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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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DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
Bauhofstr. 12
D-10117 Berlin

Executive chairwoman: Prof. Dr. med. Claudia Baldus

Phone: +49 (0)30 27 87 60 89 - 0

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

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Authors: Ralf-Dieter Hofheinz, Dirk Arnold, Markus Borner, Wolfgang Eisterer, Gerhard Faber, Gunnar Folprecht, Ullrich Graeven, Birgit Grünberger, Holger Hebart, Susanna Hegewisch-Becker, Volker Heinemann, Ron Pritzkuleit, Holger Rumpold, Marianne Sinn, Jürgen Weitz, Bernhard Wörmann

In cooperation with AIO

Previous authors: Thomas Meybier, Werner Scheithauer, Hans-Joachim Schmoll, Josef Thaler

1 Summary

Colorectal carcinoma 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. The topic of this guideline is adenocarcinoma of the colon. It accounts for 60-70% of colorectal cancers in Germany.

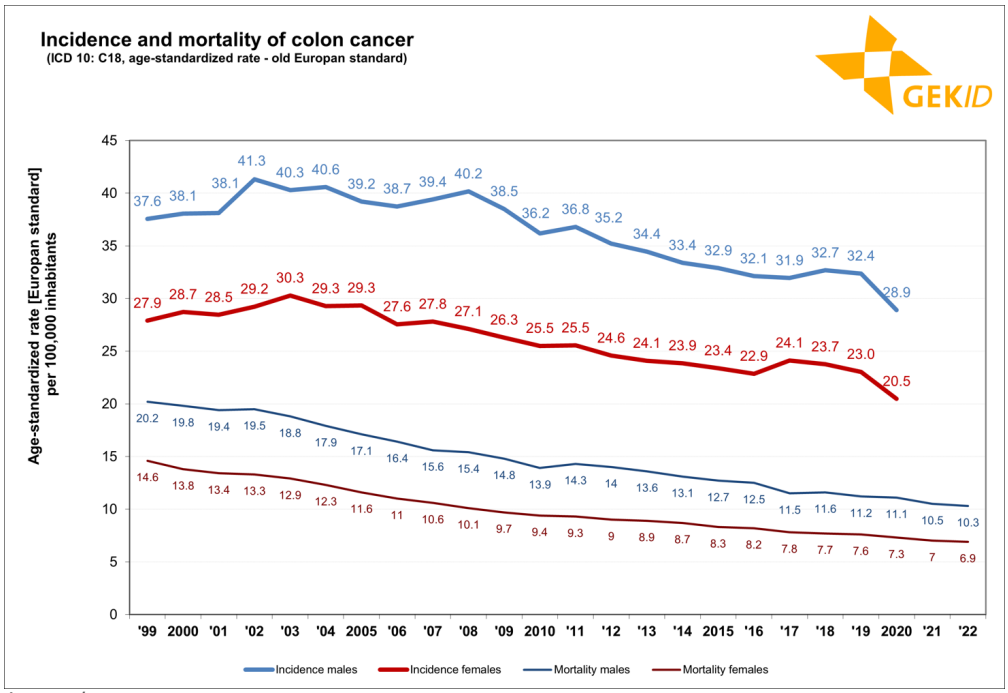
2.2 Epidemiology

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.

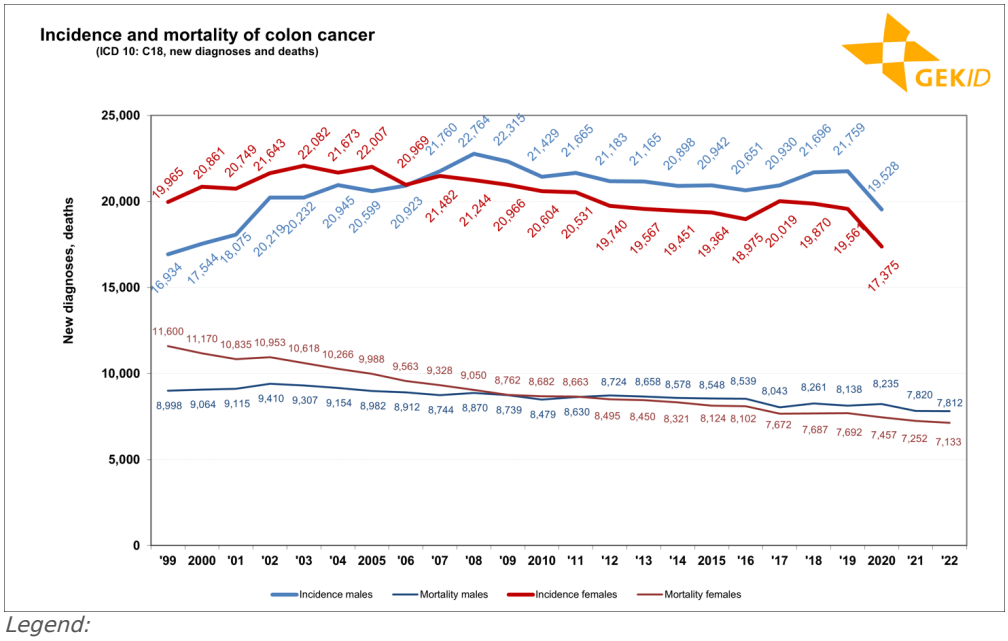
Figure 1: Estimated incidence and mortality of colon cancer (ICD 10: C18) in Germany - age-standardized rates (old European standard)



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).

