prognostically and therapeutically relevant distinction between stage II and III. Micrometastases (diameter <2 mm) are included in the N - classification. The detection of isolated tumor cells is not a criterion for the N - classification.

Details of the surgical procedures are presented in chapter 6.2.1.

Adjuvant systemic drug treatment does not improve prognosis and is not indicated.

6.1.2 Stage II

The therapeutic goal in stage II is curative. An evaluation of the GEKID Cancer Survival Working Group showed a relative, age-adjusted 5-year survival rate for localized stages I+II of 89.5% for the years 2002-2006 [6]. The essential therapeutic procedure is complete surgical resection of the primary tumor. The local recurrence rate is low after radical surgical resection according to the oncological principles depicted in chapter 6.1.1 Details of surgical procedures are presented in chapter 6.2.1.

In stage II, adjuvant systemic fluoropyrimidine-based therapy results in a reduction in recurrence and an increase in survival at 5 years. Differences from observational groups are in the range of 3-5%. The MOSAIC trial of the benefit of oxaliplatin in addition to 5-FU showed an improvement in disease-free survival but no overall survival benefit in the overall stage II patients and is therefore not recommended in patients without clinical risk factors.

In each patient, the potential benefit should be weighed against the chemotherapy-associated morbidity and the associated potential impairment of quality of life. Adjuvant chemotherapy is particularly recommended for subgroups of patients at higher clinical risk of recurrence. Clinical risk factors to be considered include:

- T4 stage
- Tumor perforation
- Intraoperative tumor rupture
- Surgery under emergency conditions
- Less than 12 examined lymph nodes
- Histopathologically documented lymphatic or blood vessel infiltration, undifferentiated tumor (G3, not applicable in MSI).

In approximately 20% of patients with stage II colon cancer, sporadic microsatellite instability (MSI) is detectable in tumor tissue. This genetic marker correlates with localization in the right colon, poor histologic differentiation, and subtype of mucinous adenocarcinoma. Patients with microsatellite instability have a better prognosis. The potential benefit of adjuvant chemotherapy is lower than in patients without MSI. In stage II patients without risk factors, the absence of microsatellite instability can be used as an argument for adjuvant chemotherapy and, conversely, the detection of microsatellite instability can be used as an argument against adjuvant chemotherapy. However, results of prospective randomized trials based on microsatellite instability are not available.

6.1.3 Stage III

Also in stage III, the therapeutic goal is curative. An evaluation by the GEKID Cancer Survival Working Group showed a relative, age-adjusted, 5-year survival rate for locally advanced stages of 65.4% for the time period 2002-2006 [6]. Surgical resection is the first-line therapy. The local recurrence rate is low after radical surgical resection according to oncological principles, see chapter 6.1.1. Details of the surgical procedure are presented in chapter 6.2.1.

In stage III, adjuvant systemic therapy results in a significant reduction of recurrence rates and a significant increase in survival at 5 years. As yet, biomarkers do not have an impact on recommendation for adjuvant therapy. Clinical risk factors, especially comorbidity and age, influence the choice of drugs and intensity of treatment. Data from randomized clinical trials including the IDEA analysis can be summarized as follows:

- The first effective substance in adjuvant therapy of patients with colon carcinoma was 5-fluorouracil.
- Modulation of 5-FU metabolism by folinic acid enhances efficacy.
    - Capecitabine is (at least) as effective as 5-FU/folinic acid.
    - The combination of 5-FU/folinic acid with oxaliplatin results in further improvement of long-term relapse-free survival and to an increase in overall survival. It is now a standard of care. Therapy with capecitabine/oxaliplatin (CAPOX) and 5-FU/folinic acid/oxaliplatin (FOLFOX) is (at least) equieffective. Infusional protocols with 5-FU administration over 46 - 48 hours in a pump such as FOLFOX6 should be preferred over FOLFOX4.
    - In patients at low recurrence risk (T1-3 and N1 stage), a 3-month oxaliplatin-containing regimen in combination with capecitabine (CAPOX) is non-inferior to a 6-month oxaliplatin-containing regimen with fluoropyrimidines in terms of disease-free survival. Accordingly, a regimen with capecitabine/oxaliplatin (CAPOX) should be preferred. Shortened adjuvant therapy reduces toxicity, especially long-term neurotoxicity.
    - For patients at high risk of recurrence (N2 stage), the non-inferiority of 3-month therapy could not be proven in the IDEA analysis. However, especially for N2 tumors - as they show a hazard ratio almost identical to N1 tumors in the final analysis of the IDEA study - a 3-month CAPOX therapy can be considered sufficient. Cumulative (neuro)toxicity should be thoroughly weighed against therapeutic benefit [14].
    - For patients with contraindications to oxaliplatin, adjuvant chemotherapy with 5-FU/folinic acid or capecitabine is recommended. 5-FU is administered as infusional 5-FU.
    - There is no defined upper age limit, however, only few data are available for patients over 75 years of age. In particular, the use of oxaliplatin is controversial in

