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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

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Table of contents

Colon Cancer

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1 Summary

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

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

The prognosis of patients with colon cancer depends on the stage of the disease at initial diagnosis and other biological risk factors. Treatment is based on tumor stage. For localized colon cancer in stages I-III, surgery is the first choice. 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 disease control, i.e., to alleviate or prevent symptoms and prolong survival. In a subgroup of patients, however, a cure is also possible in this stage, particularly when surgical resection of metastases is feasible. For systemic drug therapy in stage IV, multiple agents (chemotherapy, monoclonal antibodies and targeted molecules) are available. The optimal combination and sequence are the subject of current scientific debate.

Advances in the diagnosis and treatment of colorectal cancer have led to a continuous reduction 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 (lower margin) is 16 cm or less from the anocutaneous line when measured with a rigid rectoscope [1]. Carcinomas located more proximally up to and including the ileocecal valve are defined as colon cancer. The ESMO consensus proposes a new definition taking into account the different measurement results in the imaging 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 on rectal carcinoma.

Histologically, more than 95% of patients have an adenocarcinoma. Besides that, rare tumors in the colon are neuroendocrine tumors, lymphomas, sarcomas or squamous cell carcinomas.

Colon and rectal cancer have many similarities in terms of etiology and histology. However, they differ in their preoperative, surgical and adjuvant treatment strategies. These are addressed separately in the current Onkopedia guidelines on colon and on rectal cancer. The topic of this guideline is adenocarcinoma of the colon. It accounts for 60-70% of colorectal cancers in Germany.

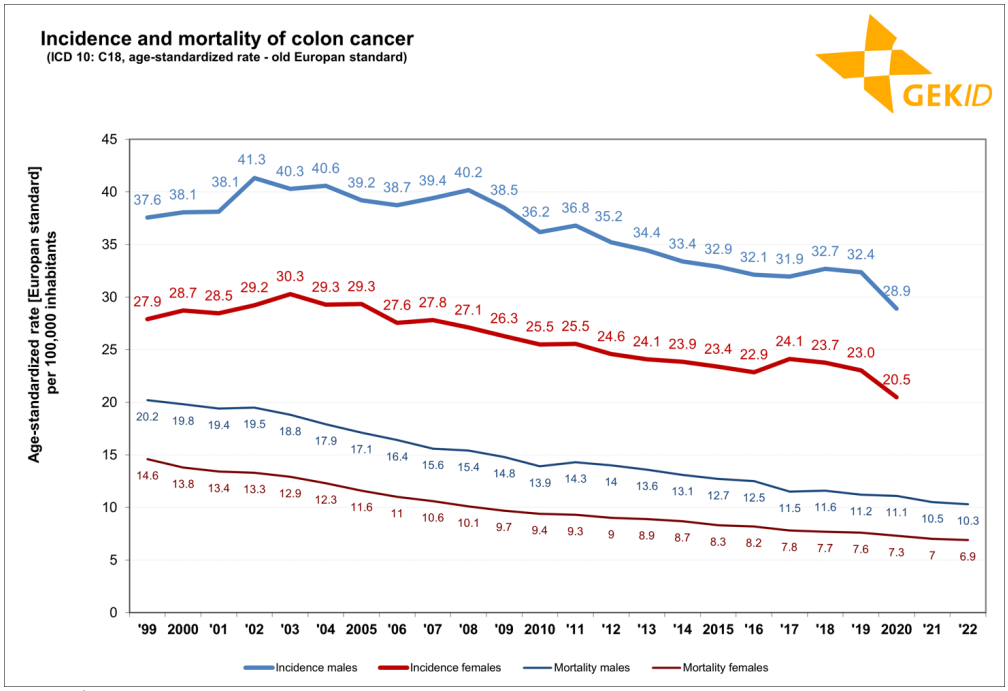
2.2 Epidemiology

Every year, almost 40,000 new cases of malignant neoplasm of the colon are diagnosed in Germany. The number of cases is almost the same for both sexes (men: 21,000, women: 19,500), which represents around 8% of all malignant tumors. Colorectal cancer has an intermediate prognosis among all different malignancies. Every year, around half as many people die (approx. 16,000) from colorectal cancer as are diagnosed [3].

The average age of onset for men (74 years) is four years higher than for all cancers in total (70 years) and for women (77 years) is even eight years higher than for all cancers in total (69 years). The mean age of death is 74 years (men), one year below and 78 years (women), one year above the mean age of death for cancer overall (75 years and 76 years respectively).

The age-standardized morbidity rates, i.e., the probability of developing the disease, as well as the age-standardized mortality rates - the probability of dying - show a declining 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 rates for men have fallen by an average of 1.8% per year, and those for women by as much as 2.2% (incidence). This is even more evident in the mortality rates, which have fallen by an average of 3.1% (men) and 3.3% (women) per year.

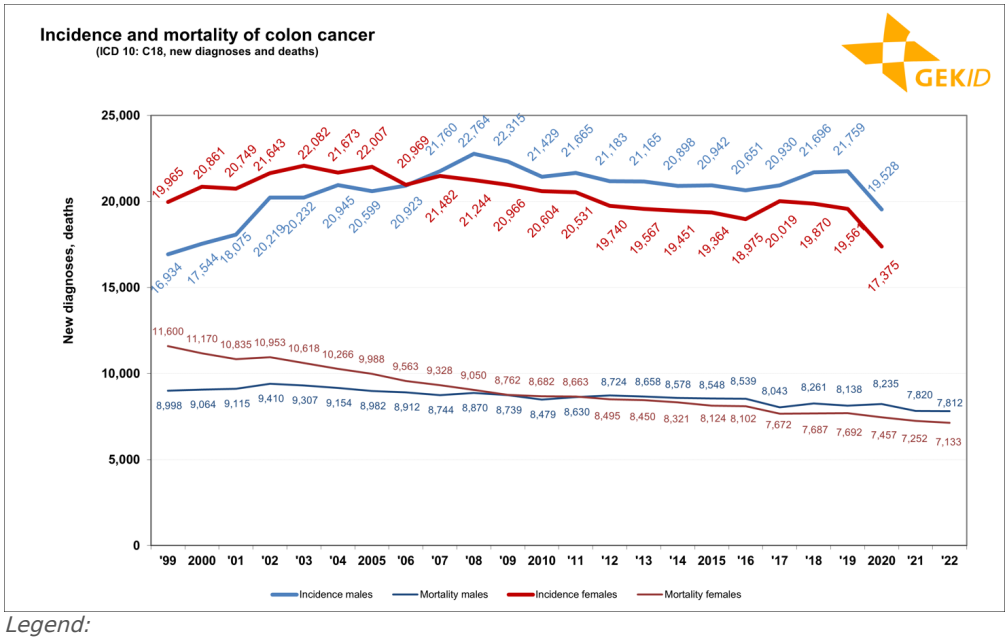
Figure 1: Estimated incidence and mortality of colon cancer (ICD 10: C18) in Germany - age-standardized rates (old European standard)



Legend:
Source: Center for Cancer Registry Data [3]

While the age-standardized onset rates 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 towards an older society and the fact that the “baby boomers” are reaching the age cohorts most likely to develop colon cancer, the progression of new cases and deaths differs from the progression of the rates. The higher the age at onset of the disease, the stronger this effect is. This is more pronounced in men than in women. Despite falling morbidity and mortality rates, the number of new cases and deaths from colorectal cancer in men has remained almost constant since 2003. For women, as with the rates, falling case numbers are also observed for incidence and mortality, although the decline of 1.3% per year (incidence) and 2.0% per year (mortality) is lower than for the rates (Figure 2).

