

Evidenced-based Guideline for Colorectal Cancer

Version 1.1 – August 2014

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Guideline (Long Version)

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1. Information on this Guideline

1.1. Editors

German Guideline Program in Oncology (GGPO) of the AWMF, German Cancer Society, and German Cancer Aid

1.2. Leading Professional Society

German Society for Digestive and Metabolic Diseases (DGVS)



Steering committee for development and implementation through the DGVS:
Univ.-Prof. Dr. Wolff Schmiegel
Dr. Christian P. Pox

1.3. Guideline Funding

This guideline was funded by the German Cancer Aid as part of the German Guideline Program in Oncology.

1.4. Contact

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1.5. Citation Method

German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, AWMF): Evidenced-based Guideline for Colorectal Cancer, long version 1.0, AWMF registration number: 021-007OL, <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>

1.6. Special Note

Medicine is continuously developing. Therefore, all information, especially diagnostic and therapeutic procedures, only corresponds to the knowledge at the time the guideline is published. The greatest possible care was taken with the recommendations on therapy as well as choice and dose of drugs. Nonetheless, the users are requested to call on the manufacturer's instruction leaflet and the SmPC and in case of doubt to consult a specialist. In the GGPO-editors' general interest, relevant discrepancies should be reported.

The users are responsible for each diagnostic and therapeutic application, medication, and dosage.

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1.7. Goal of the German Guideline Program in Oncology

With the German Guideline Program in Oncology (GGPO), the committee of the Scientific Medical Professional Societies (AWMF), the German Cancer Society (DKG), and the German Cancer Aid (DKH) have the goal to fund and support the development, update, and implementation of evidence-based and practical oncologic guidelines. The program is based on medical-scientific knowledge of the professional societies and the DKG, the consensus of medical experts, users and patients, as well as regulations of the guideline preparation of the AWMF and the expert support and funding by the German Cancer Aid. To show the current medical knowledge and to take medical progress into consideration, guidelines have to be reviewed and updated. The AWMF-regulations will be used as a basis for the development of high quality oncologic guidelines. Since guidelines are an important quality assurance and quality management tool in oncology, they should be specifically and sustainably implemented in routine care. Thus, active implementation measures and evaluation programs are an important aspect of the GGPO-support. The goal of the program is to establish professional and intermediately funded prerequisites for the development and preparation of high quality guidelines in Germany. These high-grade guidelines serve not only the structured transfer of knowledge, but they may also find their place in health care system structuring. Worth mentioning here are evidence-based guidelines as the basis for preparing and updating disease management programs or for the implementation of quality indicators taken from guidelines for the certification of organ tumor centers.

1.8. Guideline Authors

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1.8.1. Composition of the Guideline Group 2011/2012

The expert group for the update of Chapters 3, 4, 5, 7, 10 (see section 2.2.1) is made up of a total of 53 elected representative and plenum members of the following professional societies, professional associations, and patient associations:

Professional Societies

- **DKG** (German Cancer Society)
 - **ASORS** (Task force of the DKG "Supportive measures in oncology, rehabilitation, and social medicine")
 - **PRIO** (Task force of the DKG Prevention and integrated medicine in oncology)
 - **PSO** (Task force of the DKG: German task force for psychooncology)
 - **KOK** (Task force of the DKG: Conference oncologic patient and pediatric patient care)
- **DGVS** (German Society of Gastroenterology, Digestive and Metabolic Diseases)
- **DEGAM** (German Society for General and Family Medicine)
- **DEGRO** (German Society for Radiooncology)
- **DGAV** (German Society for General and Visceral Surgery)
- **CACP** (Surgical working group for coloproctology)
- **CAMIC** (Surgical working group for minimally invasive surgery)
- **CAO-V** (Surgical working group for oncology)
- **DGCH** (German Society for Surgery)
- **DGEM** (German Society for Nutrition Medicine)
- **DGHO** (German Society for Hematology and Oncology)
- **DGIM** (German Society for Internal Medicine)
- **DGKL** (German Combined Society for Clinical Chemistry Laboratory Medicine)
- **DGN** (German Society for Nuclear Medicine)
- **DGP** (German Society for Pathology)
- **DRG** (German Radiological Society)
- **GfH** (German Society for Human Genetics)

Other Institutions

- **bng** (Professional Association of Practicing German Gastroenterologists)
- **HÄV** (German Association of General Practitioners)
- **AQUA** (Institute for Applied Quality Assurance and Research in the Health Care System)
- **ZI** (Central Institute of the Ambulatory Health Care in Germany)
- Felix-Burda-Foundation
- Foundation Lebensblicke

Patient Associations

- **DCCV** (German Crohn`s Disease/Ulcerative colitis Association)
- **Deutsche ILCO** (Association for Stoma Carriers and Persons with Colon Cancer)

Table 1 shows the members of the guideline group 2011/2012 under the direction of Prof. Dr. W. Schmiegel (DKG, DGVS)

Table 1: Members of the Task Forces for the Update of Chapters 3, 4, 5, 7, 10

Chapter 3: Prevention Asymptomatic Population	
Coordinator: J.F. Riemann	DGIM, DGVS, Foundation Lebensblicke
Members:	
S. C. Bischoff	DGEM, DGVS
F. Kolligs	DGVS
J. Ockenga	DGEM, DGVS
W. Scheppach	DGEM, DGVS
Chapter 4: Early Diagnosis/ Prevention Asymptomatic Population	
Coordinators: C. Pox, A. Sieg	both DGVS
Members:	
L. Altenhofen	ZI
H-J. Brambs	DRG, DGAM
H. Brenner	expert (not entitled to vote)
P. Engeser	HÄV
A. Theilmeier	bng, DGVS
Chapter 5: Risk Groups	
Coordinators:	
N. Rahner	GfH
K. Schulmann	DGVS
Members:	
G. Baretton	DGP
B. Bokemeyer	bng, DGVS
J. Epplen	DGHG
U. Melle	DGVS
R. Porschen	DGVS
J. Weitz	DGAV
C. Witte	DCCV
Chapter 7: Preoperative Diagnostics and Surgery	
Coordinators:	
W. Hohenberger	DKG, DGAV
S. Post	DKG, DGAV, CACP
Members:	
M. Anthuber	DGAV

W. Bechstein	DGAV
U. Graeven	DGVS
M. Haß	Dt. ILCO
M. Heike	DGHO
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T. Vogl	DRG
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C. Wittekind	DGP
Chapter 10: Follow-Up Care	
Coordinator:	
A. Holstege	DGVS
Members:	
P. Heußner	PSO
T. Höhler	DGHO
J. Hübner	DKG, PRIO
J. Körber	DKG, ASORS
M. Landenberger	DKG, KOK
H. Link	DKG, ASORS
Additional Participants at Plenum	
S. Ludt	AQUA
P. Lux	Co-Author (not entitled to vote)
C. Maar	Felix-Burda-Foundation

1.8.2. Coordinators of the Guideline Group 2007/2008

The coordinators of the update of Chapters 6, 8, and 9 in 2007/2008 were:

Chapter 6 – Endoscopy: Implementation and management of polyps:

J.F. Riemann, W. Schmitt

Chapter 8 – Adjuvant and neoadjuvant therapy:

R. Porschen, R. Sauer

Chapter 9 – Therapeutic approach in patients with metastases and in the palliative situation: U. Graeven, H-J. Schmoll

1.8.3. Composition of the Task Force Quality Indicators

The suggestions on quality indicators were developed by the task force listed in Table 2.

Table 2: Members of Task Force Quality Indicators

Name	Institution
Coordinators: W. Schmiegel C. Pox	DKG, DGVS DGVS
Members: M. Haß	Dt. ILCO
W. Hohenberger	DKG, DGAV
A. Holstege	DGVS
F. Kolligs	DGVS
M. Klinkhammer-Schalke	Task Force of German Tumor Centers (ADT)
I. Kopp	AWMF
S. Ludt	AQUA
J. Ockenga	DGVS
S. Post	DKG, DGAV, CACP
A. Tannapfel	DGP
S. Wesselmann	German Cancer Society (DKG), Department of Certification

1.8.4. Methodological Support

By the German Guideline Program in Oncology:

- Prof. Dr. Ina Kopp (AWMF), Marburg
- Dr. Markus Follmann, MPH MSc (DKG), Berlin

1.9. Available Documents on the Guideline and Implementation

This document is the long version of the Evidenced-based Guideline for Colorectal Cancer that is accessible via the following links:

- * German Guideline Program in Oncology (<http://www.leitlinienprogramm-onkologie.de/OL/leitlinien.html>)
- * AWMF (www.leitlinien.net)
- * German Cancer Society (http://www.krebsgesellschaft.de/wub_llevidenzbasiert,120884.html)
- * German Cancer Aid (<http://www.krebshilfe.de/>)
- * Guidelines International Network (www.g-i-n.net)
- * Participating professional societies (z. B. <http://www.dgvs.de/508.php>)

In addition, the long version of this guideline will be published in the "Zeitschrift für Gastroenterologie".

Aside from the long version, the following complementary documents for this guideline exist:

- * short version
- * guideline report
- * translation (English)
- * patient guideline (lay version)
- * external evidence report

All these documents can also be accessed via the mentioned links.

The external evidence report for Chapter 4 (Screening/prevention) and parts of Chapter 7 (Preoperative diagnostics and surgery) was prepared by the University of Witten/ Herdecke (Institute for Research in Operative Medicine) in cooperation with the University of Duisburg/ Essen (Alfried Krupp von Bohlen and Halbach Foundation Professorship for Medicine Management).

A nationwide distribution of these evidence-based updated recommendations is needed in particular to improve the quality of patient information and care. With the help of standardized methods, quality indicators were derived from the recommendations. Aside from implementation, the guideline serves primarily the quality assurance and the improvement of patient relevant processes.

2. Introduction

2.1. Scope and Purpose

2.1.1. Goal and Issues

Colorectal cancer (CRC) is one of the most common malignant tumors in Germany with over 73,000 newly-diagnosed cases and about 27,000 deaths per year. For the first time in 1999, the DGVS in cooperation with the German Cancer Society published an S3 guideline for CRC, which was intended to provide an exhaustive, standardized, high-value set of patient care guidelines based on evidence-based medicine. In the meantime, a European colorectal cancer guideline has also been published. The guideline committee felt specifications are necessary, because of the heterogeneous health care systems and care standards in the European countries. This German guideline covers additional aspects that are not covered by the European guideline. It strives to consider all issues relevant for Germany.

The guideline is divided into eight topic complexes (TC):

- * TC I: Prevention Asymptomatic Population (see Chapter 3)
- * TC II: Screening Asymptomatic Population (see Chapter 4)
- * TC III: Risk Groups (see Chapter 5)
- * TC IV: Endoscopy: Implementation and Management of Polyps (see Chapter 6)
- * TC V: Preoperative Diagnostics and Surgery (see Chapter 7)
- * TC VI: Adjuvant and Neoadjuvant Therapy (see Chapter 8)
- * TC VII: Management of Patients with Metastases and in the Palliative Situation (see Chapter 9)
- * TC VIII: Follow-up Care (see Chapter 10)

In order to keep these recommendations at the most current stage of scientific knowledge, the guideline has since been regularly updated in close cooperation with the AWMF (2004 completely and 2008 the TC IV, VI, and VII). The current update affects the TC I, II, III, V, and VIII, as well as individual sections of IV, VI, and VII.

During the update process in 2012/2013, the guideline group decided that recommendations would be made on the following issues:

- * Which prevention measures can reduce the CRC risk?
- * Which methods should be used for screening/prevention?
- * Which procedures should be implemented in preoperative diagnostics for CRC?
- * What has to be taken into account when constructing stomas?
- * What is the role of laparoscopic resections?
- * When does tumor follow-up care start?
- * How important are rehabilitation and tertiary prevention after curative tumor operations?

Based on these questions, all recommendations were reviewed whether they were up-to-date. If necessary, they were updated after literature searches.

Each recommendation box contains the date of the last update (2008 or 2013).

2.1.2. Audience

This guideline is mainly directed at:

- Physicians who work on prevention and treatment of CRC in the ambulatory and inpatient sector,
- Cooperation partners of the medical profession (health care faculties),
- Benefactors.

2.1.3. Period of Validity and Update Processes

The period of validity of topics I, II, III, V, and VIII and Chapters 3, 4, 5, 7, 10 updated 2011/ 2012 is estimated to be 5 years. They will be subject to a new revision by 2017 at the latest. Updating of the remaining topics IV, VI, and VII and Chapters 6, 8, 9 is planned for 2014.

The updating processes will be coordinated by the responsible guideline coordinator. The members of the guideline groups will observe newly-emerging scientific knowledge. If necessary, the individual topics will be updated accordingly. All updates will be published separately (as an addendum to the internet version, scientific publications) and will finally be worked into the full-text version of the guideline.

Comments and instructions for the updating process from clinical practice are encouraged and can be addressed to the guideline secretary.

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2.2. Basis for the Method

The methodological procedure is based on the AWMF regulations (<http://www.awmf-leitlinien.de>) and is shown in the guideline report of this guideline (see e.g. <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>).

2.2.1. Scheme of Evidence Level According to Oxford

To classify the distortion risk of the identified studies, the system of the Oxford Centre for Evidence-based Medicine version 2009 (available under www.cebm.net) shown in Table 3 was used for this guideline. This system provides a classification for studies on different clinical issues (benefit of therapy, prognostic relevance, diagnostic importance).