patients over 70 years of age. The benefit is lower in these patients than in younger patients. Physiological age and comorbidities should be considered.

Further information on the drugs used is summarized in chapter 6.2.3.

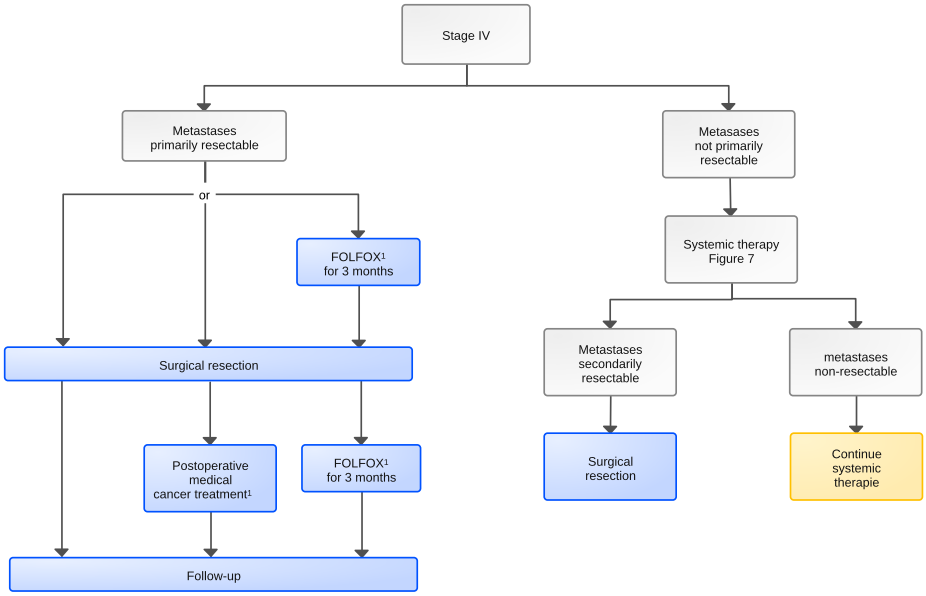
Numerous other substances from the group of cytostatic drugs, immunotherapy or monoclonal antibodies have been and are also being evaluated in the adjuvant situation. So far, no other substance has shown a significant advantage over the chemotherapy standard with 5-FU/folinic acid (or capecitabine) and oxaliplatin.

Combination of proton pump inhibitors with capecitabine-containing therapy, e.g., in the CAPOX or XELOX regimen, should be avoided because several retrospective data sets suggested adverse effects on capecitabine efficacy [43, 44].

6.1.4 Stage IV

The therapeutic goal of stage IV patients used to be considered exclusively palliative. Over the past 20 years, it has become evident that up to 25% of patients with colorectal cancer and synchronous hepatic metastases have a curative potential [15, 16]. 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 Figure 6 and Figure 7.

Figure 6: Treatment structure in stage IV colon cancer



Legend:
[1] the usefulness of perioperative medical cancer treatment is undefined; 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, treatment goals, and molecular factors (MSI, RAS and BRAF mutations, etc.) in different hierarchical levels, as criteria for treatment selection [17]. These classifications provide a pragmatic orientation, but their criteria have not been prospectively validated. In particular, the localization of the primary (so-called sidedness) should be considered as an important predictive criterion for the use of anti-EGFR antibodies [18].