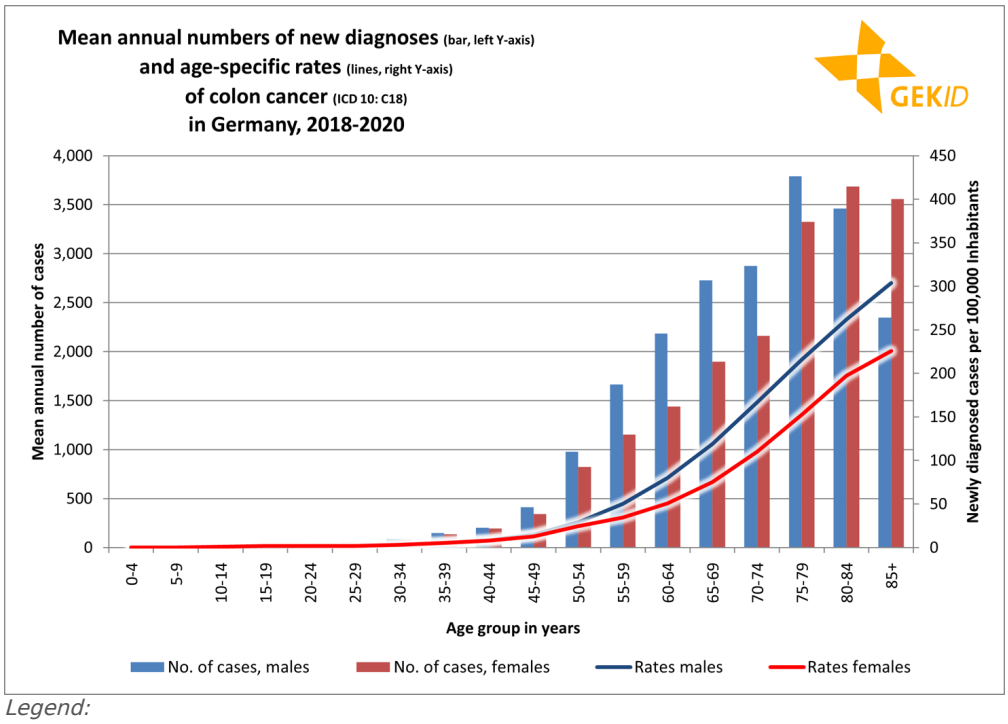
Figure 2: Estimated incidence and mortality of colon cancer (ICD 10: C18) in Germany - case numbers



Legend:
Source: Center for Cancer Registry Data [3]

Until the age of 40, tumors of the colon epidemiologically play a marginal role. From then on, the disease rates increase steadily in both sexes and reach their peak in the highest age group (85 years and older) (see Figure 3 [lines]). From the age of 35, the rate for men is always higher than that for women. The number of cases is somewhat different due to the population distribution. The number of new cases increases up to the age group of 75 to 79 years (see Figure 3 [bars]). After that, the number of men affected drops significantly, which is due to the fact that the number of men is lower due to life expectancy. The higher life expectancy of women implicates that among older age groups (80+), women are at a higher risk. This is reflected in the significantly higher number of cases among women over 80, as compared to men. The highest number of new cases is observed above 85 years of age.

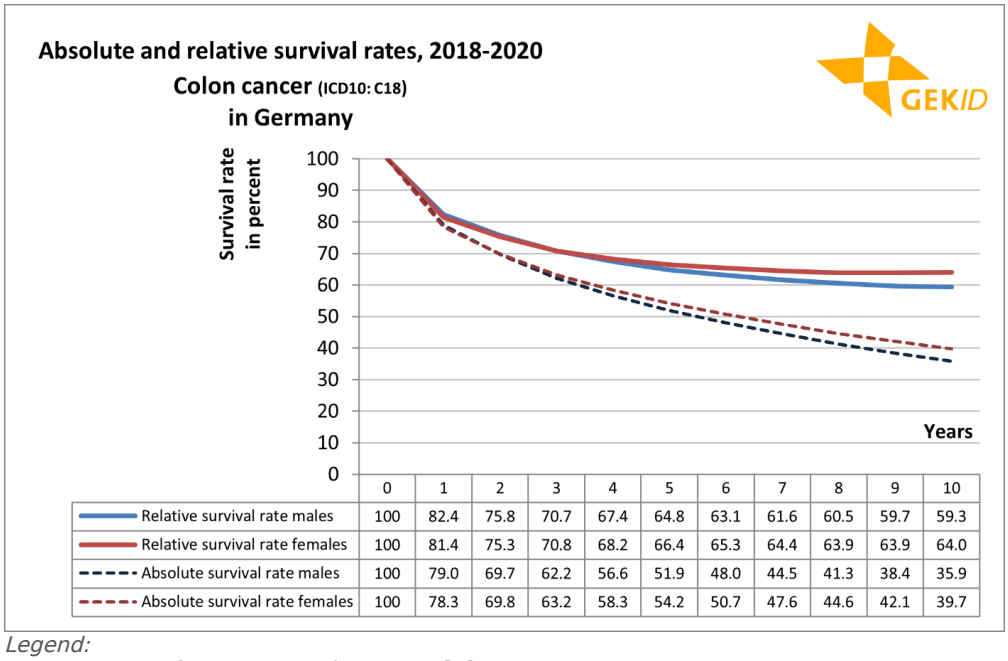
Figure 3: Age distribution of the incidence of colon cancer (ICD 10: C18) - age-specific case numbers and rates



Legend:
Source: Center for Cancer Registry Data [3]

The prognosis of colorectal cancer is in the middle range of all cancers. 52% of men and 54% of women are still alive five years after diagnosis (Figure 4). Due to the relatively high age of onset, there is a clear difference between the absolute survival rate, i.e., the percentage of patients who survive a certain time, and the relative survival rate, i.e., the ratio of absolute survival to the expected survival in the general population. Although only 36% (men) and 40% (women) are still alive 10 years after diagnosis, the relative survival rate is 59% (men) and 64% (women), as a number of people in the general population have also died in these 10 years. There are only slight differences between the sexes, with a small advantage for women.