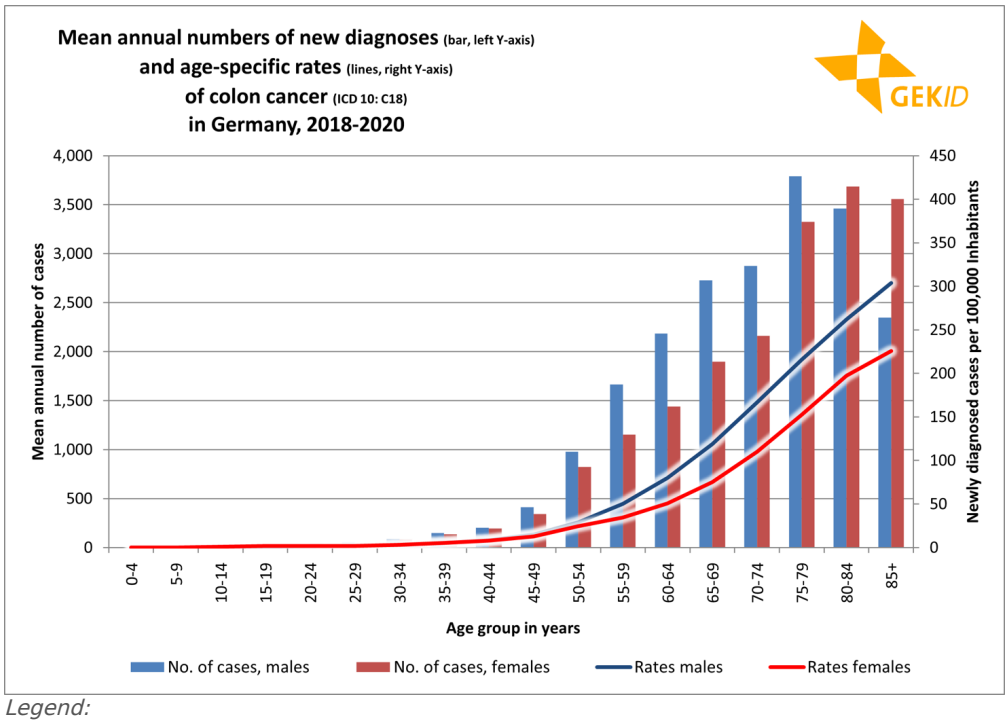
Figure 2: Estimated incidence and mortality of colon cancer (ICD 10: C18) in Germany - case numbers



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.

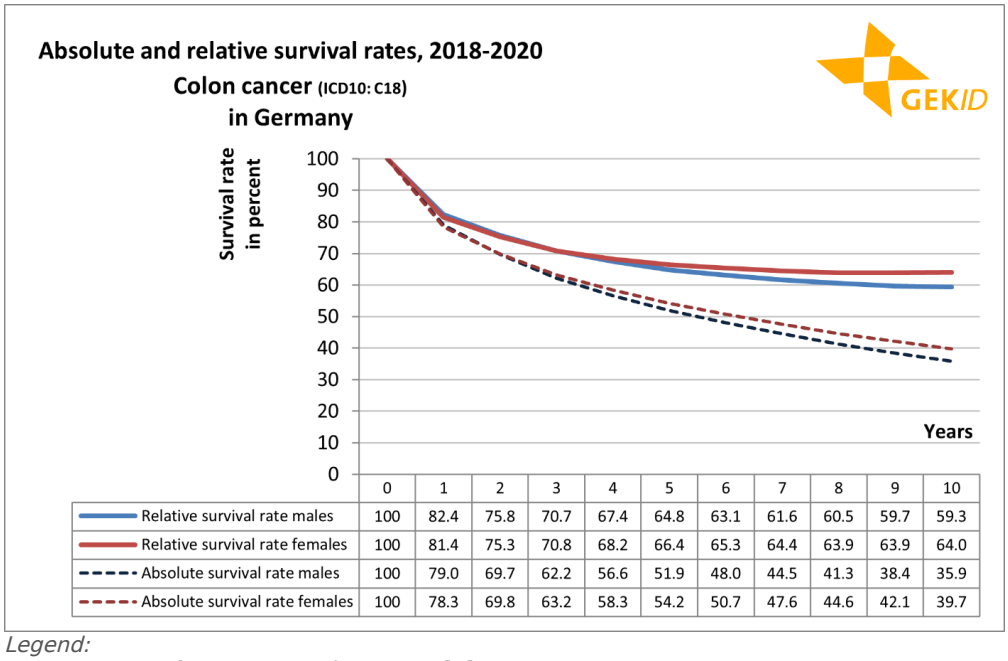
Figure 3: Age distribution of the incidence of colon cancer (ICD 10: C18) - age-specific case numbers and rates



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 hemoglobin 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

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

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

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

3.2.2 Risk groups

3.2.2.1 Relatives of patients with colorectal cancer

First-degree relatives should undergo 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 European Society for Medical Oncology (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 pan-

colitis 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)	Postoperatively at the latest, if not done preoperatively

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. 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.