Table 3: Scheme of Evidence Level According to Oxford (Version 2009)

Level	Therapy/ Prevention, Etiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1 economic studies
1b	Individual RCT (with narrow confidence interval)	Individual inception cohort study with > 80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical center	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level >2 diagnostic studies	SR (with homogeneity) of Level 2b and better studies	SR (with homogeneity) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses

Level	Therapy/ Prevention, Etiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
2c	“Outcomes” research; ecological studies	“Outcomes” research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case- control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual case-control study		Non- consecutive study; or without consistently applied reference standards	Non- consecutive cohort study; or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case- control studies)	Case-series (and poor quality prognostic cohort studies)	Case-control study, poor or non- independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”			

2.2.2. Scheme of the Grade of Recommendation

The GGPO-method requires the allocation of recommendation levels by the guideline authors in a formal consensus process. Therefore, a chaired, multi-part, nominal group process was implemented by the AWMF. At the end of this process, the recommendations were formally voted on by the elected representatives who were entitled to vote (see Chapter 1.8). The results of each vote were allocated to the recommendations according to the categories in Table 5.

For all evidence-based statements (see Chapter 2.2.5) and recommendations, the evidence level (see Chapter 2.2.1) of the underlying studies as well as for recommendations the degree of recommendation (recommendation level) are shown. Three degrees of recommendation are distinguished in this guideline (see Table 4) which also reflect the formulation of the recommendations.

Table 4: Scheme of the Grades of Recommendation

Grade of Recommendation	Description	Phrasing
A	Strong recommendation	shall/has to
B	Recommendation	should
0	Recommendation open	can

2.2.3. Clinical Evaluation – Classification of the Grade of Recommendation

(according to the recommendations of the European Council 2001)

In general, the evidence classification determines the recommendation level. Deviations are possible for justified reasons (see further criteria in Figure 1).

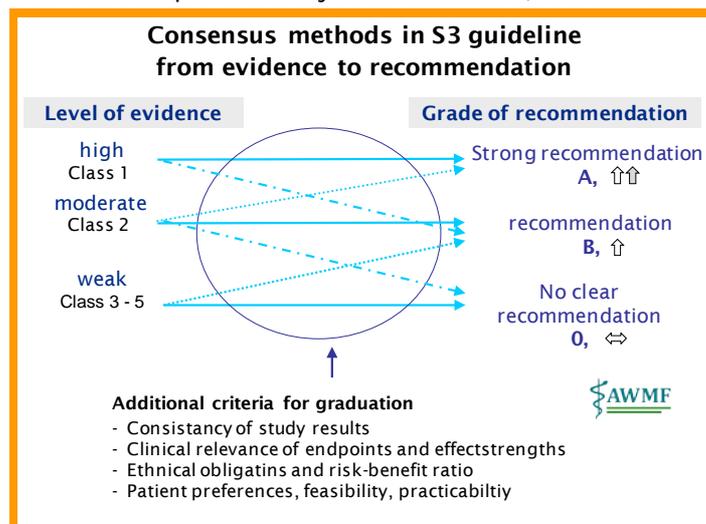


Figure 1: Overview of Recommendation Grading

2.2.4. Classification of the Degree of Consensus

Table 5: Classification of the Degree of Consensus

Degree of consensus	Percent agreement
Strong consensus	Agreement from >95% of participants
Consensus	Agreement from >75-95% of participants
Majority Agreement	Agreement from >50-75% of participants
No Consensus	Agreement from less than 50% of participants

2.2.5. Statements

Statements are interpretations or comments on specific issues and problems without direct call for action. They are passed in a formal consensus process according to the procedure for recommendations. They are based either on study results or expert opinion.

2.2.6. Good Clinical Practice (GCP)

Recommendations are declared as 'Good Clinical Practice (GCP)' if no literature search was done. In general these recommendations address procedures of good clinical practice to which no scientific studies are necessary or expected. No symbol was used for the level of GCPs. The degree of recommendation results from the wording that is used (must/should/can) according to the grading in Table 4.

2.2.7. Independence and Declaration of Possible Conflict of Interest

This guideline was financed by the German Cancer Aid as part of the German Guideline Program in Oncology. The financial means were used for personnel costs (medical documentation specialists), office materials, literature acquisition, and telephone and consensus conferences (room charges, equipment, expenses, moderator honoraria, travel costs for the participants). The travel costs were reimbursed according to the German Travel Cost Law and/or according to the guidelines normally followed in universities. The editorial updating of the guidelines was independent of financing organizations. All members of the guideline groups presented a written declaration of any potential conflicts of interest (see guideline report under <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>). We thank them for their strictly honorary work, without which this guideline could not have been prepared.

2.3. Abbreviations Used

Abbreviation	Explanation
AFAP	Attenuated FAP
AHB	Follow-up treatment
ASS	Acetylsalicylic acid
AWMF	Task Force of Scientific Medical Professional Societies
BMI	Body Mass Index
CEA	Carcino-embryonic Antigen
CRC	Colorectal cancer
CT	CT scan
CTC	CT-Colonography
CU	Colitis Ulcerosa
DGE	German Society for Nutrition
EGD	Esophagogastroduodenoscopy
FAP	Familial Adenomatose Polyposis
FOBT	Fecal occult blood test
HNPCC	Hereditary colorectal cancer without polyposis
IEN	Intra-epithelial neoplasia
iFOBT/ FIT	Immunologic FOBT
IHC	Immunohistochemical test
LITT	Laserinduced interstitial thermotherapy
LL	Guideline
MAP	MUTYH-associated polyposis
MMR	Mismatch-repair gene
MSA	Microsatellite analysis

Abbreviation	Explanation
MSCT	Multi-slice-CT
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSI-L	Microsatellite instability low
MSS	Microsatellite stability
OR	Odds Ratio
PCI	Peritoneal cancer index
PET	Positron emission tomography
PJS	Peutz-Jeghers-syndrome
PSC	Primary sclerosing cholangitis
RCT	Randomized controlled study
RFA	Radiofrequency ablation
RR	Relative risk
SIRT	Selective internal radiation therapy
SR	Systematic review
WHO	World Health Organization

2.4. Editorial Note:

The current update affects Chapters 3, 4, 5, 7, and 10 as well as individual sections from Chapters 6, 8, and 9. The date of the last respective update is shown in the recommendation box. For the updated chapters, the citations are given in the background text as well as in the recommendation box. In the chapters that were updated in 2007/2008 references are merely mentioned in the text.

In a pilot project, an external expert (PD Dr. A. Riphaut) was commissioned to exemplarily do a literature search on gender-specific differences for the topic prevention and follow-up care. The systematic search revealed that no recommendation can be given on gender-specific treatments.

Therefore, in this guideline the term "patient" is used for women and men. This merely makes reading the text easier.

3. Prevention Asymptomatic Population

3.1. Lifestyle Habits

3.1.	Recommendation	2013
Grade of Recommendation B	To reduce the risk of colorectal cancer regular physical activity is recommended.	
Level of Evidence 2a	Evidence from update literature search ¹ : [1-12]	
	Strong consensus	

3.2.	Recommendation	2013
Grade of Recommendation B	To reduce the risk of colorectal cancer weight reduction is recommended for overweight persons.	
Level of Evidence 2a	Evidence from update literature search: [1, 8, 13-18]	
	Strong consensus	

3.3.	Recommendation	2013
Grade of Recommendation A	It is recommended to refrain from smoking.	
Level of Evidence 2a	Evidence from update literature search: [1, 10, 19-25]	
	Strong consensus	

Background

Cross-studies and prospective cohort studies have shown that people with a high level of physical activity have fewer colon polyps (adenomas). In addition, they have an up to

¹ Systematic research for a limited time interval (starting 2003, the end point for the de novo literature search for the last guideline update)

30 % lower risk of cancer. Already 30 to 60 minutes of moderate physical activity per day is associated with a lower cancer risk [1-12].

There is a positive association between occurrence of colon polyps (adenomas) and colorectal cancer and a higher BMI as well as an increase in waist circumference. This effect is seen with a BMI >25 kg/m², increases linearly with the BMI, and is more pronounced in men than women. The risk of colon cancer was up to twice as high in overweight persons especially with truncal obesity [18]. It is not clear whether the risk increase is due to obesity, altered hormone levels, increased calorie uptake, or absence of physical activity [1, 8, 13-18].

Smoking is associated with a risk for colon adenomas that is twice as high and an increased risk of cancer [1, 10, 19-25].

3.2. Diet Recommendations

3.4.	Statement	2013
Level of Evidence 2b	A specific diet recommendation to reduce the CRC risk can currently not be given.	
	Evidence from update literature search: [26-32]	
	Consensus	

3.5.	Consensus-based Recommendation	2013
GCP	The general diet recommendations of the DGEM should be followed.	
	Consensus	

Background

In a detailed literature review from 2010, a connection between a "healthy" or an "unhealthy" diet and colorectal cancer was viewed as probable. A "healthy" diet was designated by the authors as including a high consumption of fruit and vegetables as well as reduced intake of red and processed meat. In contrast, an "unhealthy" was characterized by a large uptake of red and processed meat, potatoes, and refined starch [26]. Original publications in the last years have repeatedly observed an association between diet factors and the manifestation of CRC. They were rated with an evidence level between 2b and 4 [27-30]. However, there have also been studies that found no correlation between diet factors and CRC [31, 32]. These are associations and not intervention studies. Whether these observations warrant specific diet recommendations for the prevention of CRC has not been studied so far. Therefore, despite the outlined relationships, currently no specific diet recommendations can be made. Instead, to reduce the risk of cancer, it is recommended to follow the current diet recommendations of the DGE. The associations between the uptake of specific foods and the risk of CRC will be demonstrated in more detail below. It should also be stressed here that a diet that does not cause weight gain is recommended (see Chapter 3.1).

3.6.	Recommendation	2013
Grade of Recommendation B	To reduce the risk of CRC fiber uptake should be at least 30 g per day.	
Level of Evidence 2a	Evidence from update literature search: [33-37]	
	Consensus	

Background

Despite controversial data, the evidence is sufficient to recommend a fiber rich diet of 30 g/day [33-37]. A current British study that summarizes data from seven cohort studies showed an inverse correlation between fiber uptake and cancer risk. The comparison of the daily fiber consumption of 10 and 24 g in this study demonstrated that a higher consumption was associated with a colon cancer risk reduction of 30 % [33]. In another study which summarized 13 prospective cohort studies showed similar results. Although the *pooling project of prospective studies of diet and cancer* demonstrated an even greater range between the lowest and highest quintile of fiber uptake, a significant inverse correlation was observed between fiber consumption and cancer risk after age-adjusted analysis, but not after adjustment according to other diet related risk factors [36]. These limited positive data may be due to the fact that the recording of the fiber consumption was merely done at the start of the study, which may reflect an incorrect long-term uptake. Despite the limited results, the remaining statements are very robust, because they are based on a large collective. Therefore, the recommendation level B was determined.

3.7.	Recommendation	2013
Grade of Recommendation B	To reduce the risk of CRC alcohol consumption should be restricted.	
Level of Evidence 2a	Evidence from update literature search: [38-41]	
	Consensus	

Background

There is a positive correlation between high alcohol consumption and the development of CRC [38-41] especially in persons with low folic acid and/or methionine uptake [39]. Abstinent persons and persons who drink little alcohol have a significantly lower cancer risk [38-41]. A meta-analysis of 14 prospective cohort studies showed that already an alcohol intake of 100 g per week is associated with a 15 % increase in colon as well as rectal cancer risk [41]. The risk correlates with the amount of alcohol consumed not with the type of alcoholic beverage [39].

3.8.	Recommendation	2013
Grade of Recommendation B	Red or processed meat should only be consumed in small amounts (not daily).	
Level of Evidence 2a	Evidence from update literature search: [37, 42-46]	
	Consensus	

Background

A high consumption of red meat (beef, veal, pork, and lamb) and processed meat is associated with a higher CRC risk [37, 42-46]. There is no positive correlation between poultry and/or poultry products [45]. The positive association is most likely due to the processing and preparation as demonstrated by data of the *Prostate, lung, colorectal, and ovarian cancer trials*. Especially the regular consumption of well-done red meat, bacon, and sausages correlates with a significantly increased CRC risk [46].

3.9.	Statement	2013
Level of Evidence 2a	No recommendation can be given about an increased fish consumption.	
	Evidence from update literature search : [42, 44, 45, 47-49]	
	Consensus	

Background

A meta-analysis by Geelen et al. which summarized 19 cohort studies investigated the influence of fish consumption on the CRC risk. A comparison of the lowest and highest weekly fish uptake showed that higher consumption is associated with a 12 % lower cancer risk. The greater the difference between the lowest and highest fish uptake was, the more pronounced the correlation became [47]. However, the data are contradictory. This is probably due to the different amounts of fish that were consumed in the different studies [42, 44, 45, 47-49]. Even though it can be assumed that eating more fish can slightly lower the CRC risk, no recommendation is currently given, because the data are not conclusive.

3.10.	Consensus-based Statement	2013
GCP	A connection between consumption of coffee/tea and a reduced risk of CRC has not been confirmed. Therefore, no recommendation can be given for coffee and tea consumption.	
	Strong consensus	

Background

There are three meta-analyses on this issue that did not find a correlation between coffee and/or tea consumption and CRC risk [50-52].

3.11.	Consensus-based Recommendation	2013
GCP	Even though the data on the prevention of CRC are not conclusive, increased amounts of fruits and vegetables should be eaten (5 portions per day).	
	Consensus	

Background

In a case control study and a cohort study an inverse correlation was seen between increased ingestion of fruits and vegetables and a reduced CRC risk [53, 54]. However, a meta-analysis showed that increased fruit and vegetable consumption is merely associated with a 6-9% reduced CRC risk. A stronger inverse correlation was observed for distal colon cancer [55]. However, it is unknown which components (fiber, secondary plant products) have this protective effect. Even though the data on the reduction of CRC risk are not consistent, it is viewed as beneficial to eat more fruits and vegetables, because regular consumption probably decreases disease risk in general.