6.1.4.1 Stage IV with resectable metastases

6.1.4.1.1 Resectability

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

In addition to the technical question of resectability of metastases, criteria of tumor biology have a significant impact on the recurrence rate. In patients with colorectal liver metastases, various models have been developed for the calculation and prognostic evaluation of risk factors. Widely used is the application of the Fong Score [19], see Table 4, which is based on data of primarily surgically treated patients without perioperative systemic cancer treatment. The risk score facilitates a benefit-risk assessment. It is not a static tool for determining contraindications. Recent retrospective analyses show that these criteria are also valid for resection after perioperative chemotherapy [20].

Table 4: 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 systemic cancer treatment in patients with 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 [15], 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 [21].

6.1.4.2 Conversion therapy of potentially resectable metastases

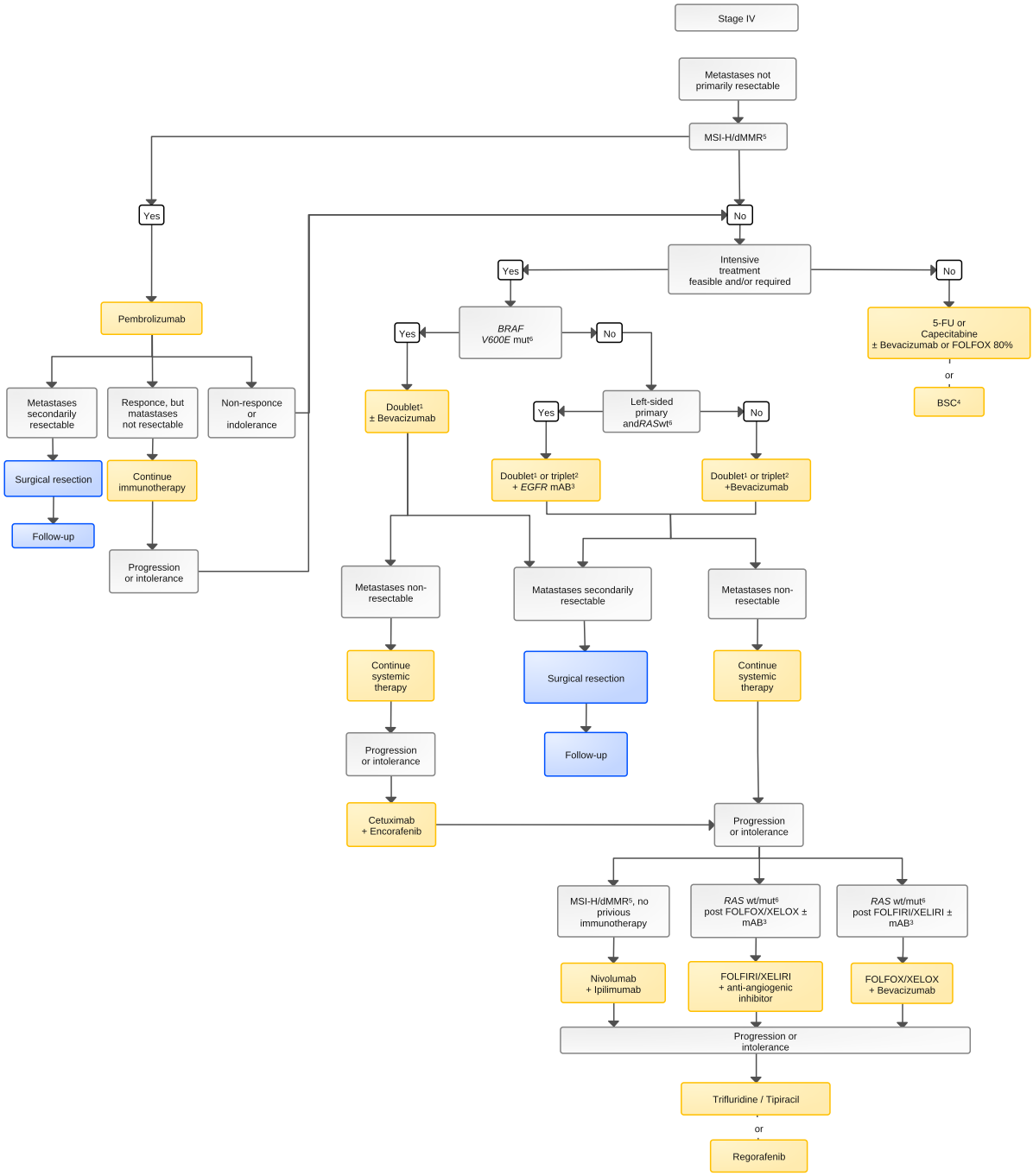
The group of patients with potentially resectable metastases can be enlarged by a so-called conversion therapy. The goal of this therapy is to achieve technical resectability by downsizing the metastases. Accordingly, treatment protocols with high response rates and the chance of greater volumetric shrinkage of metastases are recommended. Two-drug combinations plus antibody or three-drug combinations ± antibody from the palliative situation have been used in randomized and non-randomized phase II studies, see Section 6.2.3 and Section 6.1.4.3. The METHEP trial presented at the 2018 ASCO Annual Meeting, which randomized doublet versus triplet, each + mAb (depending on *RAS* status) as conversion therapy, found no statistically significant improvement in R0/R1 resection rates; disease-free and overall survival were also not significantly different. However, in the smaller OLIVIA study (80 patients) [22] with more clearly defined and stricter inclusion criteria regarding irreversibility, a benefit was found for triplet therapy + bevacizumab versus FOLFOX + bevacizumab. In this respect, it should be decided on a case-by-case basis by 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 triplet chemotherapy resulted in high remission rates and improved resection rates, mainly in younger patients. An improvement in overall survival was not shown. This therapy is relatively toxic and should only be offered to selected patients [23].