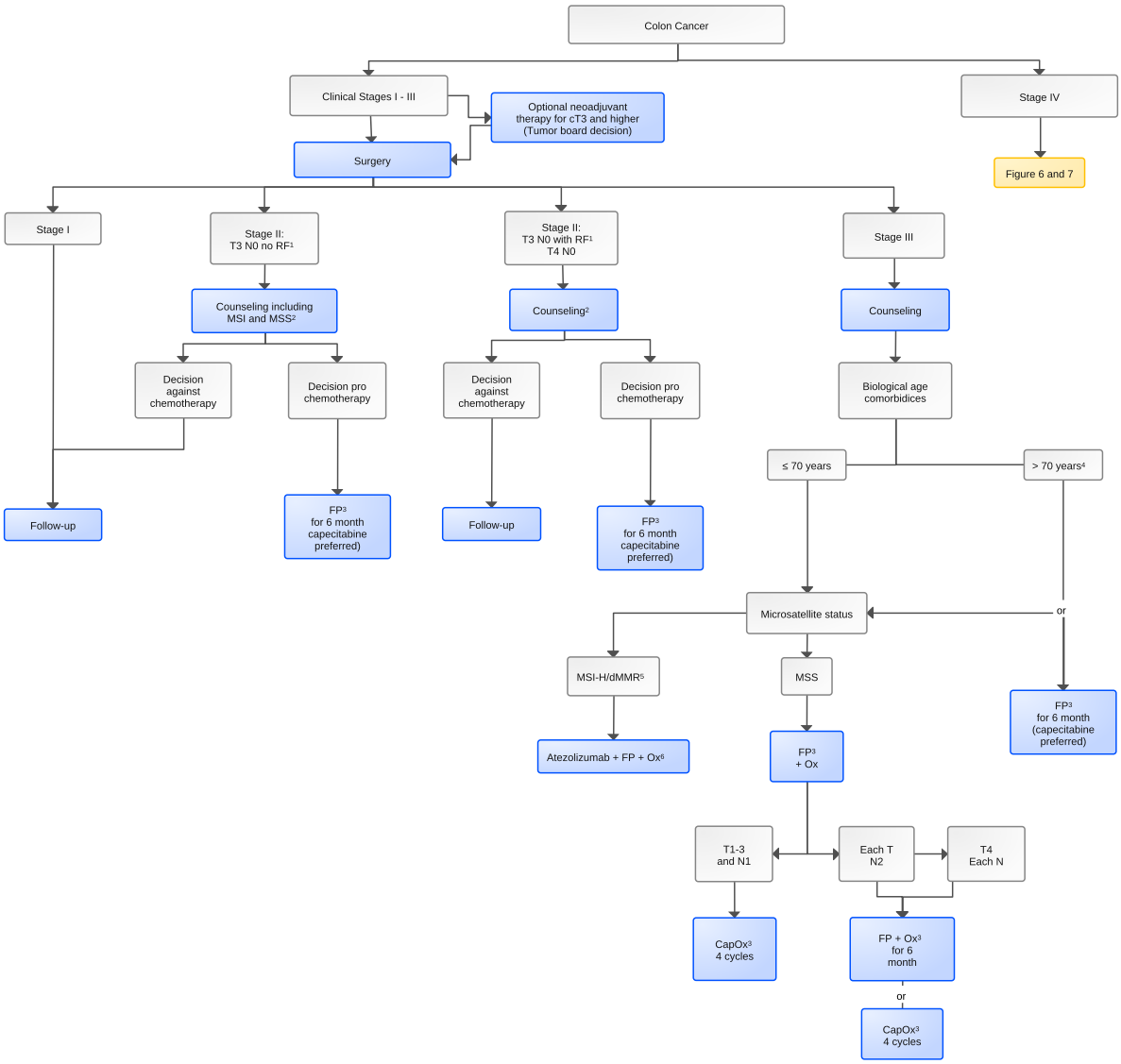
6 Therapy

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). 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:
[1] RF – risk factors, see Chapter 6.1.2;
[2] Advice on possible benefits, taking into account microsatellite status: Patients with MSS (microsatellite stability) have a poorer prognosis and are more likely to benefit from adjuvant chemotherapy; patients with MSI (microsatellite instability) have a better prognosis and only a marginal benefit from adjuvant chemotherapy
[3] Cap – capecitabine, FP – fluoropyrimidine: infusion of 5-FU/folinic acid or capecitabine; Ox – oxaliplatin
[4] The efficacy of oxaliplatin in older patients is controversial. The use of this drug should be critically evaluated on a case-by-case basis in patients of advanced biological age. There is no definitive age cut-off
[5] MSI-H (high) – high microsatellite instability; dMMR – deficient mismatch repair
[6] Atezolizumab is not yet EU approved for adjuvant therapy in colon cancer (as of July 23, 2025)

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).

In approximately 20% of patients with stage II colon cancer, microsatellite instability (MSI) is detectable in the tumor tissue. This genetic biomarker correlates with localization in the right colon, poor histological differentiation, and the subtype of mucinous adenocarcinoma. 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, while the detection of microsatellite instability can be used as an argument against it. However, there are no results from prospective randomized studies based on microsatellite instability.

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 (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. 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 treatment 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 treatment protocols for colorectal carcinoma.
    - 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 Treatment protocols and Approval status.

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 adverse effects on capecitabine efficacy [43, 44].

6.1.4 Neoadjuvant therapy in localized stages

Neoadjuvant treatment for clinical T3 or T4 tumors has been investigated in several studies, both for patients unselected for microsatellite/MMR status and for patients with MSI-H/dMMR tumors.