3.12.	Consensus-based Statement	2013
GCP	There is no connection between food preparation or food fat components and CRC risk.	
	Consensus	

Background

It has been repeatedly discussed whether food preparation or the proportion of potentially toxic fatty acids e.g. trans fatty acids resulting from cooking increase the risk of CRC. The data from the literature on this issue are scarce and inconsistent. Thus, it must be concluded that there is no clear connection. This was studied in the US in a recent prospective population-based cohort study. This trial in 35,000 women confirmed that trans fatty acids do not increase the risk of CRC [56].

Furthermore, there are no specific recommendations on the consumption of fat with respect to CRC risk reduction. Several studies exist that did not find a connection between fat consumption and manifestation of CRC. An effect resulting from cofactors such as intake of red meat or type of preparation cannot be sufficiently differentiated [30, 31, 37, 47, 57-59].

3.13.	Statement	2013
Level of Evidence 2b	There is no connection between acrylamide uptake and CRC risk.	
	de Novo: [60-63]	
	Strong consensus	

Background

A Swedish prospective population-based cohort study in more than 45,000 men found no connection between acrylamide in food and CRC risk using a Food Frequency Questionnaire (FFQ) [60]. This study confirmed previous trials that showed no connection between acrylamide and CRC manifestation in men and women [61-63].

3.3. Micronutrients

3.14.	Recommendation	2013
Grade of Recommendation B	At this time there are no verified data on the effective prevention of colorectal cancer by micronutrients. Therefore, supplementation with these substances is not recommended for primary CRC prevention.	
Level of Evidence	This recommendation is valid for...	Evidence basis
2b	...vitamins...	de Novo: [64]
3b	... including -carotene	de Novo: [64]
3b	... vitamin A	de Novo: [64]
4	... vitamin C, vitamin D, vitamin E	de Novo: [64-66]
1a	... and folic acid	de Novo: [67-71]
1b	These recommendations are also valid for calcium	Update literature research: [65, 66, 72-74]
2b	... magnesium	de Novo: [75]
2b	... and selenium.	de Novo: [76, 77]
	Strong consensus each	

Background

The following list pertains to micronutrient supplements, some in pharmacological doses which can usually not be reached by eating foods such as fruits, vegetables, and milk products.

A moderate clinically non-relevant inhibitory effect on the recurrence of colon adenomas was observed for calcium [72-74]. However, data on a CRC risk reducing effect of calcium or vitamin D, alone or in combination, were not convincing [65, 66].

There is no evidence that the intake of beta-carotene, vitamin A, or vitamin E can reduce the CRC risk. A meta-analysis [64] demonstrated, on the contrary, that supplementation of the aforementioned vitamins, alone or in combination was associated with an increased general mortality.

There is no clear evidence that taking high doses of vitamin C will reduce CRC risk.

A CRC risk reducing effect of folic acid has so far not been conclusively proven [67]. Studies on the recurrence of colon adenomas led to divergent results [68-71].

An intervention study with a selenium supplement and the primary endpoint "CRC-incidence" has not been done to date. The correlation of low selenium levels in serum and an increased adenoma risk is not sufficient to make a recommendation on selenium supplementation [76, 77].

3.4. Drugs

3.15.	Recommendation	2013
Grade of Recommendation A	COX-2 inhibitors shall not be taken prophylactically against CRC by the asymptomatic population.	
Level of Evidence 3b	de Novo: [78-81]	
	Consensus	

3.16.	Recommendation	2013
Grade of Recommendation B	Statines should not be taken as a primary prophylaxis against CRC.	
Level of Evidence 2b	de Novo: [82]	
	Strong consensus	

3.17.	Recommendation	2013
Grade of Recommendation A	Acetylsalicylic acid shall not be taken prophylactically against CRC by the asymptomatic population.	
Level of Evidence 2a	Guideline adaptation: [83-86]	
	Consensus	

3.18.	Recommendation	2013
Grade of Recommendation A	Hormone therapy ² should not be given for CRC risk reduction in women.	
Level of Evidence 1a	Guideline adaptation: [87, 88]	
	Strong consensus	

Background

One positive case control study, but no randomized studies exist for the use of cyclooxygenase-2 (COX-2) inhibitors for primary CRC prevention [78]. Three randomized studies on the secondary prevention with Celecoxib or Rofecoxib following polypectomy show consistently that COX-2-inhibitors significantly decrease the relapse risk for colorectal adenomas [79-81]. However, all three studies showed a pronounced increase in cardiovascular morbidity.

A current meta-analysis of case control, cohort, and randomized studies confirms a significant, but small effect of statines on primary prevention of CRC [82]. A phase III study on secondary prevention of colon adenomas demonstrated that ursodesoxycholic acid only reduced the risk of adenomas with high-grade dysplasia, but not for adenomas in general [89]. Prospective studies on the primary prevention of adenomas using ursodesoxycholic acid do not exist.

A meta-analysis of 2 large randomized studies with a total of 7500 participants showed that the use of 300 mg or more of acetylsalicylic acid per day for 5 years reduces the risk of CRC with a latency of 10 and more years [84]. Another meta-analysis of 8 randomized studies with a total of 25,570 participants indicates that the daily use of at least 75 mg ASS reduces the mortality of CRC with a latency of 10 years [85]. Cohort and case control studies on the use of non-steroidal antirheumatics (NSAR) describe a reduced incidence of CRC. However, this has not been confirmed in

² The expression "hormone replacement therapy" is misleading. Therefore the expression "hormone therapy" is used in the guideline instead.

randomized studies [84]. Due to the frequent incidence of gastrointestinal bleeding under ASS [86] and the missing evaluation of the benefit/risk ratio, the guideline group follows the guideline of the US Preventive Services Task Force on the use of ASS or NSAR for the primary prevention of CRC from the year 2007. It does not recommend the use ASS and NSAR for the primary prevention of CRC [83].

Hormone therapy can reduce the risk of CRC [88]. Due to the increased incidence of adverse events especially venous thromboembolisms, hormone therapy can be recommended for postmenopausal women, but not for primary prevention of CRC. The guideline group is following the recommendations of the U.S. Preventive Services Task Force Guideline on the use of hormone therapy in postmenopausal women [87] and the guideline Hormone Therapy in Peri- and Postmenopause of the German Society for Gynecology and Obstetrics [90].

4. Screening Asymptomatic Population

Asymptomatic Population – Definition:

Persons who do not belong to a colorectal cancer risk group.

4.1. Screening -Age

4.1.	Consensus-based Recommendation	2013
GCP	Colorectal cancer screening should begin at the age of 50 for asymptomatic persons. Due to the increased life expectancy, no upper age limit for screening can be given for colon cancer screening. An individual decision should be made considering comorbidities.	
	Strong consensus	

Background

The incidence of CRC increases significantly after age 50 [91, 92]. A prospective colonoscopy study showed that there was a lower rate of advanced adenomas among 40 to 49 year old subjects (3.5%) [93]. Of great importance is the identification of persons with an increased risk of CRC, for whom special recommendations apply (see Chapter 5).

There are no prospective studies concerning an age limit for colorectal cancer screening. FOBT-studies included only persons up to age 75. The US Preventive Task Force discourages screening persons over 85 years of age and generally recommends that screening should not be done in persons age 76 to 85 years [94]. However, it may be considered for individual cases. The incidence of advancing neoplasias increases with age [95]. Performing endoscopic procedures also seems to be safe in older patients [96]. However, in a cohort study the complication rate increased with age [97]. In another study the relative five-year survival rate after curative operations of colorectal cancer for patients over 74 years of age were comparable with patients aged 50 to 74 [98]. Therefore, the use of CRC screening should be considered individually depending on "biological age" and existing comorbidities. There are insufficient data on the benefit/risk ratio for colorectal cancer screening in different age groups.

4.2. Methods of Colorectal Screening/Prevention

Two types of methods must be differentiated for the screening of CRC. One detects mainly cancer (FOBT, genetic stool tests, M2-PK) and the other can additionally detect adenomas (colonoscopy, sigmoidoscopy, CT-colonography, capsule endoscopy). The following procedures will be discussed:

- * Colonoscopy
- * Sigmoidoscopy
- * FOBT
- * Genetic and other stool tests
- * CT-colonography
- * Capsule endoscopy

4.2.1. Endoscopic Methods

Colonoscopy has the highest sensitivity and specificity of all methods for the early detection of colorectal neoplasia (therefore it is considered as 'gold standard'). Only endoscopic methods are diagnostic as well as therapeutic methods and have the advantage that they can detect non-bleeding cancer and adenomas with high sensitivity. By removing adenomas, the development of cancer can be effectively prevented (interruption of the adenoma-carcinoma sequence) [99, 100]. In addition, as was recently demonstrated, the CRC-associated mortality is reduced [101].

Although the participation rate was low compared to FOBT, individual randomized studies showed that in an intention to screen analysis both sigmoidoscopies [102] and colonoscopies [103] detect more advanced neoplasias. This was particularly due to the clearly higher sensitivity for advanced adenomas.

4.2.1.1. Colonoscopy

4.2.	Recommendation	2013
Grade of Recommendation B	The complete quality assured colonoscopy has the highest sensitivity and specificity for the detection of cancer and adenomas and therefore should, be used as the standard CRC screening test. After a negative examination, colonoscopies should be repeated every 10 years. Colonoscopies should be performed according to the German Prevention Guidelines [104] including a digital rectal examination. For those taking part in colonoscopy screening according to the guideline additional FOBT screening is not necessary.	
Level of Evidence 3b	De Novo: [97, 105-120]	
	Strong consensus	

Background

In contrast to FOBT and sigmoidoscopy no results from randomized studies exist for CRC screening and prevention. Such studies have been initiated in Europe and the US. However, results are expected at the earliest in 15 years. Nonetheless, the use of colonoscopy is supported by indirect evidence. An external literature search identified a study from Germany. In this study patients with a CRC diagnosed by screening colonoscopy had a better prognosis than patients who had a colonoscopy because of symptoms. [105]. Another US trial demonstrated that a cohort of 715 persons who had screening colonoscopies had a significantly reduced CRC-associated mortality and incidence compared to the control collective [106].

Large cohorts including from Germany showed colonoscopies can detect a large number of cancer at an early stage as well as adenomas in the whole colon [97]. In Germany, about 1/3 of the detected cancer in screening colonoscopies are located proximal to the colon descendens [97]. In further studies, 46 to 52% of patients with proximal neoplasias had no additional distal adenomas [107, 108]. A diagnosis of neoplasias using sigmoidoscopy would have been impossible in these patients.

The results of the sigmoidoscopy case-control studies and the randomized UK study on sigmoidoscopy which both show reduction of cancer incidence and mortality should be

transferable to colonoscopy [109-112]. However, the effect in the proximal colon seems to be smaller than in the distal colon [113-115]. The protective effect shown in FOBT studies ultimately results from performing colonoscopies in patients with positive tests.

The colonoscopy complication rate in a German study with volunteers was very low [116]. These results have recently been confirmed [97]. However, it is likely that not all complications were detected, because late complications were only incompletely recorded. Tandem examinations showed that larger adenomas were seldom missed (0-6%) [117].

If a colonoscopy is negative, it should be repeated after 10 years. Colonoscopies performed 5.5 years after negative endoscopy results, showed no cancer and less than 1% advanced neoplasias [118]. Case control studies indicate that after a negative colonoscopy the cancer risk remains very low even after more than 10 years [113, 119].

It is very important that the colonoscopy is performed with the best possible quality. In Germany, there are clear guidelines for performing colonoscopies [104].

4.2.1.2. Sigmoidoscopy

4.3.	Recommendation	2013
Grade of Recommendation B	Quality assured sigmoidoscopies should be offered as a screening measure to those who refuse a colonoscopy.	
Level of Evidence 2b	De Novo:[121]	
	Strong consensus	

4.4.	Recommendation	2013
Grade of Recommendation B	For the possible detection of proximal cancer, an annual FOBT test should be performed in addition to a sigmoidoscopy.	
Level of Evidence 3b	De Novo:[109, 112, 122-129]	
	Strong consensus	

Background

The effectiveness of sigmoidoscopy as a screening method for CRC has been proven. An English randomized study comparing a single sigmoidoscopy to no screening after a follow-up of 11.2 years, showed that the CRC associated mortality was reduced by 43

% and the incidence of colorectal cancer by 33 % [121]. The incidence of distal cancer was 50 % lower.

However, it should be taken into consideration that not all sections of the colon can be viewed using sigmoidoscopies. In accordance, a sigmoidoscopy study showed that the incidence of proximal cancer was not affected. In this case colonoscopies are superior to sigmoidoscopies.

The protective effect of sigmoidoscopies for distal neoplasias appears to last for 6 to 10 years [112, 122], and in one study even as long as 16 years [123]. However, a study with 9,417 subjects who underwent a sigmoidoscopy 3 years after a negative one showed advanced adenoma or cancer in the distal colon in 0.8% of the cases [124]. Another study in 2,146 participants with negative sigmoidoscopies compared screening/follow-up intervals of 3 and 5 years [125]. The rate of advanced neoplasias did not differ significantly (0.9% vs. 1.1%). Thus, a follow-up exam after a negative result is recommended after 5 years.

Because proximal tumors cannot be detected with a sigmoidoscopy, an additional annual FOBT is recommended. It should be performed before sigmoidoscopy, because a positive test requires a colonoscopy and, thus, an additional sigmoidoscopy can be avoided. However, a reduction of CRC-related mortality using a combination of sigmoidoscopy and FOBT has not yet been proven. A prospective non-randomized study found a lower CRC-related mortality for the combination, but the results failed to meet the test for significance and the compliance was exceptionally low [126]. In several studies, however, a combination of sigmoidoscopy and one-time FOBT was not significantly better than sigmoidoscopy alone [127, 128]. In the most recent study from Japan, a combination of sigmoidoscopy and FIT detected 10% (absolute) more advanced neoplasias [129].