Figure 4: Absolute and relative survival rates for colon cancer (ICD 10: C18)



	0	1	2	3	4	5	6	7	8	9	10
Relative survival rate males	100	82.4	75.8	70.7	67.4	64.8	63.1	61.6	60.5	59.7	59.3
Relative survival rate females	100	81.4	75.3	70.8	68.2	66.4	65.3	64.4	63.9	63.9	64.0
Absolute survival rate males	100	79.0	69.7	62.2	56.6	51.9	48.0	44.5	41.3	38.4	35.9
Absolute survival rate females	100	78.3	69.8	63.2	58.3	54.2	50.7	47.6	44.6	42.1	39.7

Legend:
Source: Center for Cancer Registry Data [3]

Based on the current incidence of colon cancer and the 15th coordinated population projection of the Federal Statistical Office (G2L2W2, moderate development), the number of cases can be expected to increase by around 24% to more than 48,500 new cases (2050) over the next 25 years, solely due to the shift in the age structure of the population.

2.3 Pathogenesis

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

2.4 Risk factors

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

- Defined genetic diseases (about 3% of new cases)
  - Hereditary colorectal cancer without polyposis (HNPCC, Lynch syndrome [OMIM ID # 120435] [9] with mutations in the genes:
    - MSH2 (HNPCC1): about 60% of patients
    - MLH1 (HNPCC2): about 30% of patients
    - PMS1 (HNPCC3), PMS2 (HNPCC4), MSH6 (HNPCC5), TGFBR2 (HNPCC6), MLH3 (HNPCC7)
  - Familial adenomatous polyposis (FAP) with germline mutations within the APC gene (1%) (OMIM ID #175100) [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
- Familial genetic burden
  - One or more first-degree relatives before the age of 50 are affected
- Colorectal adenomas as precursors of sporadic carcinomas (adenoma-carcinoma sequence)
- Chronic inflammatory bowel diseases
  - Ulcerative colitis
  - Crohn's disease
- Toxic*
  - High alcohol consumption
  - Smoking
- Nutritional*
  - Low in fiber
  - high in fat
  - High proportion of red meat and processed sausages
  - low proportion of vegetables
- Lifestyle*
  - Obesity

    - Lack of exercise

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

3 Prevention and early detection

3.1 Prevention

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

- Ablation of adenomas
    - The ablation of adenomas is a preventive measure through removing the precursor stages of carcinoma. This procedure is carried out as part of the endoscopic screening measures.
- Lifestyle habits
    - Weight reduction for overweight people
    - Regular physical exercise
    - Refrain from excessive alcohol consumption
    - Abstaining from tobacco consumption
- Nutrition
    - High fiber intake (30 g/day)
    - Rich folic acid, calcium and vitamin B6 intake
    - Increased consumption of fruit and vegetables
    - No daily consumption of red or processed meat

The most extensive data for drug prevention is 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 cohort analysis after at least 6 years of use, although lower doses may be necessary for longer-term use (at least 10 years) [41, 42]. In HNPCC gene carriers, daily intake of 300-600 mg ASA reduces the risk of colorectal cancer by 37%.

These and numerous other studies on the association between colorectal cancer and certain forms or components of 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 generally long time between the appearance of polyps and their malignant transformation offers the opportunity for early detection and prevention. Examination of the stool for occult blood using the guaiac test (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 changes and human hemo-

globin leads to a further increase in sensitivity, but also to a substantial rate of false positive results.

Sigmoidoscopy with prophylactic polypectomy reduces cancer-specific mortality [11]. The effect is stronger than the effect of examination of the stool for occult blood. Total colonoscopy increases the detection rate of carcinomas and precancerous changes, but has not yet been prospectively validated using mortality as an endpoint. The acceptance of endoscopy is significantly lower than the acceptance of non-invasive test procedures. 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 people with a low risk of disease.

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

Table 1: Colorectal cancer screening

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

Legend:
** Further, individual instructions for repeating the colonoscopy are given by the examiner*
D - Germany

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

3.2.2 Risk groups

3.2.2.1 Relatives of patients with colorectal cancer

First-degree relatives should undergo their first colonoscopy at an age 10 years prior to the patient's onset of disease, but no later than 50 years of age [11, 12]. This recommendation also applies to first-degree relatives of patients who were diagnosed with colorectal adenomas before the age of 50. If the findings are unremarkable, colonoscopy should be repeated in this risk group after a maximum of 10 years.

3.2.2.2 Hereditary colorectal cancer

Diagnostic procedures should be carried out in accordance with the guidelines for the diagnosis of genetic predisposition to cancer of the German Medical Association, those of the Austrian Society for Gastroenterology & Hepatology (ÖGGH) in Austria and the ESMO guidelines [2, 12]. The specific genetic aberration determines the risk of disease and is the basis of the individualized early detection and prevention plan.

3.2.2.3 Ulcerative colitis

Aminosalicylate can be used for prophylaxis; results of randomized studies with the primary endpoint of preventing colorectal cancer are not available. The recommendations for early detection depend on the extent of the colitis and the duration of the disease. Patients with pancolitis for more than 8 years or with left-sided colitis for more than 15 years should undergo 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

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

4 Clinical characteristics

4.1 Symptoms

Characteristic early symptoms are absent. Emerging symptoms can be:

Local symptoms

- Blood in 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 are jaundice and liver failure from advanced liver metastases, cough and dyspnea from pulmonary and/or pleural metastases, and less commonly bone pain from skeletal metastases or neurological symptoms from cerebral metastases.

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis

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

Table 2: Diagnostics for new onset of symptoms and for staging

Setting	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 and treatment planning	Abdominal sonography	Recommendation S3 guideline
	CT or MRI abdomen	Additionally recommended, as sonographic staging is examiner-dependent
	Chest radiography in 2 planes	Recommendation S3 guideline [11]
	CT thorax	Additionally recommended
	CEA (carcinoembryonic antigen)	In serum
	MSI (microsatellite instability)	Preoperativley; if not done, at the latest after resection of the primary

Positron emission tomography (PET) is not standard in the primary staging of colon cancer

5.3 Classification

The 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 staging criteria, see Table 3.

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

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

5.4 Prognostic factors

In addition to the TNM stage, there are numerous biological factors that have an impact on prognosis but have not yet been predictive for the choice between specific therapeutic procedures. The data on the relevance of the location of the primary tumor are new. Patients with right-sided colon carcinoma, i.e., proximal to Flexura coli sinistra, have a less favorable prognosis in stages III and IV than patients with left-sided colon carcinoma. Right-sided carcinomas more frequently show hypermethylation with the CpG Island Methylator Phenotype (CIMP), hypermutations due to microsatellite instability (MSI), and *BRAF mutations*. The prognostic differences are less clear in stages I and II. MSI should be assessed as a significant prognostic and predictive factor when colorectal cancer is first diagnosed. For this purpose, an immunohistochemical analysis is sufficient in most cases.