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 for bevacizumab-containing therapy. The value of continuing chemotherapy after R0 or R1 resection, in terms of completing chemotherapy for 6 months of total therapy duration, 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 in patients with 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 and chapter 6.1.4.2. For the treatment algorithm, see Figure 7.

Figure 7: Treatment structure for stage IV colon cancer with initially 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

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 cases overall survival in clinical studies. The combination of chemotherapy and antibodies result in a median progression-free survival of about 10 months and a median overall survival of about 30 months [18, 19]. 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 are available from smaller randomized trials with selected patient cohorts, in which improved conversion rates of primarily non-resectable liver metastases have been documented [23]. The size of these studies does not allow definite conclusions regarding long-term survival. In combination with bevacizumab, triplet chemotherapy results in longer progression-free survival than doublet + bevacizumab [24]. Prolongation of the time to progression, thus possibly to symptomatic disease requiring renewed intensive therapy, is also a clinically relevant therapeutic goal for patients in a clearly palliative setting.

A meta-analysis did not confirm a better efficacy of triplet chemotherapy compared to doublet for patients with *BRAF V600E* mutated tumors [25]. 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 [26]. 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 any of the anti-EGFR antibodies.

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 [27] 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 [28], this difference could not be replicated, see also AIO statement [29]. 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 *RAS*wt tumor *was* analyzed [18]. 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 their primary tumor in the right hemicolon did not benefit from the administration of anti-EGFR antibodies in terms of progression-free and overall survival despite *RAS*wt*. 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 [29].

6.1.4.3.1.2 RAS mutations

In patients with defined *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 instability in their tumor tissue, 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 within and outside the study). 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 [30].

6.1.4.3.2 Maintenance therapy

In 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 [29].

As all these studies used oxaliplatin-containing induction therapies, it is unclear whether the results described would be transferable to irinotecan-containing induction.