However, it should be considered that currently in Germany sigmoidoscopies are not covered by the health insurance catalogue of benefits and, thus, they cannot be charged. Furthermore, in contrast to screening colonoscopies no quality assurance measures are established for sigmoidoscopies. In England, a requirement for the participation in a sigmoidoscopy study was at least 50 supervised and 100 independent sigmoidoscopies [109]. Every examination was documented on video. The colon depth that was reached, the quality of colon preparation, and the results were recorded.

4.2.1.3. Capsule-Colonoscopy

4.5.	Recommendation	2013
Grade of Recommendation B	Capsule colonoscopy should not be used for colon cancer screening in the asymptomatic population.	
Level of Evidence 4	De Novo: [130-136]	
	Strong consensus	

Background

A literature search on capsule colonoscopy for screening did not identify any studies. There are a number of case series on sensitivity and specificity of colorectal neoplasias using the first capsule generation [130-134]. For the second capsule generation (PCC2) with improved technical characteristics, a sensitivity of 84-89% was reported for polyps larger than 6 mm [135, 136]. However, this was a small cohort with preselected patients so that currently its use for colorectal cancer screening cannot be recommended for the general population.

4.2.2. Stool Tests³

4.2.2.1. Fecal Occult Blood Test (FOBT)

4.6.	Recommendation/Statement	2013
GCP	For persons with an average CRC-risk who do not want a colonoscopy, a FOBT should be conducted annually.	
	Strong consensus	

4.7.	Statement	2008
Level of Evidence 1a	A positive test result requires endoscopic examination of the entire colon.	
	Strong consensus	

4.8.	Statement	2013
Level of Evidence 1b	Annual FOBTs are better to reduce CRC-associated mortality than testing once every two years.	
	De Novo: [137]	
	Strong consensus	

4.9.	Statement	2008
Level of Evidence 1a	For those who take part in colonoscopy screening, there is no need for any additional FOBT or other screening tests.	
	Strong consensus	

³ Prof. Schmiegel did not take part in the votes on the recommendations concerning FOBT/iFOBT, genetic stool tests and M2-PK because of a potential conflict of interest.

4.10.	Recommendation	2013
Grade of Recommendation 0	Immunologic FOBTs (iFOBT) with a proven high specificity of >90% and sensitivity may be used alternatively to the Guaiac test.	
Level of Evidence 3a	De Novo: [102, 138-146]	
	Strong consensus	

Background

The basic principle of stool testing for occult blood is that colorectal cancer bleed more often than normal colorectal mucosa. Traditional FOBTs use filter paper impregnated with Guaiac resin which after adding hydrogen peroxide turns blue in the presence of hemoglobin in the stool. In Germany, there are currently three Guaiac tests available: Hemoccult®, HemoCare®, and HemoFEC®. The most sensitive gFOBT (Hemoccult Sensa®) is not available in Germany. Because many cancer bleed intermittently [147], repeated testing is required in order to improve detection of CRC [148, 149]. Accordingly, in the studies three consecutive stools with 2 samples per stool were tested using test cards with two fields each (i.e. 6 fields total) [150].

The results of four large randomized studies exist on the effectiveness of FOBT as a screening method for colorectal cancer [137, 151, 152]. In the most recent meta-analysis of these studies, a reduction of CRC-associated mortality by 25% was shown for those patients who had an FOBT at least once (relative risk 0.75, 95%CI 0,66 – 0.84) [153]. In three of the four studies a gFOBT was done every 2 years. When comparing tests every year with tests every two years, the annual testing was better with regard to reduction of mortality [137].

Test sensitivity and specificity are particularly dependent upon test handling and patient instruction. A rehydration of the test fields before their development increases screening sensitivity, but clearly reduces specificity (in one study from 97.6% to 90.2%, in another study from 97 to 85.4% [137, 154]) and is, therefore, not recommended. There is evidence that instructing patients before conducting the test on nutrition and interfering drugs can reduce the number of false positive tests and, therefore, the number of necessary colonoscopies [155-157]. Therefore, it seems helpful to explain to patients the factors which can influence test results. The influence of plant peroxidases can alternatively be prevented by waiting for 3 days before test development [158]. However, the necessity of dietary restrictions for FOBT was questioned in a meta-analysis [159].

If one test field is positive for occult fecal blood, a complete colonoscopy after digital rectal examination is mandatory. Unfortunately, even under study conditions in some cases less than 90% of all persons with positive FOBT had a colonoscopy [160]. In one study it was even only 64% [161].

The effect of FOBTs on CRC-mortality results from the diagnosis of colorectal cancer at an earlier stage with a more favorable prognosis. Advantages of FOBT include an easy

test performance as well as low costs. A disadvantage is the moderate sensitivity for cancer and the low sensitivity for adenomas. In one randomized study a reduction in colorectal cancer incidence was shown; it must be considered, however, that in the context of this study over 30% of the participants underwent a colonoscopy [162].

Immunological tests specifically detect human hemoglobin. Thus, no change in diet is necessary during testing. In contrast to the gFOBT, some tests also have the option of automated analysis and changing the hemoglobin threshold values which would be considered positive. Tests are either called immunologic FOBT (iFOBT) or fecal immunochemical tests (FIT). Currently in Germany, they are not covered by health insurance. In contrast to the gFOBT, there are no studies with an endpoint of CRC-associated mortality reduction. However, there are a number of randomized studies which compare individual iFOBTs directly with certain gFOBTs. In a meta-analysis of these studies identified in a literature search individual iFOBTs (OC-Sensor) were significantly better at detecting advanced neoplasia than the Hemoccult® test (pooled odds ratio (OR) of 2.12 (95% CI 1.66–2.71) [138]. In two studies which compared the gFOBT HemoFEC® or Hemoccult Sensa® with an iFOBT (Inform® or FlexSure®), however, no significant difference was found [138]. In particular, in the two largest randomized studies from The Netherlands a significant difference was found suggesting a superiority of the iFOBT used (OC-Sensor) over the Hemoccult.

Sensitivity and specificity of iFOBT available in Germany vary greatly so that the general use of iFOBTs is not recommended [140]. It seems necessary to prove a sufficient sensitivity and especially the specificity individually for each iFOBT that will be used for screening. The lowest acceptable specificity limit is considered to be 90%. The results of screening studies suggest that, if a corresponding cut-off is adjusted, a similarly high specificity of >90% as for the gFOBTs can be reached for the iFOBT with much higher sensitivity [141, 142]. Currently, the optimal hemoglobin content at which the iFOBT should be considered positive is under discussion. In both Dutch publications the limit was 100 ng/ml. In the included studies one stool sample each was examined using the iFOBT. Some data show that the testing of several stool samples increases its sensitivity [143-145]. However, a trial from The Netherlands shows that reducing the cut-off has a similar effect [146].

Overall the data show that iFOBT, for which there are appropriate data, are a useful substitute for gFOBT.

4.2.2.2. Genetic Screening Tests

4.11.	Recommendation	2013
Grade of Recommendation B	Stool tests that measure DNA changes cannot be recommended for CRC screening in the asymptomatic population.	
Level of Evidence 3b	De Novo: [163-168]	
	Strong consensus	

Background

In many cases, the development of colorectal cancer through the intermediate step of the adenoma takes place with characteristic genetic changes. Isolation and testing of DNA from colon epithelial cells in the stool is possible [163-166]. This procedure has the advantage that theoretically non-bleeding lesions could also be identified. In a study by Imperiale which included almost 5,500 asymptomatic persons, stool samples of 2,500 participants were tested for a total of 23 genetic variants. They were then compared to the gFOBT [167]. The sensitivity of the genetic tests was higher than for the gFOBT. However, it was merely 50% for cancer and 15% for advanced adenomas with costs of several hundred US Dollars per test and a tedious procedure. A literature search identified only one other study [168]. In this prospective study 3,764 asymptomatic persons aged 50 to 80 years had a gFOBT and a colonoscopy. Of these, 2,497 participants had stool samples tested with a DNA-panel I with the same markers as in the Imperiale study and 217 with a DNA-panel II with only 3 mutations including the methylation marker vimentin. The sensitivity for relevant neoplasias was 20% for DNA-panel I and 40% for DNA-panel II. The sensitivity for the Hemocult®-test was 11%, for the Hemocult-Sensa® 21%. The specificity for the DNA-panel II was not determined. Overall panel I was better than one of the gFOBTs (Hemocult®) and equal to the other gFOBT (HemocultSensa®). Panel II seemed to be better than both gFOBT. However, it was only tested in a small proportion of the participants.

In summary, the data and results are not sufficient when considering the effort and costs of each test. Therefore, they can currently not be recommended.

4.2.2.3. M2-PK

4.12.	Recommendation	2013
Grade of Recommendation B	The M2-PK stool test should not be used for colon cancer screening in the asymptomatic population.	
Level of Evidence 4	De Novo: [169, 170]	
	Strong consensus	

Background

The majority of studies were done on preselected patient collectives. Thus, no conclusion can be made on the relevance of the test for screening the asymptomatic population. In externally performed literature searches two studies were identified on analyzing screening populations [169, 170]. One study compared the M2-PK test with colonoscopies in 1082 asymptomatic persons. The sensitivity for advanced adenomas was 21.7% with a specificity of 82%. Another study including 1,079 participants compared the M2-PK test with different FOBT. The sensitivity for advanced neoplasia was 27.3% (compared to 7.3-20.0% for the FOBT) and a specificity of 86.2% (FOBT 92.9-94.0%). The positive predictive value for advanced neoplasia was 11.5% and lower than all FOBTs tested. Overall, the data are not sufficient to recommend the test for the screening of the asymptomatic population.

4.2.3. Radiologic Tests

4.13.	Recommendation	2013
Grade of Recommendation B	Neither CT-colonography nor MR-colonography should be used for colon cancer screening in the asymptomatic population. In case of an incomplete colonoscopy (e.g. adhesions) and if the patient still insists on complete colon analysis a CT- or MR-colonography should be done.	
Level of Evidence 3b	De Novo:[171-173]	
	Strong consensus	

Background

For the use of MR-colonography there are only individual small studies which do not provide enough data to recommend its use for screening. More data are available for CT-colonography (CTC). The two most current meta-analyses identified in the literature search comparing CTC with colonoscopy as screening procedures in the asymptomatic population showed a high sensitivity of 100 % detection for cancer and 87.9 % for adenomas ≥ 10 mm. The sensitivity for smaller adenomas was not as high [171, 172]. Furthermore, there is significant heterogeneity between the different studies. It remains unknown whether the study results that were attained at experienced centers are applicable to clinical practice. Also the relevance of extracolonic results is unclear. The method involves radiation exposure, which in Germany is prohibited according to the Radiation Protection Ordinance (StrlSchV §80). Thus, it is not allowed if alternative methods are available. The exact neoplasia risk due to CTC using modern equipment with reduced radiation dose is not known. It is also unclear which polyp size mandates a colonoscopy and in which interval patients with negative CTC or smaller polyps should be monitored [173].

Patients who had an incomplete colonoscopy for technical reasons should be offered to repeat the procedure e.g. in a hospital or to have a CTC as an alternative to analyze the rest of the colon (see Chapter 6.1.)

4.3. Cost Effectiveness

4.14.	Statement	2013
GCP	FOBT as well as sigmoidoscopy, colonoscopy, and the combination of sigmoidoscopy and FOBT have been shown to be cost-effective (in comparison to screening procedures for other diseases).	
	Consensus	

Background

Prospective studies looking at cost-effectiveness of different CRC screening procedures do not exist. Mathematical model calculations suggest that colonoscopy, sigmoidoscopy, and FOBT are cost-effective [139, 174-184].

4.4. Recommendations of Other Included Guidelines

According to the DELBI-criteria 2 guidelines were included for CRC screening, the recommendations of the US Preventive Task Force from 2008 [94] and the Asian Pacific consensus recommendation from 2007 [185]. The US-Preventive Task Force recommends the following methods: a sensitive FOBT (Hemoccult Sensa® and IFOBT/FIT) annually, a sigmoidoscopy every 5 years with an FOBT every 3 years, or a colonoscopy every 10 years. The use of CT-colonography and genetic stool tests is not recommended. Capsule endoscopy and the M2-PK-test are not listed. It should be mentioned that the Hemoccult Sensa® is not available in Germany.

The Asian Pacific guideline recommends a FOBT (gFOBT und iFOBT) every 1-2 years, a sigmoidoscopy every 5 years, and a colonoscopy every 10 years. A CT-colonography is not recommended, and genetic stool tests, capsule endoscopies, and M2-PK-tests are not mentioned.

5. Risk Groups

Persons who due to a special predisposition have a higher risk for the development of colorectal cancer in comparison to the normal population, usually belong to one of three defined risk groups:

- People with a familial increased risk (genetic reasons not yet known) for a colorectal cancer
- Proven or possible carriers for hereditary colorectal cancer
- Persons at risk due to inflammatory bowel disease

5.1. Sporadic Colorectal Cancer

5.1.1. Risk Groups

5.1.1.1. Relatives of Patients with Colorectal Cancer

5.1.	Statement	2013
Level of Evidence 2a	First degree relatives of patients with CRC have an increased risk of developing colorectal cancer.	
	Evidence from update literature search: [186-200]	
	Consensus	

5.2.	Statement	2013
Level of Evidence 2b	Second degree relatives have a slightly increased risk of developing colorectal cancer.	
	Evidence from update literature search: [186, 187, 190, 191, 201, 202]	
	Consensus	

Background

About 20-30% of CRC cases occur as "familial cumulation" i.e. a cumulation of cancer can be observed within a family, although no specific genetic cause can be identified. In these cases the term "familial colorectal cancer" is used [186]. For first degree relatives (parents, siblings, children), the average CRC risk is increased by a factor of two to three. A further, three to four-fold risk increase is present if the index patient developed colorectal cancer before age 60 and/or more than one first degree relative had CRC [187-199]. In this group, there are also cases of undiscovered hereditary colon cancer (e. g. HNPCC; see below). The risk is higher for colon cancer than for rectal cancer (relative risk 2.4 vs.1.9). For first-degree relatives of affected patients, the CRC risk can be divided further. The risk for siblings is about 2.5-times higher than for the children. If the index patient developed colorectal cancer after age 60, the CRC risk for first degree relatives is only slightly increased [188, 200].