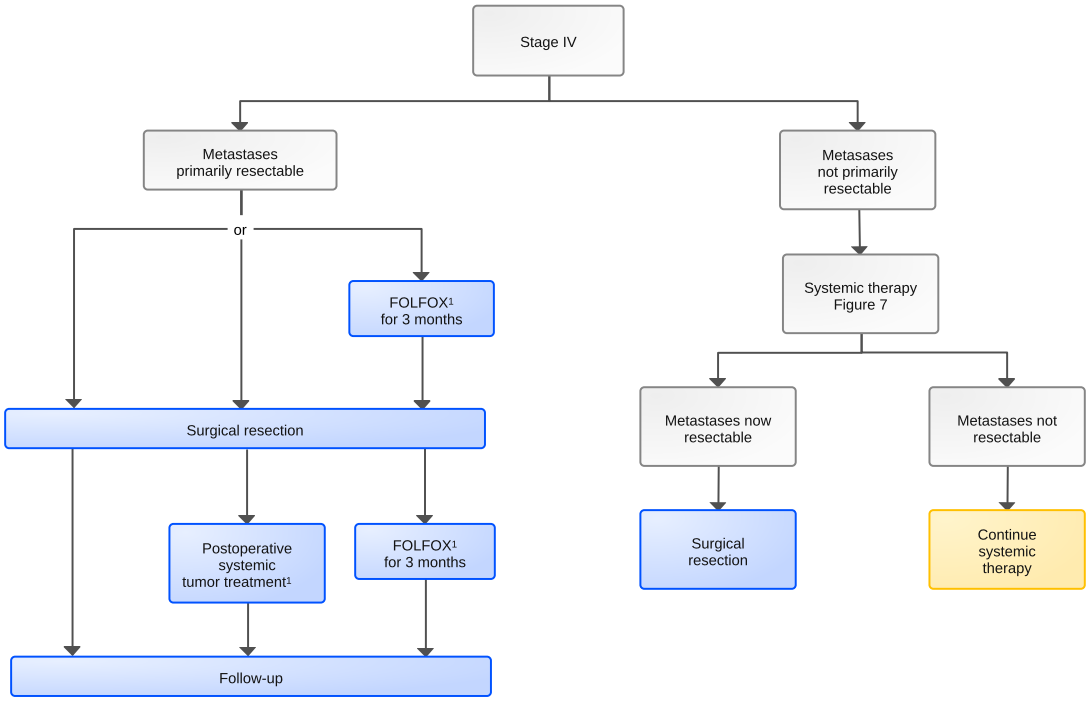
The results of the pivotal phase III FOXTROT study published in 2023 [46] can be summarized as follows: Patients with radiologically staged T3−4, N0−2, M0 colon cancer were randomized 2:1 in this study to receive FOLFOX therapy for 6 weeks preoperatively plus 18 weeks postoperatively (NAC group) or 24 weeks postoperatively (control group). The primary endpoint was recurrence-free survival within the first two years. Secondary endpoints included surgical morbidity, histopathological stage, degree of regression, completeness of resection, and mortality. Of the 699 patients assigned to NAC, 674 (96%) started therapy and 606 (87%) completed it. A total of 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, intestinal obstruction occurred, necessitating earlier 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 achieved: fewer NAC patients experienced recurrence within 2 years (16.9% (118/699) vs. 21.5% (76/354); HR 0.72 (95% CI 0.54–0.98); $p = 0.037$). Tumor regression correlated with recurrence-free survival. No benefit of NAC was observed 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 assessed on a case-by-case basis by a tumor board.

Neoadjuvant immunotherapy has been investigated in various phase II studies for MSI-H/dMMR tumors; in the NICHE2 study [58], for example, it led to very high rates of pathohistological complete remission (67%) and good disease-free survival (>95%), so that - at least for patients with questionable R0 resectability due to locally advanced tumor growth – neoadjuvant immunotherapy should be considered. Significant (pathohistological) remissions were achieved in NICHE2 after a very short treatment duration of 4 weeks (ipilimumab 1 dose, bi-weekly nivolumab 2 doses).

6.1.5 Stage IV

The therapeutic goal of stage IV patients used to be considered as 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 6.1.5.1 and Chapter 6.1.5.2), see Figure 6 and Figure 7.

Figure 6: Treatment structure in stage IV colon cancer



Legend:
[1] The significance of peri-/postoperative drug therapy has not been clearly clarified; ongoing studies should be supported. See also chapter 6.1.5.1.4

In previous versions of the S3 and ESMO 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].

6.1.5.1 Stage IV with resectable metastases

6.1.5.1.1 Surgical resectability

The disease-free survival rate of patients with resectable liver or lung metastases is up to 50% after 5 years. The criterion for 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.

6.1.5.1.2 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% calculated functional residual liver tissue postoperatively
- Sufficient safety margins to critical hepatic vessels
- No hepatic insufficiency, no liver cirrhosis Child B or C
- ECOG performance score 0 - 2
- No severe comorbidity

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

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

6.1.5.1.3 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 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).

6.1.5.1.4 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. 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.

6.1.5.2 Conversion therapy for potentially resectable metastases

The number of patients with potentially resectable metastases can be inceased 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 6.1.5.3. 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., right hemicolonic primary, *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.