5.6 General condition and comorbidity

For objective assessment of the general condition, geriatric assessment is recommended, see Geriatric Oncology Knowledge Base (in German only). 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 certain treatment modalities are not yet available for colorectal cancer.

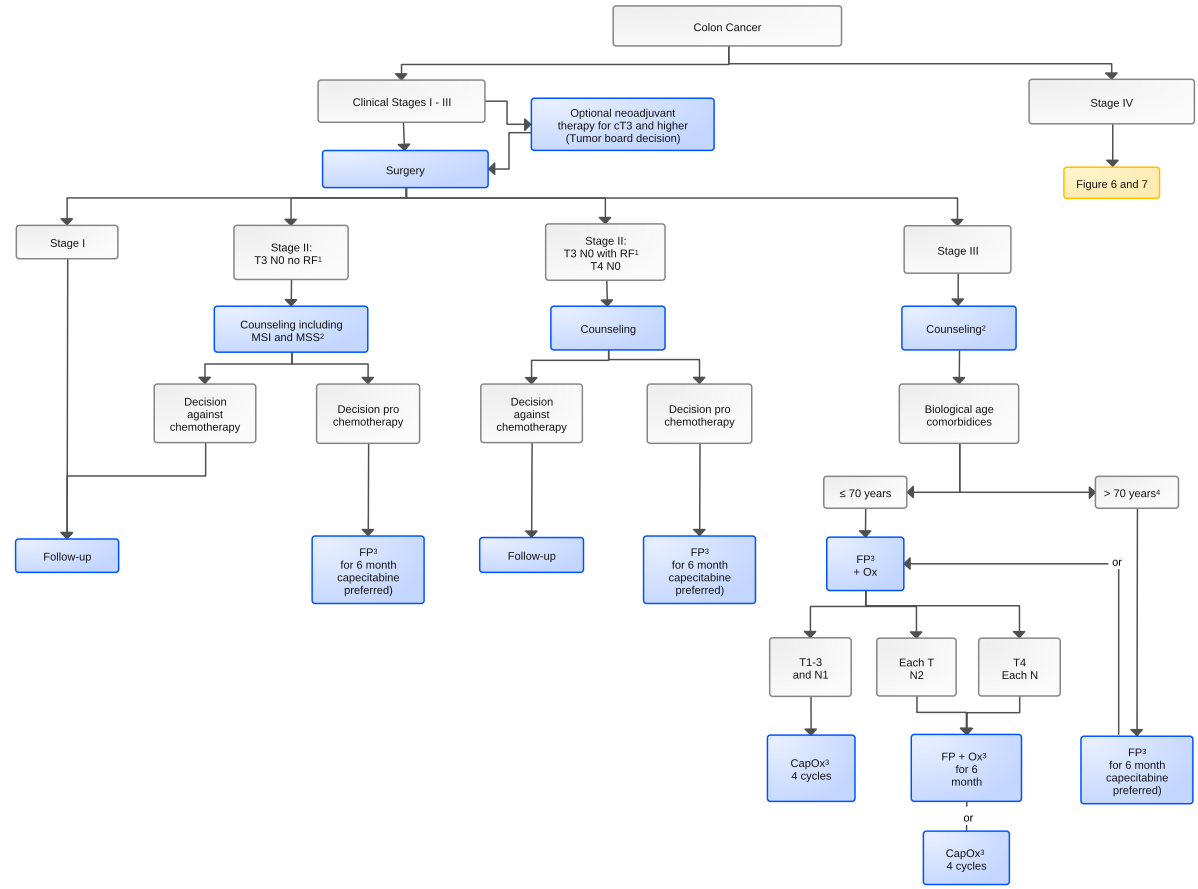
6 Therapy

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]. Treatment algorithms are shown in Figure 5 and Figure 6 and Figure 7.

In Germany and Austria, a mutation in the four most important dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded prior to chemotherapy containing 5-flurouracil (5-FU) or capecitabine. Recommendations for the procedure resulting from this mutation analysis, i.e., the extent of 5-FU dose reduction in the case of heterozygous DPD mutations and the omission of 5-FU in the case of homozygous DPD mutations, were 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 for colon cancer



Legend:
curative intention; non-curative intention

[1] *RF - risk factors, see chapter 6.1.2;*

[2] *Advice on possible benefit, taking into account the MSI status if applicable: Patients with MSS (microsatellite stability) have a less favorable prognosis and are more likely to benefit from adjuvant chemotherapy; patients with MSI (microsatellite instability) have a more favorable prognosis and only have a marginal benefit from adjuvant chemotherapy*

[3] *Cap - capecitabine, FP - fluoropyrimidine: infusional 5-FU/folinic acid or capecitabine; Ox - oxaliplatin*

[4] *The efficacy of oxaliplatin in the elderly is controversial. The use of this substance in patients of advanced biological age should be critically assessed on a case-by-case basis. A dedicated age cut-off does not exist.*

6.1.1 Stage I

The therapeutic approach in stage I is curative. The essential procedure is the complete surgical resection of the primary tumor. By now, individual variations of radical surgical resection in colon carcinoma 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 ≥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 procedure are described in chapter 6.2.1.

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

6.1.2 Stage II

The therapeutic approach in stage II is curative. An evaluation by 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 period 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 in accordance with oncological principles depicted in Chapter 6.1.1 Details of surgical procedures are addressed 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 all 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 lymph nodes examined
- Histopathologically documented lymphatic or blood vessel infiltration, undifferentiated tumor (G3, not applicable in MSI).

Neoadjuvant chemotherapy for clinical T3 or T4 tumors has been investigated in several studies. The results of the pivotal phase III FOXTROT trial published in 2023 [46] can be summarized as follows: Patients with radiologic stage T3-4, N0-2, M0 colon cancer were randomized 2:1 in this trial between treatment with FOLFOX for 6 weeks preoperatively plus 18 weeks postoperatively (NAC group) or 24 weeks postoperatively (control group). The primary endpoint was recurrence-free survival within the first two years. Secondary endpoints included surgical morbidity, histopathologic stage, degree of regression, completeness of resection and mortality. Of 699 patients assigned to NAC, 674 (96%) started treatment and 606 (87%) completed treatment. In total, 686 of 699 (98.1%) NAC patients and 351 of 354 (99.2%) control patients underwent surgery. In 30 patients (4.3%) assigned to NAC, an obstruction occurred that necessitated rapid surgery. Overall, however, fewer serious postoperative complications were observed in the NAC arm. NAC led to significantly better T and N downstaging and better tumor regression. In addition, the R0 resection rate was higher in the NAC arm: 94% (648/686) versus 89% (311/351), $p < 0.001$. The primary endpoint was met: fewer NAC patients had a recurrence within 2 years (16.9% [118/699] versus 21.5% [76/354]; HR 0.72 [95% CI 0.54-0.98]; $p = 0.037$). Tumor regression correlated with freedom from recurrence. NAC showed no benefit in MSI-H/dMMR tumors. Neoadjuvant chemotherapy is therefore a new option for locally advanced T3 or T4 MSS tumors. The indication should be discussed and reviewed on a case-by-case basis in the tumor board.