Second degree relatives (grandparents, siblings of the parents, grandchildren) of patients with colorectal cancer have a slightly increased cancer risk (RR 1.5); however, this has not been adequately studied and verified in clinical practice [187, 190, 191, 201, 202]. Third degree relatives of patients with colorectal cancer do not seem to be at an increased cancer risk.

5.1.1.2. Relatives of Patients with Colorectal Adenomas

5.3.	Statement	2013
Level of Evidence 2b	First degree relatives of patients with a colorectal adenoma before age 50 have an increased colorectal cancer risk.	
	Evidence from update literature search: [188, 191, 203-206]	
	Consensus	

Background

The risk for these relatives to develop colorectal cancer is on average about two-fold higher compared to the general population [188, 191, 203-206]; there is an 80% higher risk for parents and siblings of adenoma patients in comparison to their spouses [203]. Again the risk level depends on the age of the index patient: If this person is younger than 60, the average risk is only slightly increased. If the person is younger than 50, the risk is increased about 4.4 fold [204]. If the index patient is older than 60, the colorectal cancer risk is not significantly increased.

Due to the data available, there is no evidence that the relatives of patients with hyperplastic polyps have an increased risk of developing a colorectal cancer. An exception is the extremely rare hyperplastic polyposis syndrome.

5.1.1.3. Patients with Colorectal Adenomas

5.4.	Statement	2008
Level of Evidence 2b	Every histologically verified adenoma poses an increased risk for a colorectal cancer. This is especially true for: <ul style="list-style-type: none"> • multiple (≥ 3) adenomas • large (>1 cm) adenomas 	
	[99, 100, 207, 208]	
	Consensus	

Background

In general, the removal of small singular adenomas results in a reduced risk of up to 90% to develop metachronous colorectal cancer [99, 100, 207, 208]. This reflects the preventive value of colonoscopies in the context of the adenoma-carcinoma sequence. The purpose of control examinations is especially to discover missed or metachronous adenomas.

Adenomas larger than 1 cm are associated with a four-fold increase in cancer risk [191, 208-215]. In addition, multiple adenomas are also associated with an increased risk (4-6fold) of developing a metachronous cancer [191, 208, 210, 211, 213, 214]. On the one hand, this increased risk is likely due to a higher individual disposition and, on the other hand, to an increased rate of missed polyps during the initial colonoscopy. In case of detection of ≥ 3 polyps during colonoscopy there is a significantly higher chance of missed polyps [117, 216].

5.5.	Consensus-based Recommendation	2013
GCP	An increased familial colon cancer risk is identified by medical history. However, there is no mandatory documentation of the family history or their repetition in intervals. The use of standardized questionnaires may be useful to improve the identification of persons with increased risk.	
	Strong consensus	

Background

A risk assessment is usually performed by the physician using the medical history. One possibility to integrate the risk assessment in medical care would be the use of standardized questionnaires in the general practitioner's office at the age of 35 years as part of the check-up exam that is offered at this time.

If the patient does not come to the practice at the abovementioned time, the questioning can be done later by integrating it as a memo into the practice software. A corresponding concept is currently being considered in the Joint Federal Committee.

Other relevant sites are gynecologic practices, because regular visits are recommended for gynecologic cancer screening as well as gastroenterologic practices.

Furthermore, a number of questionnaires are freely accessible via the internet:

- * http://www.onkozert.de/hinweise_zertifizierung_genetische_beratung.htm
- * <http://www.netzwerk-gegen-darmkrebs.de/index.php?id=103>
- * <http://www.felix-burda-stiftung.de/darmkrebs/fragebogen/index.php?f=2>
- * <http://www.lebensblicke.de/darmkrebs/>
- * <http://www.ilco.de/darmkrebs/erblicher-darmkrebs.html>
- * <http://www.krebsrisikotest.de/>

The questionnaire used by the "Netzwerk gegen Darmkrebs" has been evaluated [217]. There are currently no data on the other questionnaires.

5.1.2. Primary Prevention

5.6.	Statement	2013
Level of Evidence 1b	Special recommendations compared to those of the general population cannot be given for primary prevention (dietetic measures, chemoprevention) due to contradictory data available for the mentioned risk groups.	
	Evidence from update literature search: [218-221]	
	Strong consensus	

Background

In general, the recommendations for the average risk population (see Chapter 3) also apply for members of risk groups; there is no confirmed data for special measures [218-221].

5.1.3. Screening Tests

5.1.3.1. First-degree Relatives of Patients with Colorectal Cancer

5.7.	Consensus-based Recommendation	2013
GCP	First-degree relatives of patients with colorectal cancer should undergo a complete colonoscopy starting at an age 10 years before the age at which the index patient was diagnosed with CRC. However, this should be done at the latest at the age of 40-45 years. Colonoscopies should be repeated at least every 10 years if initially the colon was free of polyps.	
	Strong consensus	

Background

The risk of a first-degree relative of a CRC patient to develop a colorectal cancer is increased especially if the index patient's age at diagnosis is less than 50 [191, 193, 200, 202, 222-227].

The recommendation follows the American guideline recommendation [228]. It recommends a colonoscopy at the age of 40 years if a first-degree relative developed CRC before the age of 60 or if two or more first-degree relatives had CRC (independent of the age at diagnosis).

There is no data on the maximum examination interval for this group; at this time it appears probable that an interval of 10 years is usually adequate. However, the 10-year interval should not be exceeded. The American guideline recommends a 5-year interval.

5.8.	Consensus-based Recommendation	2013
GCP	<p>First-degree relatives from patients' families who fulfill the Amsterdam Criteria and who also have microsatellite stability (MSS) in their cancer should be closely monitored:</p> <p>If at least two independent cancer from a family show MSS, colonoscopies should be performed in 3-5 year intervals from age 25.</p> <p>If only one cancer from the family was examined and showed MSS, additional screenings for endometrial cancer and gastric cancer in 3-5 year intervals should be done.</p>	
	Strong consensus	

5.9.	Consensus-based Recommendation	2013
GCP	<p>First-degree relatives of patients with colorectal cancer from families who fulfill the Bethesda-Criteria, but not the Amsterdam-Criteria should have colonoscopies in shorter intervals:</p> <p>If no tumor tissue is available to test for HNPCC-typical characteristics, the interval should not exceed 3 years.</p>	
	Consensus	

5.10.	Recommendation	2013
GCP	If the tumor tissue demonstrates microsatellite stability (MSS) or a low-grade microsatellite instability (MSI-L), the interval should be 3-5 years.	
	Consensus	

Background

A HNPCC-syndrome diagnosis (see section 5.2.1) should be considered in persons who are relatives of young index patients. A microsatellite analysis and/or immunohistochemical tests for mismatch repair proteins should be done. In clinical practice there are repeatedly families who have an accumulation of colorectal cancer, who do not fulfill the diagnosis criteria for HNPCC (Amsterdam II-criteria). If in these families there is no tumor tissue available or if they demonstrate a microsatellite stability (MSS), an as yet unknown hereditary gastrointestinal tumor disposition cannot be completely excluded. An examination interval of 10 years seems insufficient for this constellation, even if so far the issue has not been clarified. An interval of 3-5 years should be adequate for the familial risk.

Previously, analogous to those patients with diagnosed MSI, an annual screening was recommended for patients from families who fulfill the Amsterdam-criteria, but where a microsatellite instability was excluded. The data indicate that this is not necessary. Intervals of 3-5 years are adequate [229, 230]. Surveillance of extracolonic tumors outside the standard cancer screening procedure is not necessary for these persons.

5.1.3.2. Relatives of Patients with Colorectal Adenomas

5.11.	Consensus-based Recommendation	2013
GCP	First-degree relatives of index patients with an adenoma detected before age 50, should undergo a colonoscopy at an age 10 years before the age at which the adenoma was discovered. If the initial colonoscopy did not reveal any polyps, it should be repeated at least once every 10 years. If polyps were detected, the recommendations of Chapter 6.5 apply.	
	Strong consensus	

Background

The recommendation is based on the higher risk in this population as demonstrated in section 5.1.1 [92, 193, 202, 204].

5.2. Hereditary Colorectal Cancer

5.12.	Consensus-based Recommendation	2013
GCP	If it can be assumed that a patient has a hereditary colon cancer or if a healthy person has a high risk of hereditary colon cancer, the patient should be referred to an interdisciplinary center with an established expertise in the field of hereditary colon cancer.	
	Consensus	

Background

Monogenic-inherited colorectal cancer are rare (less than 5% of all colorectal cancer). The diagnosis has significant consequences for patients and their relatives. In case of suspicion of hereditary colorectal cancer, an experienced center for familial colon cancer or an equivalent with corresponding expertise should be contacted. A molecular genetic diagnosis of affected patients serves to confirm the diagnosis and makes it possible to conduct predictive testing of family members. A relevant germ cell mutation test should be conducted following the guidelines for diagnosis of the genetic disposition for cancer diseases of the Federal Physician's Association and the genetic diagnostics regulations (GenDG) [120]. As an example, the algorithm for the HNPCC-/Lynch-syndrome is shown in Figure 2. Analogously, it is valid for the other hereditary syndromes with increased colon cancer risk. All patients and persons with higher risk in these groups have, in addition to an increased risk for colorectal cancer, an increased risk for extracolonic neoplasias. Due to the usually autosomal-dominant inheritance process, first-degree relatives of index patients have a 50% risk of having inherited this genetic predisposition. A predictive genetic test according to the GenDG always has to be preceded by genetic counseling of the patient concerned and can only take place if a clear pathogenic germ cell mutation has been identified in an affected family member (see Fig. 2) [120].

5.13.	Consensus-based Recommendation	2013
GCP	The possibility and benefit of psychosocial counseling and care should be pointed out to already affected persons, index patients, and persons at risk for monogenous hereditary disease who have an increased risk for colorectal cancer.	
	Strong consensus	

Background

In patients and their family the diagnosis of manifested hereditary tumor syndromes, the knowledge of a highly increased disease risk, or the definite detection of a mutation may be accompanied by numerous psychosocial stress factors. Corresponding studies were done in particular for FAP. These included not only adults and adolescents, but also children and their parents [231-233]. Relevant stressors included altered physical perception, fear of surgical interventions, screening tests, and future tumor progression, fear of occupational limitations, communication of the illness to the social environment, insecurity about having children, as well as coming to terms with family members who died early of cancer and corresponding conflict within the family.

Predictive testing of under age persons is also associated with special challenges. These include an inability of these persons to decide for themselves and their limited understanding of the meaning and consequences of the testing. In addition to clinical and human genetic counseling, psychosocial patient counseling can help patients and persons at risk in making their decision for or against having genetic diagnostics and coming to terms with the test results.

5.2.1. Risk Groups

5.2.1.1. HNPCC (Hereditary Colorectal Cancer Without Polyposis)/ Lynch-Syndrome

5.14.	Statement	2013
GCP	Risk persons for HNPCC are persons from families who fulfill the Amsterdam criteria or one of the Bethesda criteria with evidence of a microsatellite instability (MSI). This includes relatives who due to the form of inheritance could be mutation carriers.	
	Strong consensus	

Background

HNPCC-syndrome is defined according to family history criteria (Amsterdam-I- and -II-criteria, see Chapter 12.2). To identify additional persons at risk the revised Bethesda-criteria are used (Bethesda-criteria, see Chapter 12.3). The literature prefers to refer to carriers of pathogenic germline mutations in one of the MMR genes as persons with Lynch-syndrome. In contrast, the term HNPCC is often used for patients in whom no pathogenic germline mutation was identified. For reasons of simplicity only the term HNPCC is used in the following.

Mutation carriers have a very high risk of developing colorectal cancer (50-70%) or endometrial cancer (20-60%). This is also true to a lesser extent for other neoplasias such as ovarian, gastric, and small intestine as well as urothelial cancer of the renal pelvis and the ureter.

5.15.	Consensus-based Recommendation	2013
GCP	Whether a patient fulfills the Bethesda- or Amsterdam-criteria for HNPCC should be decided upon based on the family history by the treating physicians.	
	Strong consensus	

Background

In contrast to FAP, it is not easy to clinically identify HNPCC. This is because a conspicuous phenotype is lacking. For this reason, criteria have been defined which suggest to initially examine the tumor tissue and if appropriate followed by a mutation search. A diagnosis of HNPCC can be made clinically if, in the family of the patient, the so-called Amsterdam I criteria are fulfilled [234]. With HNPCC, in addition to CRC, there is an increased rate of endometrial and urothelial cancer, as well as cancer of the small intestine. The Amsterdam II criteria include these extra-colonic manifestations [179]. These criteria present a pragmatic implementation from a clinical point of view. Since nowadays many families are small, it is often not possible to fulfill these criteria. Therefore, a lack of positive family history—particularly in small families—is no argument against HNPCC. The less specific Bethesda criteria can be used to initiate a work up for possible HNPCC in smaller families and individual cases (Appendix 5.3) [235].

The general tumor risk for HNPCC carriers is given as 80 to 90%, whereby CRC is by far the most common manifestation. In the context of HNPCC the average age at CRC diagnosis is 44 years. Colorectal cancers are rarely seen before age 25. The cumulative lifetime risk of an HNPCC carrier to develop CRC is 60 to 70%. The risk for men is about 10 % higher than for women.