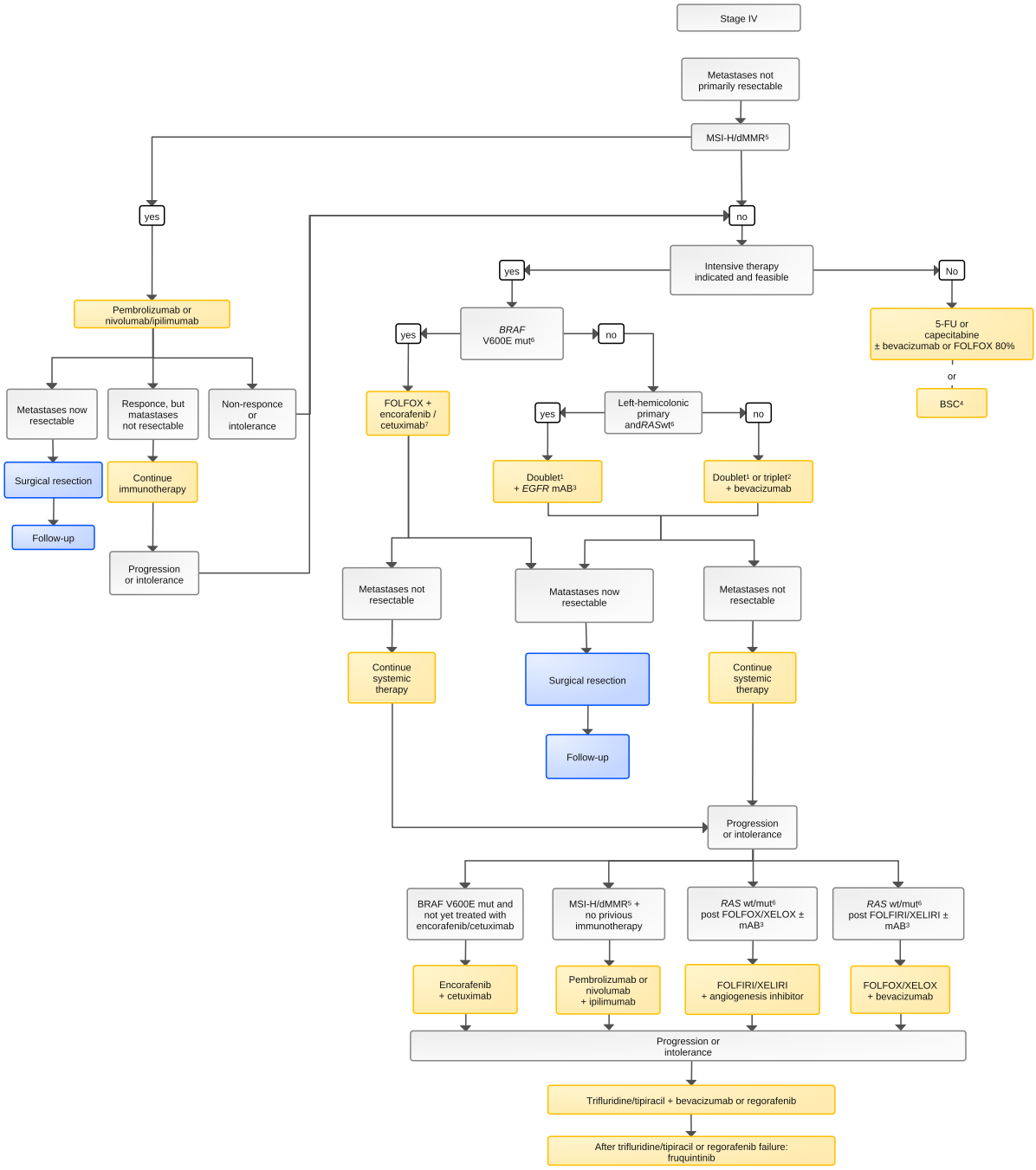
In studies with unselected patients, between 5 and 25% of initially non-resectable patients were subsequently resectable, up to 40% in the case of liver metastasis only. A treatment duration of 2 to 4, possibly up to 6 months is recommended, depending on clinical response. Once technical resectability 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.

6.1.5.3 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 6.1.5.1 and 6.1.5.2. For the treatment algorithm, see Figure 7.

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



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

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.

6.1.5.3.1 Induction therapy

The goals of induction therapy depend on disease status (see Chapter 6.1.5) 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.
- In patients whose tumors showed a *BRAF V600E* mutation, the BREAKWATER study [59, 60] showed that a combination of FOLFOX, encorafenib, and cetuximab significantly improved both the response rate and PFS (primary endpoints) as well as overall survival compared with the previous standard of care (see below).

Anti-EGFR antibodies were tested in combination with doublet chemotherapy, see chapter 6.1.5.3.1.1. Triplet chemotherapy in combination with anti-EGFR antibodies showed no advantage in terms of response and resection rates or PFS in the TRIPLETE study [53], while long-term survival was better in the triplet arm [23]. The significance of triple therapy in combination with anti-EGFR antibodies cannot therefore be conclusively assessed. In combination with bevacizumab, triple chemotherapy leads to longer progression-free survival (PFS) than a doublet + bevacizumab [24]. Prolonging the time to progression, and thus to symptoms and renewed intensive therapy, is also a clinically relevant treatment goal for patients with a clear palliative indication.

A meta-analysis did not confirm a superior efficacy of triple chemotherapy compared to double therapy in patients with *BRAF V600E*-mutated tumors [25]. In the FIRE 4.5 study, the addition of cetuximab to a triple chemotherapy regimen also showed no benefit compared to a triple regimen plus bevacizumab in patients whose tumors showed a BRAF mutation [26]. Until the publication of the BREAKWATER study, doublet chemotherapy with an angiogenesis inhibitor was therefore considered a reasonable primary therapy for these patients (e.g., FOLFOX/CAPOX + bevacizumab). In BREAKWATER, the response rates (65.7% versus 37.4%), as well as PFS

(12.8 vs. 7.1 months; HR 0.53; 95% CI 0.407-0.677; p<0.0001) and overall survival (30.3 vs. 15.1 months; HR 0.49; 95% CI 0.375–0.632; p<0.0001) showed significantly and clinically highly relevant improvements in the experimental arm. In this respect, patients with a BRAF V600E-mutated tumor should primarily be offered a therapy consisting of FOLFOX, encorafenib, and cetuximab. Approval has not yet been granted in the European Union.