In about 20% of patients with stage II colon carcinoma, sporadic microsatellite instability (MSI) is detectable in the tumor tissue. This genetic marker correlates with localization in the right colon, poor histological differentiation and the mucinous adenocarcinoma subtype. Patients with microsatellite instability have a better prognosis. The potential benefit of adjuvant chemotherapy is also lower than in patients without MSI. In stage II patients without risk factors, the absence of microsatellite instability can be used as an argument in favor of adjuvant chemotherapy and, conversely, the detection of microsatellite instability as an argument against adjuvant chemotherapy. However, results of prospective randomized studies 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 addressed 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 (T4 and/or N2), 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. In patients with T4 N1-2 tumors, the possible minor benefit of continuing chemotherapy beyond three months should be carefully weighed against the expected cumulative side effects. In the opinion of the authors, a three-month CapOx regimen may also be sufficient for these patients [14].
- Neoadjuvant chemotherapy is a new option for locally advanced T3 or T4 tumors. The indication should be discussed and reviewed on a case-by-case basis in the tumor board. (For more details, see Chapter 6.1.2).
- For patients with contraindications to oxaliplatin, adjuvant chemotherapy with infusional 5-FU/folinic acid or capecitabine is recommended, see Systemic Tumor Treatment Protocols (in German only).
- 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, in Systemic Tumor Treatment Protocols and Approval status (both in German only).

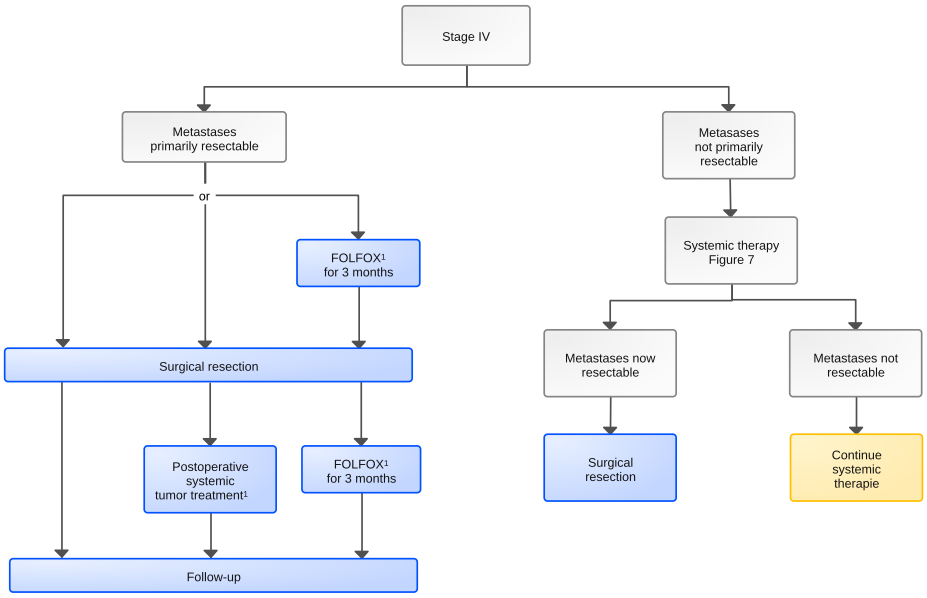
Numerous other substances from the group of cytostatic drugs, immunotherapy or monoclonal antibodies have been and are also being evaluated in the adjuvant situation. So far, no other substance has shown a significant advantage over the chemotherapy standard with 5-FU/folinic acid (or capecitabine) and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

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

6.1.4 Stage IV

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



Legend:
curative intention; non-curative intention
[1]The significance of peri-/postoperative drug therapy has not been clearly clarified; ongoing studies should be supported. See also chapter 6.1.4.1.4

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

6.1.4.1.3 Resection of lung metastases

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

- Exclusion of unresectable extrapulmonary metastases
- R0 resection possible
- Adequate pulmonary residual capacity postoperatively

- ECOG performance score 0-2
- No severe comorbidity

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

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

6.1.4.1.4 Perioperative systemic cancer treatment in patients with primarily resectable metastases

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

Based on data from the phase III EORTC 40983 intergroup study [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 plus oxaliplatin. Particularly in situations in which a low recurrence risk after metastasectomy is expected, additive or "secondary adjuvant" chemotherapy appears to be dispensable because of only small effects on survival parameters. Recent data from a randomized Japanese trial showed an improvement in progression-free survival from 6 months of FOLFOX chemotherapy, but no benefit in terms of overall survival [21]. Ongoing studies should therefore be supported.

6.1.4.2 Conversion therapy for potentially resectable metastases

The number of patients with potentially resectable metastases can be increased by means of so-called conversion therapy. The aim of this approach is to achieve technical resectability by downsizing the metastases. Accordingly, treatment protocols with high response rates and the chance of greater volumetric shrinkage of the metastases are recommended. In randomized and non-randomized phase II trials, doublet combinations plus antibodies (mAb) or triplet combinations ± mAb derived from the palliative setting were used, see Chapter 6.2.3 and Chapter 6.1.4.3. The PRODIGE-14 trial, which randomly tested doublet versus triplet, each + mAb (choice depending on *RAS* status), as conversion therapy, did not find a statistically significant improvement in R0/R1 resection rates; disease-free and overall survival were also not significantly different [52]. However, in the smaller OLIVIA study (80 patients) [22] with more clearly defined and stricter inclusion criteria with regard to irresectability, a benefit was found for triplet therapy + bevacizumab versus FOLFOX + bevacizumab. In the randomized CAIRO-5 study, significantly more R0/R1 resections were also achieved with FOLFOXIRI + bevacizumab compared with FOLFOX + bevacizumab in patients with non-EGFR-sensitive tumors (i.e., pri-

mary in the right hemicolon, *BRAF V600E* MUT or *RAS* MUT) (51 versus 37%) [54, 55]. In this respect, a triplet plus bevacizumab should be preferred in this patient group.

For *EGFR*-sensitive tumors in the VOLFI study (a randomized phase II study), the addition of panitumumab to a dose-reduced chemotherapy triplet led to high remission rates and consecutively improved resection rates in patients who tended to be younger. An improvement in overall survival was not shown [23]. However, the phase III TRIPLETE study [53] showed no benefit of a triple over a doublet therapy (each in combination with panitumumab) in terms of response and resection rates as well as PFS, so that a chemotherapy doublet should be chosen for patients who are to receive conversion therapy including an *EGFR*-mAb.