Regarding maintenance therapy with EGFR inhibitors, according to data from the PANAMA trial, continuation of 5-FU and the anti-EGFR antibody is recommended after 3 months of induction chemotherapy [31]. 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 [32]. 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 [33].
- After pretreatment with chemotherapy, the combination of nivolumab and ipilimumab can be used in patients with MSI-high tumors in accordance with current approval [34].
- 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 Resection of an asymptomatic primary tumor of the colon

In a purely palliative situation, an asymptomatic primary tumor should not be surgically resected. Two randomized studies showed no survival benefit from resection of an asymptomatic primary of the colon. After a randomized trial from Japan had already shown no survival benefit, [21] the results of the Synchronous trial, which was mainly conducted in Germany, were also presented at the annual meeting of ASCO 2022. In this study, primary tumor resection showed no survival benefit in primary metastatic disease (median survival without surgery 18.6 versus 16.7 months with surgery). Patients in the surgery arm were significantly less likely to receive systemic palliative chemotherapy (24% versus 6.4%). In contrast, gastrointestinal tract-related SAEs were slightly more common in the chemotherapy arm (10.7% versus 4.8%) [45].

On the basis of this study, surgical resection of asymptomatic primary colon cancer in a palliative treatment setting cannot be recommended.

6.1.4.3.5 Local therapy for oligometastasis

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

For local therapy of irresectable liver metastases, different procedures have been described, mainly in case series. The best evaluated is intra-arterial liver perfusion. Compared with intravenous therapy with 5-FU/folinic acid, it leads to higher remission rates, but not to a prolongation of survival. The effect of systemic chemotherapy is documented more clearly [35].

Other approaches include radiofrequency ablation, laser therapy, stereotactic radiotherapy, or SIRT (selective internal radiation therapy). Randomized clinical studies comparing these methods with systemic tumor therapy are sparse. As complementary measures to systemic chemotherapy, they should be evaluated on a case-by-case basis. The additional administration of selective internal radiotherapy (SIRT) in conjunction with first-line chemotherapy showed no benefit for either progression-free or overall survival in a large pooled ITT analysis, and is therefore not recommended [36]. The indication should be discussed in the multidisciplinary tumor board, taking into account the overall treatment plan and the potential, sometimes considerable, toxicity.

6.1.4.3.6 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 surgical intervention (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 adjunctive hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin could not be demonstrated [37]. In this respect, HIPEC with oxaliplatin after CRS currently cannot be recommended. Cytoreductive surgery alone can be considered a basic standard treatment option at specialized centers. Criteria for decision-making are good general condition, localized and exclusively peritoneal metastasis (peritoneal carcinomatosis index PCI ≤ 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

The basis of colon cancer therapy is radical surgical resection. The quality of surgery has a direct impact on long-term survival of patients. Regarding the oncological principles of surgical therapy of colon carcinoma, see chapter 6.1. The type and extent of resection are dictated by the localization, the supplying vessels and the lymphatic drainage area defined by these. The surgical technique depends on the localization of the primary tumor, see Table 5.

Table 5: Surgical procedures

Localization	Operation
Cecum	Right-sided hemicolectomy
Ascending colon	Right-sided hemicolectomy
Right flexure	Right-sided extended hemicolectomy
Transverse colon, proximal	Right-sided extended hemicolectomy
Transverse colon, middle third	Transverse resection; extended right-sided hemicolectomy, if necessary
Transverse colon, distal	Left-sided extended hemicolectomy
Left flexure	Left-sided extended hemicolectomy
Descending colon	Left-sided hemicolectomy
Sigma, proximal	Left-sided hemicolectomy
Sigma, medium and distal	Oncological sigmoid resection

6.2.1.2 Surgical access

With appropriate expertise, the operation can be performed open, laparoscopically and probably also robotically. Advantage of open surgery is the shorter operation time. Advantages of laparoscopic surgery are cosmetic outcome, less blood loss, and potentially faster postoperative recovery. The long-term oncologic outcomes of the two approaches are probably the same [38].

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 a passive anus praeter 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.

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-containing chemotherapy [39].

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 oxaliplatin. Progression-free survival is prolonged. Overall survival data are inconsistent. Patients with defined *RAS* mutations (*KRAS* genes exon 2-4, *NRAS* genes exon 2-4) have no benefit from cetuximab therapy, and in some chemotherapy combinations even a trend towards shorter survival was observed. Because there is evidence of a negative interaction with capecitabine and bolus 5-FU protocols, that is not yet understood, the combination of cetuximab with oral fluoropyrimidines and bolus 5-FU protocols is not recommended. 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%).