Endometrial cancer is the second-most common tumor in HNPCC. The lifetime risk for female carriers to develop an endometrial cancer is 40 to 60% with a median age of diagnosis between 46 and 48 years. Cancer of the ovaries occur in about 10-15% of all carriers. Stomach cancer occur in 2 to 13% of HNPCC patients and are diagnosed on average between the ages of 51 and 56. Manifestations before age 40 are rare. Most of these cancer are of the intestinal type. For Germany a cumulative lifetime risk of 6.8% up to age 70 was found [236].

The cumulative lifetime risk for small bowel cancer in the context of an HNPCC is 4-8% [236, 237]. For 35-50% of the cases, HNPCC-associated small bowel cancer are localized in the duodenum [238]. Diseases before age 30 are rare. Cancer of the upper urinary tract (ureter/renal pelvis) often appear as second or third cancer. The average age of onset for these tumors is given as 50 to 63. The lifetime risk is reported as 1-12%. In some families a higher rate of urothelial cancer was observed. A recent Dutch study [239] reports a relative risk of urothelial cancer of the complete urogenital tract (including bladder cancer) of 4.2 for male and 2.2 for female carriers of pathogenic germline mutations in one of the MMR-genes compared to the general Dutch

population. As yet unpublished results of the German HNPCC consortium confirms these results.

The lifetime risk for biliary tumors is higher with HNPCC, but overall relatively low. Pancreatic cancer in HNPCC patients are rare, but significantly more common than in the general population (relative risk 8.6; lifetime risk 3.7%) [240, 241].

For brain tumors there is a slightly increased risk with HNPCC, histologically these are primarily astrocytomas and glioblastomas. The median age of presentation is 40 to 54 [242-244]. Muir-Torre syndrome is a rare phenotypic variant of HNPCC which on top of the typical HNPCC-associated tumors is associated with sebaceous gland adenomas or cancer [245].

5.16.	Consensus-based Recommendation	2013
GCP	Additional (molecular-) pathologic examinations for HNPCC should be performed if at least one revised Bethesda-criterion is fulfilled. In this case, either a quality assured immunohistochemical test of the expression of the DNA-mismatch-repair-proteins MLH1, MSH2, MSH6, and PMS2 can be performed or a test for microsatellite instability. If immunohistochemical expression of the DNA-mismatch-repair-proteins is normal, an additional microsatellite stability test should follow to definitely exclude HNPCC. This can only be omitted if the immunochemical testing definitely identified the loss of a DNA-mismatch-repair-protein.	
	Strong consensus	

Background

An algorithm to test for mismatch-repair-defects in tumor tissue is shown in Figure 3. Microsatellite instability can be demonstrated in about 80 % of the tumor tissue of patients who meet the Amsterdam I/II-criteria. These phenomena can be traced back to underlying defects in a DNA-repair enzyme which can no longer repair missing base matches during cell mitosis. These mismatches occur relatively easy in short repetitive DNA-fragments (so-called microsatellites). Accordingly, in repair-deficient HNPCC tumors a different microsatellite pattern compared to normal cells is found. This has led to the term "microsatellite instability." Patients from families who meet the Amsterdam-criteria and whose tumor tissue shows a microsatellite stability (MSS) should, if possible, have an independent second tumor from the family tested.

In patients whose families fulfill the Bethesda criteria, microsatellite instability is found in about 30% of the patients and, thus, is a definite suggestion for the presence of HNPCC. The classical Bethesda criteria were revised in 2004 (Appendix 5.3) [246]. The sensitivity of the microsatellite analysis in HNPCC-associated tumors is 79-93 %, the immunohistochemical test (incl. MSH6 and PMS2) is comparable with a sensitivity of 94 % [247]. In comparison to microsatellite analyses (MSA), immunohistochemistry (IHC) is more cost-effective and faster. In addition, due to the malfunction of a DNA-repair protein, it gives an indication in which of the 4 known mismatch-repair-genes the disease causing germline mutation is located. If the IHC gives a definite result, the MSA can be omitted. If not, an MSA should be done.

5.17.	Consensus-based Recommendation	2013
GCP	In patients with highly microsatellite instable tumors and absence of the MLH1-protein in the immunohistochemical test, an analysis of the somatic BRAF-mutation p.Val600Glu should be performed to exclude HNPCC.	
	Consensus	

Background

About 15% of sporadic CRC show HNPCC-typical alterations in the tumor tissue in terms of MSI-H and absence of the MLH1-protein in the immunohistochemical test (IHC). This is usually due to a somatic methylation of the MLH1-promotor. The methylation is associated with the somatic mutation p.Val600Glu in the BRAF-gene [248-251]. Therefore, for tumors with MSI-H and absence of the MLH1-protein in the IHC an additional BRAF-analysis should follow. Using this procedure it is possible to differentiate the HNPCC-associated from the sporadic CRCs, because HNPCC-associated CRCs have no BRAF-mutation. For first degree relatives of patients with sporadic MSI-H CRC the risk of developing CRC is slightly increased (standardized incidence ratio 1.60) [252]. Therefore, the screening recommendations should be done analogous to the cases with positive family history. It is possible that the risk for other tumors (stomach, ovarian) is increased for patients with BRAF-positive CRC [252].

5.2.1.2. Adenomatous Polyposis-Syndrome

5.2.1.2.1. Patients with Classic Familial Adenomatous Polyposis (FAP)

5.18.	Statement	2008
Level of Evidence 2a	All patients with untreated FAP will - with rare exceptions - develop colorectal cancer.	
	[253]	

Background

Classic (typical) FAP is characterized by the presence of more than 100 colorectal adenomas. The formation of polyps generally begins in the second decade of life. Due to the large number of adenomas, the cancer risk is nearly 100%.

In addition, most patients also develop extra colonic intestinal manifestations. The most important ones are duodenal and/or papillary adenomas, which occur in about 75% of patients and are to be regarded as pre-cancerous lesions (see below). Stomach adenomas are observed much less frequently, with an incidence of <10% of patients with FAP. Glandular polyps of the stomach, which occur in at least a third of FAP patients, are not thought to have pre-neoplastic potential.

Further extra-intestinal manifestations are abdominal and extra-abdominal desmoid tumors, thyroid gland cancer, and malignant CNS tumors (mostly medulloblastomas), hepatoblastomas as well as harmless, but often diagnostically indicative osteomas, epidermoid cysts, or pigment anomalies of the retina [253].

5.2.1.2.2. **Patients with Attenuated Familial Adenomatous Polyposis (AFAP)**

5.19.	Statement	2013
Level of Evidence 2a	Attenuated FAP (AFAP) has to be distinguished from typical familial adenomatous polyposis. Patients with AAPC are also at a very high risk for colorectal cancer, however, polyps and cancer generally develop later, and more often in the proximal colon.	
	Evidence from update literature search: [253-261]	

Background

In contrast to classic FAP, AFAP is typically characterized by less than 100 colorectal adenomas and/or a later occurrence of adenomas and CRC by about 10-15 years. The lifetime risk to develop CRC is also very high. Extra-colonic manifestations (e.g. desmoids) can occur [253-258]. The clinically defined AFAP is a heterogeneous group from a genetic point of view. Germline mutations in the APC-gene (5' and 3' end of the gene) can be detected in 15-30% of the families. The most important differential diagnosis is the MUTYH-associated polyposis (MAP) (see below) [259]. In individual cases the clinical differentiation from HNPCC can be difficult [260]. Therefore, a molecular genetic diagnosis can be very helpful (microsatellite analysis, APC, MUTYH) in the clinical differential diagnosis of some cases of attenuated FAP [261]. In the majority of patients with the clinical diagnosis AFAP, no identification of genetic mutations is possible, so it has to be assumed that additional mutations in unidentified genes exist [261].

5.2.1.2.3. **Patients with MUTYH-Associated Polyposis (MAP)**

5.20.	Statement	2013
Level of Evidence 2a	MUTYH-associated polyposis (MAP) is the most important differential diagnosis of FAP. The phenotype is similar to that of AFAP; the lifetime risk for CRC is also very high for MAP. Due to the autosomal-recessive inheritance there is only a small disease risk for patients' children and heterozygous carriers. Establishing the diagnosis is usually only possible using molecular genetic tests.	
	Evidence from update literature search: [262-269]	

Background

The autosomal-recessive hereditary MAP, which is caused by a biallele germline mutation in the MUTYH-gene, is the most important differential diagnosis of APC-associated FAP [262]. It is diagnosed in 15-20 % of the APC-mutation negative colorectal adenomatoses [263, 264].

The colorectal MAP phenotype is similar to that of the AFAP: usually between 20 and several hundred adenomas occur, the mean age of diagnosis is 45 (range 12-68 years) [265]. If untreated, the CRC lifetime risk is about 70-80 % [266]. The phenotypic MAP spectrum is still not definitely known: several large population-based studies with CRC patients showed that up to one third of the biallele MUTYH-mutation carriers develop

CRC without colorectal polyps [267]. In addition, it has been reported that up to 50 % of the MAP patients have hyperplastic polyps [268].

About 20% of patients have duodenal polyposis, the lifetime risk of duodenal cancer is about 4%. Overall, extraintestinal malignancy occurs significantly more often than in the standard population (odds ratio 1.9) and shows a certain overlap with HNPCC. However, there is no dominating tumor. Typical FAP-associated extraintestinal tumors such as osteoma, desmoides, and CHRPE do not occur [269].

5.2.2. Screening

5.2.2.1. HNPCC / Lynch-Syndrome

5.21.	Recommendation	2013
Grade of Recommendation B	Persons at risk for HNPCC should have genetic counseling when they reach legal age (usually from 18 years of age), but before the age of 25. As soon as the disease causing mutation is known in the family, persons at risk should be made aware of the possibility of predictive testing.	
Level of Evidence 1c	Evidence from update literature search: [270, 271]	
	Strong consensus	

5.22.	Statement	2008
Level of Evidence 1c	If the disease causing mutation has been excluded in a person at risk, a special surveillance is no longer necessary.	
	Strong consensus	

Background

Carriers of HNPCC have mutations in so-called mismatch repair genes. To date, germ cell mutations have been demonstrated in five different genes: MSH2, MLH1, MSH6, PMS2, and EPCAM. Almost 86% of the mutations identified up to now exist in the genes MSH2 and MLH1 [270], about 10% in the MSH6 gene and 2% in the PMS2-gene. Mutations in the EPCAM-gene are found in about 2% of the families [271]. According to the GenDG, human genetic counseling must be done before the predictive genetic tests are performed. In general, a predictive test is only possible if a definite pathogenic mutation has been identified in a family member. The identification of polymorphisms or mutations with unclear pathogenic significance is not suitable for predictive genetic testing.

5.23.	Consensus-based recommendation	2013
GCP	HNPCC-patients and persons at risk should generally undergo annual colonoscopies from the age 25.	
	Consensus	

Background

HNPCC-patients have a strongly increased cancer risk. Table 6 gives an overview of the recommended cancer screening tests. Colorectal cancer occur in HNPCC patients at a median age of 44. The chance of developing this disease increases significantly from age 30. In case of very early manifestations of familial colorectal cancer, in contrast to the abovementioned recommendation, the first colonoscopy should be done 5 years before the earliest manifestation age. More than 50% of the HNPCC-associated cancer are found on the right side of the colon [243]. This is the reason a rectoscopy and/or rectosigmoidoscopy are not sufficient as a surveillance test. A prospective study showed a significant reduction in mortality as well as CRC incidence by more than 60% for both with three-year testing intervals [272]. Due to an accelerated tumor progression with interval cancer in about 4% of all patients with three-year testing intervals, an annual interval is recommended [272-274] (Table 6). A prospective study of the German HNPCC-consortium with 1 year intervals showed a significantly better stage distribution for detected asymptomatic CRC [229].

The stage distribution and, therefore, the prognosis of HNPCC-associated colorectal cancer that have been discovered in screening programs is significantly better than cancer which were diagnosed as a result of disease symptoms [275]. The colonoscopy may be done as a chromoendoscopy. Prospective studies demonstrated a significant increase in adenoma detection rate with the use of chromoendoscopy [276-278]. However, currently it is not clear whether this improves the interval cancer rate or the mortality.

5.24.	Recommendation	2013
Grade of Recommendation B	For female patients with HNPCC and persons at risk, in addition to the annual gynecological exam, a transvaginal ultrasound should be performed from age 25, because of the risk of endometrial and ovarian cancer.	
Level of Evidence 4	[242, 279-282]	
	Strong consensus	

5.25.	Consensus-based Recommendation	2013
GCP	For female patients with HNPCC and persons at risk, in addition an endometrial biopsy should be performed from age 35.	
	Consensus	

Background

These recommendations arise from the natural progression of HNPCC (see above). For female carriers, the risk of developing an endometrial cancer up to the age of 70 is 40 to 60% and for ovarian cancer about 10-15% [242, 279]. Studies published so far on the efficacy of endometrial cancer screening in female patients with HNPCC clearly indicate that the transvaginal ultrasound (TVU) is not suitable as a screening-test, especially for pre- and post-menopausal women [280-282]. Since an endometrium biopsy using the Pipelle method in addition to TVU has been reported in the literature as the most useful alternative and since these have already been propagated in international recommendations [283], the recommendation of an annual endometrial biopsy from age 35 is sensible (see Table 7). For patients who no longer plan to have children, the possibility of a prophylactic hysterectomy and, if appropriate, an adnectomy should be discussed.