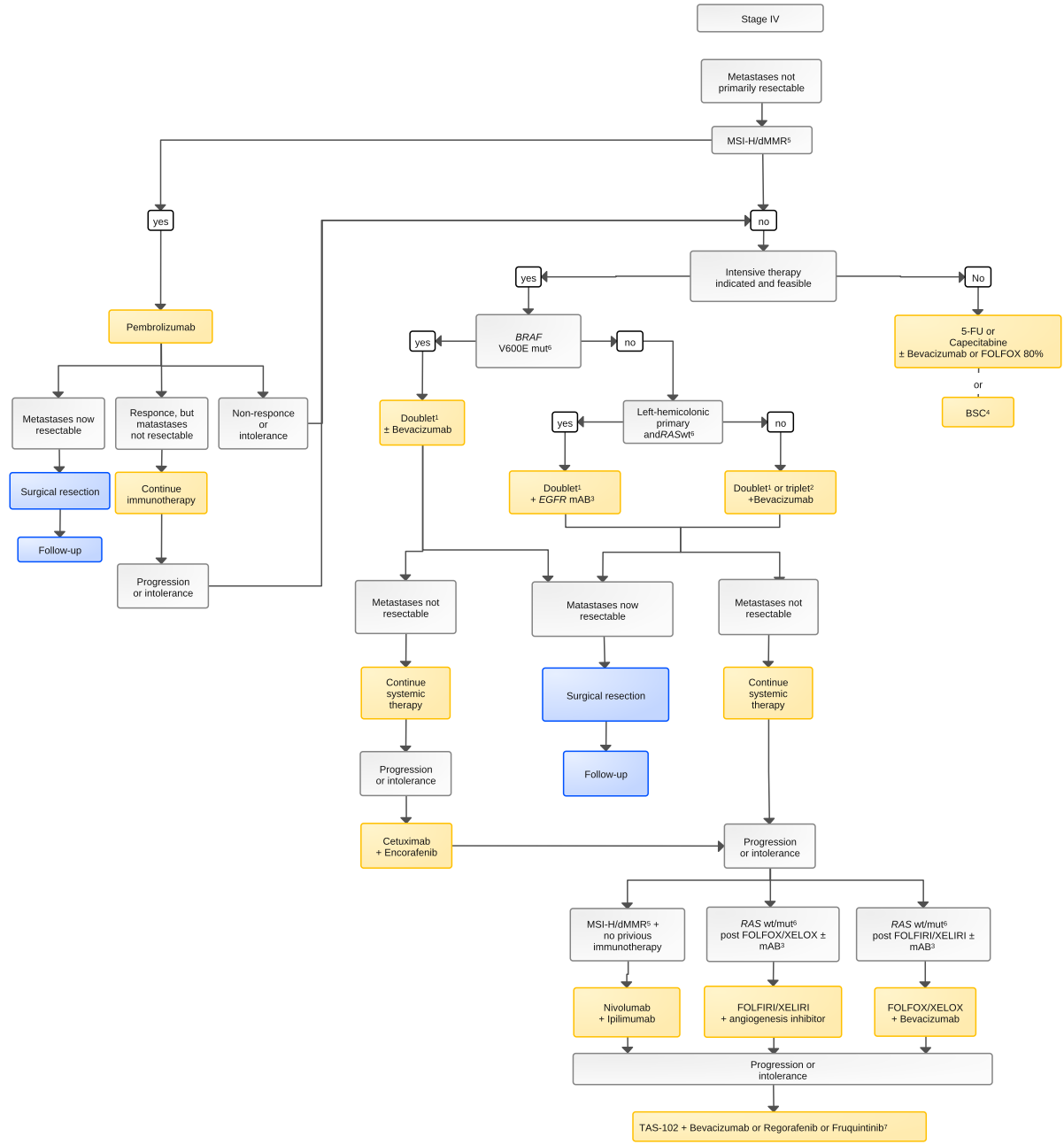
In studies with unselected patients, between 5 and 25% of initially non-resectable patients were subsequently resectable, up to 40% in the case of liver metastasis only. A treatment duration of 2 to 4, possibly up to 6 months is recommended, depending on clinical response. Once technical resectability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

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

6.1.4.3 Therapy of primarily non-resectable metastases

Despite effective primary therapy and progress in adjuvant treatment, distant metastases emerge in 35-45% of patients. The relapse rate is highest in the first two years after first diagnosis, while recurrence after more than 5 years is rare. In a subgroup of patients, a cure is also possible in this setting, see Chapters 6.1.4.1 and 6.1.4.2. For the treatment algorithm, see Figure 7.

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



Legend:
curative intention; non-curative intention
[1] Doublet - combination of fluoropyrimidine plus either oxaliplatin or irinotecan
[2] Triplet - combination of fluoropyrimidine plus oxaliplatin and irinotecan
[3] mAB - monoclonal antibody
[4] BSC - Best Supportive Care (best supportive therapy)
[5] MSI-H/dMMR - microsatellite instability-high/deficient DNA mismatch repair
[6] mut - mutated; wt - wild type (unmutated)
[7] Fruquintinib is not yet approved (February 2024)

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

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

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

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

Biological test methods for the selection of the optimal therapy, e.g., gene signatures or *in vitro* sensitivity testing, have not yet been sufficiently validated. Monitoring by serial measurement of circulating tumor cells or circulating DNA is also not a standard procedure.

6.1.4.3.1 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 were tested in combination with doublet chemotherapy, see Chapter 6.1.4.3.1.1. In the TRIPLETE trial [53], triplet chemotherapy in combination with anti-*EGFR* antibodies showed no advantage in terms of response and resection rates or PFS and should therefore not be used [23]. In combination with bevacizumab, triplet chemotherapy leads to longer progression-free survival (PFS) 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% of patients per line of therapy.

6.1.4.3.1.1 RAS wild type (RASwt)

Intact signaling via the RAS molecules is a prerequisite for the efficacy of the anti-*EGFR* antibodies cetuximab and panitumumab. Patients with tumors in which a mutation in one of the

RAS genes has been detected (i.e. *KRAS* exon 2-4 and *NRAS* exon 2-4) should not be treated with any of the anti-*EGFR* antibodies.