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.

Mutation among the four major dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded prior to 5-FU-containing chemotherapy [39].

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. The substance 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 cancer recurrent or refractory after therapy with a fluoropyrimidine, oxaliplatin and bevacizumab, it was tested in a phase III trial in combination with FOLFIRI. The addition of ramucirumab resulted in a statistically significant prolongation of progression-free survival from 4.7 to 5.7 months with a hazard ratio of 0.77 and prolongation of overall survival from 11.7 to 13.3 months with a hazard ratio of 0.84. Adverse events CTCAE grade 3/4 that occurred in more than 5% of patients treated with ramucirumab in the combination therapy in the pivotal study, and more frequently than in the control group, were neutropenia (28%) and hypertension (11%). Fatigue (12%) and diarrhea (10%) were not significantly more common than in the chemotherapy control arm.

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 at the start of therapy. 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 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 2 weeks off. 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.

6.2.3.16 S1 (Tegafur plus Gimeracil and Oteracil)

In case of intolerance of 5-fluouracil, the substance 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.

7 Rehabilitation

Both the underlying disease and the therapies (systemic, surgical, radiological, radiotherapeutic) can lead to very differently pronounced sequelae in patients with colon cancer and thus significantly impair quality of life, autonomy and possibly also the ability to work and perform.

Medical rehabilitation, both inpatient and outpatient, can correct or at least alleviate these secondary disorders.

Therefore, all patients should be offered rehabilitation after primary therapy. Intended surgical and radiotherapeutic measures must be completed for this. Drug-based tumor therapies can also be continued during rehabilitation.

The program of rehabilitation includes comprehensive information on the patient’s underlying disease as well as all diagnostic and therapeutic modalities. The patient should be trained in dealing with the consequences of the disease and the therapy (e.g., care of an anus praeter, reduction of neuropathy).

Drug therapy should be optimized in the rehabilitation clinic if necessary. The facility should be able to continue drug-based tumor therapies according to the specifications of the referring cancer center during rehab in order to avoid therapy interruptions or delays.

An initial psychological assessment is required to identify deficits in disease management or reactive moods and to initiate further action.

Dietary counseling should be provided to assist patients in making necessary dietary and "lifestyle" changes.

Comprehensive training therapies are designed to help patients regain muscular strength and endurance and motivate them to remain physically active after rehabilitation.

From a socio-medical point of view, patients in their working age must be informed about the possibilities of re-entering working life (gradual reintegration, internal reaffiliation, finding a job suitable for their condition, retraining) and must be supported in this process. Furthermore, if necessary, support must be organized in the patient's home town, both for activities of daily living and for nursing care.

The rehabilitation clinic should also, if this is not already settled, organize the patient's further medical care.

Patients should be offered a connection to self-help groups.

In general, the patient's right of choice must be respected when selecting a rehabilitation facility. However, only facilities that are able to provide professional care for patients with colon cancer should be considered, i.e., hospitals with a gastroenterological or oncological focus that are regularly certified and participate in standardized quality assurance programs.

8 Follow-up

The follow-up of patients with colorectal cancer is structured. The goals of follow-up are the early diagnosis of recurrence with the aim of prolonging survival and/or increasing the chance of cure, the detection of side effects of the therapy, and secondary prevention. In patients with colorectal cancer, coherent, structured follow-up can lead to a prolongation of survival [41], see Colorectal Cancer Study Results.

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 colon 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
CEA	X X	X X X	X X	X X X	X	X X X	X	X X X		X X		X X X		X X X		X X X
Abdominal ultrasound		X		X		X		X				X		X		X
CT Abdomen / Thorax				X X				X X				X X		X		X
Colonoscopy		X		X X X										X X		X

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

9 Literature

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14 Links

German ILCO, http://www.ilco.de/start/home.html

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16 Disclosures

according to the rules of the responsible Medical Societies.