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

6.1.5.3.1.1 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 the right-hemicolonic location of the primary tumor, i.e., proximal/oral to the Flexura coli sinistra, versus the left-hemicolonic location, 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 right-hemicolonic primary tumor. On the other hand, there was a clear benefit for patients with a left-hemicolonic primary tumor 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.

6.1.5.3.1.2 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].

6.1.5.3.1.3 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].

The combination of nivolumab and ipilimumab was compared with nivolumab monotherapy and standard-of-care chemotherapy in the 3-arm CheckMATE 8HW study [61]. Survival data are still pending. Progression-free survival was significantly and clinically meaningful improved with ipilimumab/nivolumab compared with both chemotherapy and nivolumab monotherapy (HR versus nivolumab: 0.62, 95% CI 0.48-0.81; p=0.0003). In this respect, dual checkpoint inhibition with nivolumab/ipilimumab is preferable to monotherapy with PD1/PD-L1 inhibitors. Ipilimumab/nivolumab and pembrolizumab are approved for the treatment of metastatic colorectal tumors that are MSI-H. MSI can be assessed by immunohistochemistry.

6.1.5.3.2 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 6.1.5.3.3

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.

6.1.5.3.3 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 Drug Tumor Therapy - Protocols. 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 who have not yet been treated with FOLFOX/encorafenib/cetuximab in first-line therapy, the combination of encorafenib and cetuximab in second- and third-line therapy results in a prolongation of progression-free and overall survival (see approval for colorectal cancer [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. Fruquintinib has been approved in 2024 for monotherapy after failure of all established standard treatment options including trifluridin/tipiracil, while regorafenib is still approved, but has been withdrawn from the market 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 can also be used in patients whose tumors are *RAS*mut. Patients with a *HER2* mutation showed a response with a combination of trastuzumab/tucatinib in the MOUNTAINEER study [49]. There is no approval for any of the drugs mentioned for this treatment setting; see Colorectal carcinoma approval.

- 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.

6.1.5.3.4 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. 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.

6.1.5.3.5 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 there-

fore 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.

6.1.5.3.6 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 suggested in particular by data from the Spanish HIPECT4 trial, which was 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.

6.2.2 Systemic tumor treatment agents

6.2.2.1 5-Fluorouracil

5-Fluorouracil is used in almost all forms of drug-based tumor therapy for patients with colorectal carcinoma. The best risk-benefit ratio is achieved by continuous intravenous infusion over 24 - 48 hours after prior administration of folinic acid. The 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, etc.

Before chemotherapy containing 5-FU, a mutation in the four most important dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded [39].

6.2.2.2 Aflibercept

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

6.2.2.3 Bevacizumab

Bevacizumab is a monoclonal, anti-angiogenic antibody. In combination with 5-FU / folinic acid, capecitabine, irinotecan or oxaliplatin, remission rates of around 50% and a prolongation of progression-free survival are achieved. In combination with irinotecan and 5-FU bolus protocols, an extension of overall survival was also achieved. Bevacizumab is effective in both first-line and second-line therapy. Continuation of bevacizumab therapy beyond progression led to an extension of overall survival in two randomized clinical trials. In the larger study, a significant improvement in the hazard ratio to 0.81 was achieved. The median overall survival time was extended by 1.4 months. Serious adverse events (grade 3 / 4), which occurred in more than 5% of patients in the pivotal trials, were hypertension and proteinuria. Rarer critical complications are arterial thromboembolic events and perforations in the gastrointestinal tract.

6.2.2.4 Capecitabine

The basic drug in the drug-based tumor therapy of patients with colorectal carcinoma is 5-fluorouracil. Capecitabine is an oral fluoropyrimidine that is enzymatically metabolized by the tumour to 5-FU. In clinical comparative studies, it was at least as effective as 5-FU bolus / folinic acid therapy. In monotherapy, remission rates of up to 25% are achieved, in combination with irinotecan or oxaliplatin in up to 45% of patients. Severe side effects (grade 3 / 4), which occurred in more than 5% of patients in the approval studies, were diarrhea and hand-foot syndrome. The combination of proton pump inhibitors with capecitabine-containing therapy should be avoided, as negative effects on capecitabine efficacy have been demonstrated in several retrospective studies. Before chemotherapy containing 5-FU, a mutation in the four most important dihydropyrimidine dehydrogenase (DPD) gene loci must be excluded [39].

6.2.2.5 Cetuximab

Cetuximab is a monoclonal antibody against the EGF receptor. The remission rate as monotherapy in the second line is 8%. In first-line therapy for patients with *KRAS* wild type, remission rates of 55-65% are achieved, in each case in combination with 5-FU / folinic acid and irinotecan or oxaliplatin. The progression-free survival time is prolonged. The data on overall survival are inconsistent. Patients with defined RAS mutations (*KRAS* gene exon 2-4, *NRAS* gene exon 2-4) do not benefit from the therapy and in some chemotherapy combinations there is even a trend towards shorter survival times. As there are indications of a negative interaction with capecitabine and bolus 5-FU protocols that is not yet understood, the combination of cetuximab with oral fluoropyrimidines and bolus 5-FU protocols is not recommended, see also approval Colorectal carcinoma. Severe side effects (grade 3 / 4), which occurred in more than 5% of patients in the approval studies, were acneiform dermatitis and infusion reactions. Prophylactic treatment of acneiform dermatitis should be carried out with doxycyline or minocycline. Additional prophylactic local therapy with vitamin K1 cream (Reconval K1) can be considered in

women. Drugs for the prophylaxis of infusion reactions are corticosteroids and H1 blockers. Bi-weekly administration (500 mg/m²) was equivalent to weekly cetuximab administration (400 / 250 mg/m²) in a randomized study.