The question of whether an anti-*EGFR* antibody should be used primarily in patients with wild-type *RAS* was investigated in randomized studies. The sequence doublet + cetuximab versus doublet + bevacizumab was used first line, including a protocol-defined crossover to the other antibody in the event of relapse/refractory disease as provided for in the protocol. In the first study [27], a significantly longer survival time was found for the cetuximab sequence in the first line, followed by bevacizumab in the second line, with a hazard ratio of 0.7. In a second study [28], this difference could not be reproduced, see also the 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 primary tumor in the right hemicolon, i.e., proximal/oral to the Flexura coli sinistra, versus the left hemicolon, i.e., distal/aboral, on treatment outcomes in patients with a *RAS*wt tumor was investigated [18]. On one hand, this showed a significantly worse overall survival for patients with a primary tumor in the right hemicolon. On the other hand, there was a clear benefit for patients with a primary tumor in the left hemicolon from treatment with anti-*EGFR* antibodies compared to the control arm with chemotherapy +/- bevacizumab (hazard ratio 0.75 for overall survival; 0.78 for progression-free survival). Patients with tumor site in the right hemicolon had no benefit from the administration of anti-*EGFR* antibodies in terms of progression-free and overall survival despite *RAS*wt. For the first-line treatment of patients with a *RAS*wt tumor and a primary tumor in the left-sided colon, the combination of anti-*EGFR* antibodies and combination chemotherapy is currently recommended. In patients with *RAS*wt and a right-sided location of the primary tumor, there is no benefit of an anti-*EGFR* antibody over chemotherapy or a bevacizumab combination in first-line therapy [29].

Data from the FIRE-4 and PARADIGM studies show that *RAS* mutations are detectable in the blood of around 10% of patients with a *RAS*wt status detected in the tumor tissue. Compared to patients without RAS mutations in tissue and blood, these patients show significantly poorer survival under a chemotherapy doublet with anti-*EGFR* antibodies. They should therefore not be treated with anti-*EGFR* antibodies [51]. The prerequisite for this procedure is the use of certified and quality-assured ctDNA analysis.

6.1.4.3.1.2 RAS mutations

In patients with defined *RAS mutations* (in tissue and/or blood), bevacizumab should be used as a monoclonal antibody in first-line therapy. A combination of chemotherapy with bevacizumab led to significant improvements in remission rates and progression-free survival compared to chemotherapy alone, and in some studies also in overall survival. The combination with a triplet (5-FU, folinic acid, irinotecan, oxaliplatin) leads to slightly higher remission rates and a significant extension of progression-free survival compared to a doublet (5-FU, folinic acid, irinotecan) [24].

6.1.4.3.1.3 MSI high/dMMR

For patients with microsatellite instability in their tumor tissue, pembrolizumab was compared with various "standard of care" regimens in the KEYNOTE-177 study. This showed a clinically meaningful and significant prolongation of PFS (hazard ratio 0.6 (0.45-0.80)) with significantly reduced toxicity (22% instead of 6% grade 3 / 4 side effects). Overall survival (as a secondary endpoint) was not statistically significantly prolonged (with a high rate of cross-over within and outside the study). Pembrolizumab has been approved by the EMA in February 2021 for the treatment of metastatic colorectal tumors with MSI. Analysis of MSI can be performed by immunohistochemistry [30].

6.1.4.3.2 Maintenance therapy

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

In randomized studies, post-doublet induction including oxaliplatin plus bevacizumab, maintenance therapy with a fluoropyrimidine + bevacizumab led to a statistically significant extension of the time to tumor progression compared to a watch-and-wait strategy. Bevacizumab monotherapy is not recommended. Patients who wish to interrupt therapy, or for whom this seems reasonable, can therefore be advised to take a break after 6 months of therapy without a significant worsening of the probability of survival. The significantly shorter progression-free survival time should be pointed out. Close follow-up is recommended in this situation. Immediate re-induction at first progression under maintenance therapy is only feasible in a minority of patients. Nevertheless, re-induction therapy should definitely be considered in the further course of treatment, see Chapter 6.1.4.3.3

A detailed description of the three large, randomized studies on maintenance therapy with bevacizumab can be found in the AIO statement [29].

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

Regarding maintenance therapy with *EGFR* inhibitors, according to data from the PANAMA trial, continuation of 5-FU and the anti-*EGFR* antibody is recommended after 3 months of induction chemotherapy [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, treatment goal, *BRAF* and *RAS* status, and *MSI* status. Second-, third-, or fourth-line therapy is individualized. The following principles should be considered:

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

- In second-line therapy, the combination of the anti-angiogenic antibody ramucirumab with FOLFIRI leads to prolonged survival in patients previously treated with oxaliplatin- and bevacizumab-based first-line therapy.
- Ramucirumab or aflibercept should be preferred in patients with only a short first-line PFS under bevacizumab-containing therapy.
- Patients with *RAS* wild-type who have not received anti-*EGFR* antibodies in first-line therapy and have a high remission pressure for second-line therapy, should be treated with a combination of an anti-*EGFR* antibody plus chemotherapy, see Systemic Tumor Treatment Protocols (in German only). This also includes a change of cytostatic drugs.
- Cetuximab and panitumumab should preferably be used in first-line therapy. When used for the first time in chemotherapy-refractory patients, both substances are equally effective. The use of panitumumab after failure of cetuximab-based regimens is not a standard of care, and vice versa. A rechallenge of cetuximab or panitumumab should only be carried out in patients in whom no *RAS* and/or *BRAF* mutations are detectable in a liquid biopsy.
- In patients with *BRAF* V600E mutation, the use of a combination of encorafenib and cetuximab in second- and third-line therapy in accordance with current approval leads to an extension of progression-free and overall survival, see Colorectal Carcinoma approval (in German only) [33].
- After pretreatment with chemotherapy, pembrolizumab or the combination of nivolumab and ipilimumab can be used in patients with MSI-H tumors in accordance with current approval [34].
- If established chemotherapeutic agents and monoclonal antibodies fail or are intolerable, trifluridine/tipiracil should be used in combination with bevacizumab [56].
- The oral multikinase inhibitors fruquintinib [50] and regorafenib have led to an increase in overall survival in heavily pretreated patients compared to placebo. However, fruquintinib is not yet approved (as of February 2024) and regorafenib is not available in Germany.
- For patients with *HER2* positivity (in particular, but not exclusively after anti-*EGFR* therapy and for left-sided tumors), data from various phase II studies indicate that trastuzumab/lapatinib, trastuzumab/pertuzumab, trastuzumab/tucatinib or trastuzumab-deruxtecan are treatment options. Most study data are available for *RAS*wt tumors. Trastuzumab deruxtecan, however, can also be used in patients whose tumors are *RAS*mut. Patients with *HER2* mutations showed responses with a combination of trastuzumab/tucatinib in the MOUNTAINEER study [49]. There is no approval for any of the drugs mentioned for this treatment setting; see Colorectal carcinoma approval (in German only).
- Patients with *KRAS* G12C mutations showed a significant benefit in response rate and PFS in the three-arm Phase III CodeBreaK-300 study from the combination of sotorasib (960mg) and panitumumab compared with trifluridine/tipiracil or regorafenib therapy or a combination of lower-dose sotorasib (240mg) and panitumumab [48]; sotorasib is not yet approved for the treatment of mCRC.
- Patients whose tumor shows an *NTRK* fusion can be treated with the tyrosine kinase inhibitors larotrectinib and entrectinib in accordance with current approval.