5.26.	Consensus-based Recommendation	2013
GCP	In addition, HNPCC-patients and persons at risk with HNPCC should have an EGD regularly from age 35.	
	Consensus	

Background

HNPCC-associated gastric cancer are diagnosed at a median age of 54. They are only seen in 2% of patients before the age of 35. For Germany, a cumulative lifetime risk of 6.8 % up to age 70 was determined [236]. A familial cumulation (at least 2 affected members with gastric cancer) was only observed in 26% of the MLH1- and MSH2-mutation carriers [284]. Therefore, the EGD seems to be sensible for all mutation carriers and persons at risk from 35 years of age (see Table 6). This is also suggested, because the risk for duodenal cancer is higher than for gastric cancer, and these occur from age 30. The cumulative lifetime risk for duodenal cancer in HNPCC patients is 4-8% [236, 237]. 35-50% of the small intestine cancer are located in the duodenum [238]. Due to the data available, the recommendation of the S3-guideline on gastric cancer must in the future be defined more precisely. There are no data on the issue of test intervals. In analogy to the tumor progression of colorectal cancer based on a hereditary MMR-defect, an annual interval is recommended.

Due to the increased risk of urothelial and hepatobiliary cancer, an annual upper abdominal ultrasound used to be recommended. However, its usefulness has not been confirmed and its curative potential is questionable. Therefore, it is no longer generally recommended. The benefit of the urine cytologic test has not been confirmed and has, therefore, not been generally recommended since 2004.

5.27.	Recommendation	2013
Grade of Recommendation B	Chemoprevention in HNPCC patients should not be performed.	
Level of Evidence 2b	Evidence from update literature search:[285, 286]	
	Consensus	

Background

So far, only data from one prospective randomized study exist on chemoprevention of HNPCC. The CAPP2-study tested the use of 600 mg acetylsalicylic acid and resistant starch in a 2x2 design. The primary analysis of the defined endpoints showed no significant effect of ASS [285]. After longer follow-up of 55.7 months, a significant reduction of colorectal cancer incidence (hazard ratio 0.41 (95%CI 0.19-0.86), p=0.02) as well as a non-significant reduction of other HNPCC-associated cancer (hazard ratio 0.47 (95%CI 0.21-1.06), p=0.07) was found in the subgroup of HNPCC patients who had taken 600 mg ASS for at least 2 years [286]. The study dose of 600 mg with its expected side effects seems high. The efficacy of low ASS doses for HNPCC-patients is currently not known and will be studied in a subsequent study (CAPP-3). The aim is to include as many HNPCC-patients as possible. In general, HNPCC-patients should not undergo chemoprevention with ASS until the results of this study are available.

5.28.	Consensus-based Recommendation	2013
GCP	Prophylactic colectomy or proctocolectomy in HNPCC mutation carriers shall not be performed. A subtotal colectomy in patients with a cancer should not generally be done, but should be discussed individually with the patient.	
	Strong consensus	

5.29.	Recommendation	2013
Grade of Recommendation A	After oncologic resection of a CRC in addition to the regular follow-up colonoscopy surveillance shall be performed in the same way as before surgery.	
Level of Evidence 2a	Evidence from update literature search:[272, 273, 287-290]	
	Strong consensus	

Background

Because regular surveillance can detect pre-malignant adenomas and nearly all surveillance detected cancer are UICC stage I or II [272, 273] and the penetrance of the disease is not complete, prophylactic colectomies and/or proctocolectomies are not recommended. Individual constellations such as adenomas that cannot be removed endoscopically, regularly difficult colonoscopies, insufficient colonoscopy preparation despite adequate laxative procedures, and missing compliance may justify the recommendation of a prophylactic colectomy.

When cancer have been detected the patient should have an oncologic resection according to oncologic surgical standard criteria (see also Chapter 7). However, the risk of colorectal cancer in the remaining colon and the risk of extracolonic neoplasias remains increased, so that these patients require an intensive postoperative follow up. In these cases, the postoperative tumor surveillance for sporadic CRC should be combined with the HNPCC-specific screening program for CRC and extracolonic tumors. It is currently not known whether a prophylactic extended tumor resection for the prophylaxis of metachronous CRC is better than surveillance at short intervals. Previous data from retrospective case studies are insufficient. Furthermore, due to the national difference in screening intervals, they are not applicable to Germany [287-290].

5.30.	Consensus-based Recommendation	2013
GCP	For female patients with Lynch- and HNPCC-syndrom a prophylactic hysterectomy and, if necessary, an ovariectomy at age 40 or five years before the earliest age of disease contraction in the family should be discussed.	
	Consensus	

Background

This approach is based on expert opinion of the task force gynecologic oncology (AGO) of the German Cancer Society. If possible, the intervention should not be performed until after family planning has been completed. A retrospective study showed a significant reduction of endometrial and ovarian cancer incidence in these patients [291]. Following prophylactic ovariectomy, patients should take hormone replacement therapy (HRT). After a hysterectomy, HRT can be performed using only estrogens, which reduces side effects of the therapy.

5.2.2.2. Adenomatous Polyposis Syndromes

5.2.2.2.1. Patients with Classic Familial Adenomatous Polyposis (FAP)

5.31.	Recommendation	2013
Grade of Recommendation B	Relatives of FAP patients who are potential mutation carriers due to the autosomal dominant inheritance are defined as persons at risk. For these persons predictive genetic testing should be recommended from age 10 after genetic counseling of the family if an APC-germline mutation has been identified in the family.	
Level of Evidence 4	[120, 292]	
	Strong consensus	

5.32.	Recommendation	2008
Grade of Recommendation A	If the mutation that was identified in the family was excluded in the person at risk (children, siblings, or parents of FAP-patients), a special surveillance is no longer necessary.	
Level of Evidence 1c	Not specified	
	Strong consensus	

5.33.	Recommendation	2013
Grade of Recommendation A	Persons at risk for whom the mutation is confirmed or cannot be excluded should have a rectosigmoidoscopy from age 10. If there is evidence of adenomas, a complete colonoscopy must follow, and has to be repeated annually until a proctocolectomy has been performed (see below).	
Level of Evidence 4	[191, 292, 293] [120]	
	Strong consensus	

Background

For children or persons unable to give consent genetic consultation is done together with their legal guardians. Initiating genetic diagnostics before the age of 10 is seldom necessary, because colorectal cancer are only rarely seen among children younger than age 15 [292]. Molecular genetic testing is usually done by direct mutation testing in the APC gene. In rare cases with decisive familial constellation genetic testing may be done indirectly using coupling analyses. Definite predictive testing can only be conducted in patients when the pathogenic germline mutation has been identified in

an affected family member [120]. It always has to be combined with human genetic counseling [GenDG]. A mutation is identified in about 70-80% of patients. Another method to identify gene carriers is a fundoscopic exam to identify the characteristic congenital hypertrophy of the retinal pigment epithelium (CHRPE). However, nowadays this method is used less often because of the possibility of DNA testing.

With classic FAP, polyps are always found in the rectum and sigma. If rectal polyps are identified, additional proximal adenomas or even cancer can be present. In this case, a complete colonoscopy should be performed at short interval which, depending on the findings, should be repeated at least once a year. In families where genetic testing has not been performed or has not provided definite results, all persons at risk should undergo endoscopic surveillance from age 10 [191, 292, 293]. With specific mutations, earlier cancer manifestation in the family, or presence of symptoms, initiating screening at an even earlier age should be considered.

5.34.	Recommendation	2013
Grade of Recommendation B	Patients with classical FAP should undergo prophylactic proctocolectomy (whenever possible maintaining continence) independent of the molecular genetic testing if possible no earlier than the end of puberty.	
Level of Evidence 1c	Evidence from update literature search: [261, 294-299]	
	Strong consensus	

5.35.	Consensus-based Recommendation	2013
GCP	After proctocolectomy a pouchoscopy should be performed regularly. Patients with a remaining rectal stump should undergo rectoscopies regularly. The interval depends on the test results (number, size, and histology of detected neoplasias) and should not exceed 12 months.	
	Strong consensus	

Background

The timely proctocolectomy is essential for preventing colorectal cancer [294-298]. The value of molecular genetic testing on therapeutic decisions is limited, because the identification of the mutation only rarely allows an individual assessment of the disease course. In a considerable proportion of patients who are clinically affected no causative mutation can be identified. The polyposis patient must be adequately treated regardless of the result of the mutation analysis. Therefore, necessary surgery should also be performed if a mutation has not been identified and, if necessary, performed before the mutation analysis has been completed [261]. The operation should generally be performed between the end of puberty and age 20. The exact time point should, however, be determined on an individual basis according to age, diagnosis, and endoscopic/histological findings (number of polyps and level of dysplasia) [297-

299]. In the natural course of FAP, cancer appear at a median age of 36 [300]. The option of sparing the rectum should be discussed with the patient (ileorectal anastamosis, IRA). It has to be kept in mind that after a colectomy with sparing of the rectum the risk of developing a rectal stump cancer is 13% after 25 years [301]. The long-term prognosis for IPAA (ileo-pouch anal anastamosis) concerning the CRC-rate is better [302-305]. For this reason, a proctocolectomy is recommended for patients with classical FAP. The operation should be performed in an experienced center. Carrying out a proctocolectomy with a final, permanent ileostoma can in most cases nowadays be avoided.

Because several patients develop polyps in the area of the pouch next to the ileoanal anastamosis that can progress to cancer, an annual postoperative pouchoscopy is recommended. If no proctocolectomy was performed, surveillance of the rectal stump with short intervals of no more than 12 months are necessary. If new polyps are found, these should be removed.

5.36.	Consensus-based Recommendation	2013
GCP	<p>An EGD and duodenoscopy (with side-optical view) with inspection of the papilla region should be carried out starting at age 25-30. An interval of three years is recommended if the result is negative. The interval should be shortened up to one year depending on the degree of severity of the adenoma burden (Spigelman classification).</p> <p>If duodenal-/papillary adenomas are identified, an indication for endoscopic polypectomy should be considered.</p> <p>If the duodenal polyposis is severe (Spigelman IV) or an invasive cancer without distant metastases is present, there is an indication for surgical resection.</p>	
	Consensus	

Background

The lifetime risk of developing duodenal polyps is between 80 and 90% for FAP patients [231, 232]. Fewer than 10% of the patients develop gastric adenomas, more than 50% have fundic gland polyps of the stomach. Gastric cancer, however, do not seem to occur more often than in the general population [306]. With regard to the extent of duodenal polyposis, the Spigelman classification (see Table 7) should be used [307]. The average age of patients with serious adenomatosis of the duodenum is about 43 (range 24-65) [233]. Altogether, it appears that the growth behavior of duodenal adenomas is slower than that of colorectal adenomas [308, 309] and depends more on increasing age (increases at age >40) than on the initial stage [310]. The mutation location (Codon 279-1390) correlates with the severity of the polyposis in the duodenum, but not with the possibility that a high-grade dysplasia will develop [311, 312]. The lifetime risk for a duodenal cancer for patients with FAP is between 3 and 4% [313, 314] and is, therefore, up to 300 times more common than in the general population [315]. The risk that an invasive cancer is present depends on the severity of the duodenal polyposis. Thus, the risk for an invasive cancer with Spigelman II and III is 2% versus 36% for Spigelman IV [316].

The aim of an endoscopic surveillance is not the removal of all polyps, but the detection of relevant neoplasias (high-grade intraepithelial neoplasia, villous or

tubulovillous adenomas). All polyps that are >1cm should be removed if technically possible. In case of smaller polyps, the larger ones should be removed and sent to pathology to determine the Spigelman score..

For FAP-patients with low-grade duodenal polyposis (Spigelman I and II) a three year test interval seems sufficient [308]. Due to the higher risk of cancer in Spigelman stage IV, a surgical procedure is recommended. The pancreas-maintaining duodenectomy is the preferred procedure partly due to a lower morbidity rate than with a pancreatic duodenectomy [317, 318]. An operative duodenotomy with polypectomy cannot be recommended due to a high rate of recurrence [319, 320]. In principal, even after extensive surgical treatment the appearance of new adenomas cannot be prevented [319]. Currently, it is not clear whether regular duodenal screening prolongs life [313]. There are different approaches to handling FAP-associated papillary adenomas. Overall, there are only very few publications on the issue of FAP. Whereas some groups favor a papillectomy for every patient with any type of papillary adenoma [321, 322], others prefer a monitoring strategy for small adenomas and papillectomy only in case of progression (size, histology) or development or threat of complications (e.g. cholestasis, pancreatitis) [308, 309]. In summary, the following monitoring program seems sensible: Spigelman I and II: examination every 3 years; if necessary a polypectomy should be performed; Spigelman III: annual examination and, if necessary, polypectomy, Spigelman IV: surgery.

5.37.	Consensus-based Recommendation	2013
GCP	If therapy is indicated (symptoms, progression), first-line therapy of desmoids in FAP patients consists of a combination therapy using sulindac and tamoxifen. In case of progressive desmoids under this drug therapy an interdisciplinarily approach should be undertaken. Therapy options include chemotherapy, surgery, and radiotherapy.	
	Consensus	

Background

Desmoid tumors appear in 10 to 30% of all patients with FAP. The risk for women to develop desmoid tumors is greater than for men. Apart from a clear genotype/phenotype correlation (APC mutation codon >1300) [323-325], surgical trauma can act as a trigger factor. About 50% of the desmoids appear intra-abdominally especially mesenterially and due to their local infiltrative growth often cause significant problems. For this reason, it is especially important with patients who have a positive family history or a distal APC mutation to look for the presence of desmoids before proctocolectomy and to undergo proctocolectomy as late as possible. Regular desmoid screening is not recommended if the patient has no symptoms. Desmoid screening may be done pre-operatively with suitable imaging tests. Desmoid tumors that are asymptomatic and not progressing in size often do not have to be treated. A systematic review of published clinical trials on medicinal non-cytotoxic chemotherapies demonstrates the best confirmed efficacy for treatments with sulindac (300 mg), tamoxifen (40-120 mg), or a combination therapy [326]. For raloxifen there are also comparable data from a small case series [327]. Progressive tumors under sulindac or antihormonal therapy should be treated with chemotherapy (doxorubicin and dacarbazine or methotrexat and vinblastin) or radiotherapy [328-330]. Results on surgical resections are controversial [331]. Especially for intra-abdominal desmoids, incomplete resections and high relapse rates are often reported [332-335].