6.2.2.6 Encorafenib

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

6.2.2.7 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%). It is approved for patients who failed available standard treatment including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF- and Anti-EGFR-antibodies as well as progression under or intolerability of TAS-102 (trifluridine/tipiracil) or regorafenib.

6.2.2.8 Ipilimumab

Ipilimumab is a drug from the group of monoclonal antibodies. It blocks the inhibitory T-cell regulator CTLA-4 and thereby boosts the autologous immune response. It is approved in combination with nivolumab for stage IV patients with MSI-H/dMMR. The overall response rate (ORR) for this combination was 55% in the Checkmate-142 pivotal study, with survival rates of 87% and 85% at 9 and 12 months. Treatment-related grade 3 to 4 toxicities occurred in 32% of patients: elevation of AST and/or ALT (11%), elevation of lipase (4%), anemia (3%), colitis (3%).

6.2.2.9 Irinotecan

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

6.2.2.10 Nivolumab

Nivolumab is a monoclonal anti-PD-1 antibody and belongs to the substance class of immune checkpoint inhibitors. It is approved in combination with ipilimumab for stage IV patients with MSI-H/dMMR, for first-line or after prior treatment with fluoropyrimidines. The overall response rate (ORR) for this combination was 55% in the Checkmate-142 pivotal study, with survival rates of 87% and 85% at 9 and 12 months. Treatment-associated grade 3 / 4 toxicities occurred in 32% of patients: increase in AST and/or ALT (11%), increase in lipase (4%), anemia (3%), colitis (3%).

6.2.2.11 Oxaliplatin

Oxaliplatin is a platinum derivative. It is highly effective in combination with fluoropyrimidines (5-FU/folinic acid, capecitabine). In first-line therapy, it increases remission rates to 40-60% and prolongs progression-free survival compared to 5-FU/FS. Severe side effects (grade 3 / 4), which occurred in more than 5% of patients in the approval studies, were nausea / vomiting, diarrhea, mucositis and polyneuropathy. The intravenous administration of calcium and magnesium cannot reduce the risk of polyneuropathy.

6.2.2.12 Panitumumab

Panitumumab is a monoclonal antibody against the EGF receptor. In patients with *KRAS*wt tumors, the remission rate in second-line therapy was 10% for monotherapy and 35% for the combination with FOLFIRI after failure of oxaliplatin ± bevacizumab. The response to panitumumab is dependent on mutations in the *RAS* genes. In the pivotal study, patients with *RAS*wt showed a statistically significantly longer survival time for the panitumumab/chemotherapy combination compared to the chemotherapy-only arm. Patients treated with panitumumab in the presence of a mutation in one of the *RAS* genes had poorer progression-free and overall survival. Severe side effects (grade 3/4), which occurred in more than 5% of patients in the pivotal studies, were acneiform dermatitis. Prophylactic treatment of acneiform dermatitis should be carried out with doxycyline or minocycline. Additional prophylactic local therapy with vitamin K1 cream (Reconval K1) can be considered in women.

6.2.2.13 Pembrolizumab

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

6.2.2.14 Ramucirumab

Ramucirumab is a human IgG1 antibody that binds specifically to the vascular endothelial growth factor receptor-2 (VEGFR2). It is approved for second-line therapy in patients with adenocarcinoma of the stomach or gastroesophageal junction. It was tested in combination with FOLFIRI in a phase III trial in patients with metastatic colorectal carcinoma in recurrence or refractory after treatment with a fluoropyrimidine, oxaliplatin and bevacizumab. The addition of ramucirumab led to a statistically significant increase in progression-free survival from 4.7 to 5.7 months with a hazard ratio of 0.77 and an increase in overall survival from 11.7 to 13.3 months with a hazard ratio of 0.84. Side effects CTCAE grade 3 / 4, which occurred in more than 5% of patients treated with ramucirumab in the combination therapy in the approval study and more frequently than in the control group, were neutropenia (28%) and hypertension (11%). Fatigue (12%) and diarrhea (10%) were not significantly more frequent than in the chemotherapy control. Information on approval status is summarized in Colorectal carcinoma approval.

6.2.2.15 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 who have failed all established chemotherapies, two phase III studies have shown that regorafenib monotherapy statistically significantly improves overall survival compared with best supportive care in a meta-analysis with a hazard ratio of 0.76. Regorafenib leads to symptomatic toxicity in many patients at the start of treatment. Side effects CTCAE grade 3 / 4, which occurred in more than 5% of patients treated with regorafenib 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 at the start of therapy (e.g., weekly) and, if necessary, a consistent dose reduction. Information on the approval status is summarized in Colorectal carcinoma approval.

6.2.2.16 TAS-102

TAS-102 is a new oral cytostatic drug. It consists of trifluridine, a thymidine analog, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor. The cytotoxic component is trifluridine, 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 led to a statistically significant prolongation of progression-free survival (HR 0.48; median 0.3 months) and to an extension of overall survival (HR 0.68, median 1.7 months). The remission rate was 1.6%. TAS-102 is taken for 5 days in two consecutive weeks, followed by a 2-week break. CTCAE grade 3 / 4 adverse events 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 occurred in 4% of patients. These complications require close monitoring of the blood count and a dose reduction if necessary. Information on the approval status is summarized in Colorectal carcinoma approval.