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

6.1.4.3.4 Resection of an asymptomatic primary colon tumor

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

On the basis of this study, primary tumor resection cannot be recommended for asymptomatic primary tumors.

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 a multidisciplinary tumor board, taking into account the overall treatment plan and the potentially substantial toxicity.

6.1.4.3.6 Peritoneal carcinomatosis

The median survival time of patients with proven peritoneal carcinomatosis is significantly worse than for other metastatic manifestations. Nevertheless, the PRODIGE-7 trial showed a median overall survival of 41 months for the combination of systemic chemotherapy and cytoreductive surgical intervention (CRS) in patients with isolated peritoneal carcinomatosis. In this randomized study (CRS +/- HIPEC), however, the additional benefit of supplementary hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin could not be demonstrated [37]. In this respect, HIPEC with oxaliplatin after CRS cannot be recommended at the present time. Cytoreductive surgery alone can be regarded as a basic standard treatment option, carried out at specialized centers. Criteria for decision-making are good general condition, localized and exclusively peritoneal metastasis (peritoneal carcinomatosis index PCI max. 15), as well as potential CC0 resectability. There is currently no consensus regarding the indication for HIPEC; it should be carried out either as part of clinical trials or as an individual decision using mitomycin C infusion over 60-90 minutes. The use of mitomycin C rather than oxaliplatin is sug-

gested in particular based on the data from the Spanish HIPECT4 trial, which was however conducted in a different treatment setting (tumors assessed preoperatively as T4) and showed an advantage in 3-year freedom from local recurrence [47].

6.2 Treatment modalities

6.2.1 Surgery

6.2.1.1 Primary tumor

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

Table 5: Surgical interventions

Localization	Operation
Cecum	Right hemicolectomy
Ascending colon	Right hemicolectomy
Right flexure	Extended right hemicolectomy
Transverse colon, proximal	Extended right hemicolectomy
Transverse colon, middle third	Transversum resection, Extended right hemicolectomy if necessary
Transverse colon, distal	Extended left hemicolectomy
Left flexure	Extended left hemicolectomy
Descending colon	Left hemicolectomy
Sigmoid, proximal	Left hemicolectomy
Sigmoid, medium and distal	Oncologic sigmoid resection

6.2.1.2 Surgical access

The operation can be performed open, laparoscopically and robotically with the appropriate expertise. The advantage of open surgery is the shorter operating time. The advantages of laparoscopic surgery are the cosmetic outcome, less blood loss and potentially faster postoperative recovery. The long-term oncologic results of the two approaches are presumably equivalent [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 with creation of a passive anus praeter or one-step subtotal colectomy are feasible. In patients with hereditary disease, the type 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 chemotherapy 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, see also Approval Status Colorectal Cancer (in German only). 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 mucositis, and others. Before chemotherapy containing 5-FU, a mutation in the four most important dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded [39].

6.2.3.7 Fruquintinib

Fruquintinib is an oral, selective inhibitor of VEGF receptors 1, 2 and 3. In the FRESCO-2 study [50], a significant increase in median survival time from 4.8 to 7.4 months was achieved compared to placebo in 691 patients with refractory metastatic colorectal cancer. The most common adverse events observed in the study were arterial hypertension (14%), weakness (8%) and hand-foot syndrome (6%). The marketing authorization application to the EMA was accepted for review in June 2023 and FDA approval was granted in November 2023.

6.2.3.8 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%).

6.2.3.9 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.

6.2.3.10 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%).

6.2.3.11 Oxaliplatin

Oxaliplatin is a platinum derivative. It is highly effective in combination with fluoropyrimidines (5-FU/folinic acid [FA], capecitabine). In first-line therapy, it increases remission rates to 40-60% and prolongs progression-free survival compared to 5-FU/FA. 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.

6.2.3.12 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.

6.2.3.13 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).

6.2.3.14 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. Information on approval status is summarized in Colorectal Cancer Approval Status (in German only).

6.2.3.15 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. Information on approval status is summarized in Colorectal Cancer Approval Status (in German only).

6.2.3.16 TAS-102

TAS-102 is an 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 > 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. TAS-102 should whenever possible be combined with bevacizumab based on the results of the SUNLIGHT study, showing significantly improved overall survival by the addition of bevacizumab to TAS-102 [56],. Information on approval status is summarized in Colorectal Cancer Approval Status (in German only).

6.2.3.17 S1 (Tegafur plus Gimeracil and Oteracil)

For patients with colon cancer who are intolerant 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 different degrees of secondary disorders in patients with colon carcinoma and thus significantly impair their quality of life, independence and possibly also their ability to work and perform. Medical rehabilitation, both inpatient and outpatient, can eliminate 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 take place during rehabilitation. Rehabilitation includes providing the patient with comprehensive information on the underlying disease and all diagnostic and therapeutic modalities. The patient should be trained in dealing with the consequences of the disease and the therapy (e.g., treatment of 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 in accordance with the specifications of the pre-treatment tumor center during rehab in order to avoid interruptions or delays in therapy.

An initial psychological examination should be requested in order to identify deficits in disease management or reactive moods and to initiate further measures. Dietary advice should be provided to support patients in making the necessary changes to their dietary habits and lifestyle. Comprehensive training therapies should help patients to regain muscular strength and endurance and motivate them to remain physically active after rehabilitation.

Patients of working age must be informed about the options for returning to work (gradual reintegration, internal redeployment, placement in a job suitable for the patient's condition, retraining) and supported in doing so. Furthermore, if necessary, support should be organized at home for activities of daily living or nursing care. The rehabilitation clinic should also organize the patient's continued medical care if this has not been arranged. Patients should be offered access to self-help groups.

In principle, the patient's right to choose a rehabilitation facility must be respected. However, only facilities that are able to provide professional care for patients with colon cancer can be considered, i.e., clinics 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 for patients with colon cancer

Investigation	month 3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Medical history, Physical examination	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X		X **X** X		X **X** X		X **X** X		X **X** X
CEA	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X	X **X** X		X **X** X		X **X** X		X **X** X		X **X** X
Abdominal sonography		X		X		X		X				X		X		X
CT abdomen / thorax				**X** X				**X** X				**X** X		X		X
Colonoscopy		X*		X **X** X										**X** X		X

Legend:
CEA, carcino-embryonic antigen in blood
X Recommendations in Germany
***X Recommendations in** Austria*
X Recommendations in Switzerland
**Colonoscopy should be carried out after 6 months if a complete colonoscopy was not performed preoperatively.*

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

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.