6.2.2.17 S1 (Tegafur plus Gimeracil and Oteracil)

In cases of intolerance to 5-fluorouracil, the substance S1 has been approved by the EMA since 2022. This approval is based on several studies that show that S1 is not 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 can be carried out safely. 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 in whom treatment with another fluoropyrimidine cannot be continued 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

Follow-up care for patients with colorectal cancer is structured. The aims of follow-up care are the early diagnosis of a recurrence with the aim of extending survival time / increasing the chance of recovery, the detection of side effects of therapy and prevention. In patients with colorectal carcinoma, intensive, structured follow-up care can lead to an increase in survival time [41].

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

Follow-up care is stage- and risk-adapted, see Table 6.

Table 6: Structured follow-up for 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
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 sonography		X		X		X		X				X		X		X
CT abdomen / thorax				**X** X				**X** X				**X** X		X		X
Colonoscopy		X*		X **X** X										**X** X		X

Legend:
X Recommendations in Germany;
***X Recommendations in** Austria;*
X Recommendations in Switzerland
**The colonoscopy should be carried out after 6 months if a complete colonoscopy was not performed preoperatively.*

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14 Links

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

15 Authors' Affiliations

Prof. Dr. med. Dirk Arnold
Asklepios Tumorzentrum Hamburg
Asklepios Klinik Altona
Onkologie und Palliativmedizin, mit Sektionen
Hämatologie und Rheumatologie
Paul-Ehrlich-Str. 1
22763 Hamburg
d.arnold@asklepios.com

Prof. Dr. med. Markus Borner
ONCOCARE am Engeriedspital
Riedweg 15
CH-3012 Bern
markus.borner@hin.ch

Univ.-Prof. Dr. Wolfgang Eisterer
Allgemein öffentliches Klinikum
Klagenfurt am Wörthersee
Innere Medizin und Hämatologie und Internistische Onkologie
St. Veiter Str. 47
A-9020 Klagenfurt
imuhaem.klagenfurt@kabeg.at

Dipl.-Med. Gerhard Faber
Celenus Teufelsbad Fachklinik
Abteilung Onkologie
Michaelstein 18
38889 Blankenburg
g.faber@teufelsbad-fachklinik.de

Prof. Dr. med. Gunnar Folprecht
Universitätsklinikum Carl-Gustav Carus der TU Dresden
Medizin Klinik und Poliklinik I
Fetscherstr. 74
01307 Dresden
gunnar.folprecht@uniklinikum-dresden.de

Prof. Dr. med. Ullrich Graeven
Kliniken Maria Hilf, Mönchengladbach
Innere Medizin I
Klinik für Hämatologie, Onkologie
Viersener Str. 450
41063 Mönchengladbach
ullrich.graeven@mariahilf.de

Univ.-Prof. PD Dr. Birgit Grünberger
Landesklinikum Wiener Neustadt
Abteilungsvorstand Abteilung für Innere Medizin, Hämatologie und intern. Onkologie
Corvinusring 3-5
A-2700 Wiener Neustadt
birgit.gruenberger@wienerneustadt.lknoe.at

Prof. Dr. med. Holger Hebart
Stauferklinikum Schwäbisch Gmünd
Zentrum Innere Medizin
Wetzgauer Str. 85
73557 Mutlangen
holger.hebart@kliniken-ostalb.de

Prof. Dr. med. Susanna Hegewisch-Becker
Onkologische Schwerpunktpraxis Hamburg Eppendorf
Eppendorfer Landstr. 42
20249 Hamburg
hegewisch@hope-hamburg.de

Prof. Dr. med. Volker Heinemann
Universität München, Klinikum Großhadern
III. Medizinische Klinik
Abteilung Hämatologie und Onkologie
Marchioninistr. 15
81377 München
volker.heinemann@med.uni-muenchen.de

Prof. Dr. med. Ralf-Dieter Hofheinz
Universitätsmedizin Mannheim
Mannheim Cancer Center
Theodor-Kutzer-Ufer 1-3
68167 Mannheim
ralf.hofheinz@umm.de

Dr. Ron Pritzkuleit
Institut für Krebsepidemiologie
Krebsregister Schleswig-Holstein
Ratzeburger Allee 160
23538 Lübeck
ron.pritzkuleit@krebsregister-sh.de

PD Dr. med. Holger Rumpold
Ordensklinikum Linz
Viszeralonkologisches Zentrum
Fadingerstr.1
A-4020 Linz
holger.rumpold@ordensklinikum.at

PD Dr. med. Marianne Sinn
Universitätsklinikum Hamburg-Eppendorf
II. Medizinische Klinik und Poliklinik
Onkologie, Hämatologie, KMT mit Sektion Pneumologie
Martinistr. 52
20246 Hamburg
ma.sinn@uke.de

Prof. Dr. med. Jürgen Weitz
Uniklinik Carl-Gustav-Carus Dresden
Klinik und Poliklinik
f. Viszeral-, Thorax- u. Gefäßchirurgie
Fetscherstr. 74
01307 Dresden
juergen.weitz@uniklinikum-dresden.de

Prof. Dr. med. Bernhard Wörmann
Amb. Gesundheitszentrum der Charité
Campus Virchow-Klinikum
Med. Klinik m.S. Hämatologie & Onkologie
Augustenburger Platz 1
13344 Berlin
bernhard.woermann@charite.de

16 Disclosures

according to the rules of the responsible Medical Societies.

16 Declarations on possible conflicts of interest

in accordance with the rules of the relevant professional associations.