For abdominal wall desmoids surgical procedures often lead to R0-resection and no recurrence [333].

5.38.	Consensus-based Recommendation	2013
GCP	In female FAP-patients, an annual ultrasound of the thyroid may be performed from age 15.	
	Consensus	

Background

The lifetime risk for patients with FAP to develop thyroid cancer is 1 to 12%. About 95% of all reported thyroid cancer affect women; therefore, the risk is mainly increased in female carriers. The mean age of diagnosis is between 24 and 33 years. Manifestations before age 15 are rare [336]. Cancer often appear multifocal and sometimes bilaterally. Histologically a cribriform variant of a papillary thyroid cancer is usually present.

Two prospective [337, 338] and one retrospective study [339] examined the value of a one time ultrasound screening. Benign thyroid nodules were identified in 20 to 79% of the cases. Thyroid cancer were diagnosed with a prevalence of 2.6 to 7.6%. In the largest study cancer were only detected through ultrasound and not using patient history or palpation [337]. Therefore, for female FAP-patients an annual ultrasound of the thyroid may be done from age 15. So far, there are no studies on an appropriate screening interval. The prognosis of FAP-associated thyroid cancer is good, but deaths have been reported [336, 340, 341]. The extent to which screening reduces mortality is unknown. The frequency of necessary adjuvant radiotherapy can possibly be reduced if more microcarcinomas are detected.

Hepatoblastomas are very rarely observed as a manifestation of FAP. Fewer than 0.5% of all children of FAP patients develop a hepatoblastoma almost exclusively before the age of 10 [342]. It seems, however, that the risk higher for boys is than for girls. In a some of the cases there was a positive family history [343]. Due to the rarity and the unclear data on whether the prognosis for hepatoblastoma patients can be improved, screening is not generally recommended. [344, 345].

5.39.	Recommendation	2013
Grade of Recommendation B	Drug treatment of adenomas in the lower and upper gastrointestinal tract should not be generally recommended.	
Level of Evidence 2b	Evidence from update literature search:[346-354]	
	Strong consensus	

Background

Sulindac reduces the number of colorectal adenomas by more than 50% [346-350]. However, it does not prevent the formation of new polyps [351]. Furthermore, under sulindac therapy cancer were observed in the rectal stump. Sulindac is not approved in Germany. In individual cases, chemoprevention with sulindac for FAP can be used as an additive treatment after subtotal colectomy to reduce the rectal polyp burden. However, an endoscopic surveillance is mandatory.

The selective COX2-inhibitor celecoxib which leads to a reduction of rectal adenomas [352], was approved for chemoprevention of FAP as an addition to surgical procedures and endoscopic controls. Celecoxib at high doses of 400-800mg reduces the colorectal polyp number by 28% [352] and also affects duodenal polyposis [353]. However, it is not known whether its use also reduces the risk of developing cancer in these patients. COX-2-inhibitors are associated with an increased rate of cardiovascular events [354]. The value of COX-2-inhibitors is currently unknown due to the cardiovascular side effects. Presently, they should only be used in selected cases with strict indications (risk-benefit-assessment). The drug with the ingredient celecoxib that is approved for FAP was removed from the market by the manufacturer in April 2011, because of insufficient recruitment for a post-approval study that was demanded by the European Drug Agency (EMA). In individual cases, the use of COX-2-inhibitors may be justified for selected patients to delay colectomy, after subtotal colectomy to reduce the rectum polyp burden, in patients with several duodenal polyposis and an increased surgical risk as well as an increased perforation risk or risk of bleeding with polypectomy.

5.2.2.2.2. Patients with Attenuated Familial Adenomatous Polyposis

5.40.	Recommendation	2008
Grade of Recommendation B	A patient with attenuated FAP should be treated depending on age, the number of polyps, and histological findings. With endoscopically uncontrollable polyposis a colectomy is indicated. Patients who do not undergo a colectomy should have a colonoscopy once a year for the rest of their lives.	
Level of Evidence 4	[254, 255, 257, 258, 355-358]	
	Strong consensus	

5.41.	Recommendation	2008
Grade of Recommendation C	Persons at risk from families with attenuated FAP should undergo a screening colonoscopy at age 15. If no polyps are found at this point, these persons should have an annual colonoscopy starting at age 20.	
Level of Evidence 4	[356-358]	
	Strong consensus	

Background

In patients who have an attenuated FAP, polyps occur much later and in fewer numbers than with classic FAP. The diagnosis of a CRC in adolescence has been casuistically described [355]. The polyps are often found on the right side of the colon. Hence, a complete colonoscopy must be performed for surveillance [254, 255, 257, 258]. Because of significant variations of clinical characteristics, the decision concerning therapy must be made on an individual basis. For patients with an indication for an operation, but fewer than five rectal polyps, an ileorectal anastomosis with a remaining rectal stump is reasonable. Because extra colonic manifestations can appear as in classic FAP [356-358], the recommendations for classic FAP apply. It is unclear with the current amount of data available to determine up to which age surveillance of persons at risk with negative findings should be performed.

5.2.2.2.3. Patients with MUTYH-Associated Polyposis (MAP)

5.42.	Consensus-based Recommendation	2013
GCP	Testing of the MUTYH-gene shall be performed in patients who clinically have an attenuated adenomatous polyposis with no evidence of disease causing mutations in the APC-gene.	
	Consensus	

Background

MUTYH-associated polyposis (MAP) is the most important differential diagnosis of FAP. The phenotype usually corresponds to the phenotype of AFAP. The lifetime risk of CRC is also very high for MAP. However, due to the autosomal-recessive germline there is only a small disease risk for a patient's children and heterozygous carriers. The diagnosis is usually only possible using molecular genetic methods. About 50% of patients already have a CRC when they are diagnosed with MAP. In one third of these patients a synchronic or metachronic CRC was observed. Polyps occur in the whole colon, CRCs are found on the right side of the colon in more than 50% of patients. The occurrence of MAP-associated CRC before age 29 is very rare.

5.43.	Consensus-based Recommendation	2013
GCP	Siblings of MAP-patients have a 25% disease risk and are considered person at risk, because of the autosomal-recessive inheritance. Predictive genetic diagnostics after human genetic counseling should be recommended to these persons from age 18-20.	
	Strong consensus	

5.44.	Consensus-based Recommendation	2013
GCP	If both MUTYH-mutations of the index patients have been excluded, their siblings do not need to have special surveillance examinations.	
	Strong consensus	

5.45.	Consensus-based Recommendation	2013
GCP	For relatives of MAP-patients who have only one of the index patient's MUTYH-mutations (heterozygous carrier), the same screening tests are recommended as for first degree relatives of patients with sporadic CRC (see 5.1.3.1).	
	Strong consensus	

Background

To date, MAP is the only autosomal-recessively inherited disease with an increased CRC risk. It is controversial whether heterozygous carriers have an increased risk of CRC. Some recent population- and family-based studies with large collectives indicated that there is a moderately increased risk at older age (RR 1.5-2.1) [267, 359, 360]. First degree relatives of heterozygous carriers of MAP-patients have the highest risk for CRC (RR 2.1). The mean age of diagnosis was 70 years (range 58-82). Disease risk and time point are, thus, comparable to first degree relatives of patients with sporadic CRC.

Due to the heterozygous frequency of about 1-1.5% in the Caucasian standard population, the obligate heterozygous children of MAP patients with non-consanguine partnerships only have a slight MAP disease risk (<0.5%) [262]. If predictive testing of the child is requested to assess the disease risk, a complete mutation search must be done in the MUTYH-gene of the child or the healthy parent to identify the possible 2nd germline mutation of the healthy parent. However, the benefit of conclusive genetic results is opposed to the (rare) identification of functionally unclear genetic variants. Conclusions in individual cases on their pathogenic relevance and, thus, clinical consequences (currently) are not possible. Since the presence of a second MUTYH-mutation in children of MAP-patients cannot be completely excluded because of the expected incomplete mutation detection rates, heterozygous tested children of MAP-patients (probably) have a (likely very low) remaining risk to develop MAP. A complete colonoscopy should, thus, be considered at the age of about 30 to 40 years.

5.46.	Consensus-based Recommendation	2013
GCP	<p>Asymptomatic biallele MUTYH-mutation carriers should have their first colonoscopy at age 18-20 years. If no polyps are found, patient monitoring should be continued.</p> <p>A patient with MAP should be treated based on age, polyp number, and histologic findings. If polyposis is not endoscopically manageable, a colectomy is indicated. Patients who have not been colectomized should have lifelong annual colonoscopies.</p> <p>An EGD and duodenoscopy (with side-optical view) with special inspection of the papillary region should be performed at least every three years starting from age 25-30.</p> <p>Specific surveillance examinations for extra-intestinal manifestations are not justified in MAP-patients.</p> <p>A recommendation for drug treatment of adenomas in the upper and lower gastrointestinal tract cannot be given, because of missing data.</p>	
	Consensus	

Background

The colorectal phenotype of MAP is similar to the APC-associated AFAP. Polyps and CRCs usually do not become symptomatic in patients with MAP until the fourth to seventh decade of life. About 50% of patients are not diagnosed with MAP until CRC is already present, in one third of all cases a synchronical or metachronical CRC was observed [361]. The polyps occur throughout the colon, CRCs are found in over 50% of the cases in the right-hand colon, and more than 20 % in the rectosigmoid [263]. Therefore, as a screening method a complete colonoscopy must be performed [254, 255, 257, 258]. The occurrence of MAP-associated CRCs before age 29 is rare. Since the clinical manifestation varies greatly, therapy decisions should be made individually. For patients who have an indication for surgery and who have few rectal polyps, an ileorectal anastomosis leaving a rectal stump may be justifiable [362].

Although duodenal polyposis in MAP-patients is observed less often (17%) than in FAP-patients, the risk of about 4% for developing duodenal cancer seems to be comparably high [269]. In MAP duodenal cancer sometimes also occur without pre-existing duodenal adenomas [363]. It can, therefore, not be concluded at this time, whether MAP-patients should perhaps have other screening strategies than (A)FAP-patients. Overall, extra-intestinal malignomas occur significantly more often in MAP-patients than in the standard population (RR 1.9%). They show a certain overlap to HNPCC. The only systematic study in 276 patients that investigated this issue demonstrated a small to moderate, but significant increase in ovarian, bladder, and skin cancer incidence as well as a trend toward increased risk of breast cancer [269]. However, there was no dominating extra-intestinal tumor and no shift towards an earlier manifestation (median age at diagnosis of the 4 malignomas was between 51 and 61 years of age). Desmoides were not observed.

5.2.2.3. Non-Adenomatous Polyposis-Syndromes

5.47.	Statement	2013
Level of Evidence 2a	These include especially hamartomatous polyposis-syndromes (Peutz-Jeghers-syndrom, familial juvenile polyposis, Cowden-syndrom), hyperplastic polyposis-syndrom, and hereditary mixed polyposis. Some of these diseases are very rare (their proportion of all CRCs is less than 0.1 %). Carriers have an increased risk of CRC as well as of other syndrome specific intestinal and extra-intestinal tumors (stomach, breast, etc.).	
	Evidence from update literature search: [261, 364-394]	

Background

In individual cases the differential diagnosis of non-adenomatous polyposis-syndromes can be very difficult and demands interdisciplinary collaboration of gastroenterologists, surgeons, pathologists, human geneticists, radiologists, and other clinical experts (especially gynecologists, urologists). The patient's diagnosis and clinical care should, therefore, be done in coordination and cooperation with centers that have experience with these syndromes [261, 364]. Hamartomatous polyposis-syndromes follow autosomal-dominant inheritance. Thus, children (and if present siblings) of an affected person have a 50% risk of inheriting the underlying genetic mutation and to develop the disease in the course of their lifetime.

Peutz-Jeghers-syndrom (PJS) is an autosomal-dominant inheritable disease. It is characterized by the occurrence of hamartomatous gastrointestinal polyps and mucocutaneous melanin pigmentation which is especially visible peri-oral. The latter often fade during the course of life and are not specific. Peutz-Jeghers-polyps occur especially in the small intestines and demonstrate characteristic histology. The disease cause are germline mutations in the STK11/LKB1-gene. A mutation can be identified in more than 90% of patients who fulfill the clinical-diagnostic criteria [365]. The age of manifestation is very different. Some patients already develop symptoms in the first years of life. Complications in children include an acute abdomen caused by invaginations or an obstructive ileus as well as chronic bleeding with secondary anemia. Up to 30% of patients have had a laparotomy at the age of 10 years [366]. PJS is associated with a significantly higher risk for several intestinal and extra-intestinal tumors [367-373]. Aside from CRC, especially the risk for cancer of the breast, small intestine, pancreas, testicles, ovaries, and uterus is increased [375, 376]. The cumulative lifetime risk for malignant tumors is reported to be about 85-90%. Overall, for tumors in the gastrointestinal tract there is a cumulative lifetime risk of 57%. The CRC-risk alone is 35-39% and is, thus, the second most frequent cancer in PJS. The lower limit of the 95% confidence interval is 30 years. The tumor risk increases quickly after age 50 [374-376]. The lifetime risk for gynecologic tumors is reported at 13-18% [375, 376]. Ovarian tumors in PJS are usually SCTAT and of non-epithelial origin. Some are already diagnosed in small girls (mean age 28 years, range 4-57 years). Cervical cancer occur with a lifetime risk of 9% and are histologically similar to adenoma malignum in more than 75 % of the cases [375]. The mean age of onset is 34 years (range 23-54 years). The risk of endometrial cancer is about 10%.

Familial juvenile polyposis (FJP) is suspected in case of a diagnosis of five or more juvenile polyps in the colon, if extracolonic juvenile polyps are detected, or if juvenile polyps with corresponding positive family history are identified. The correct diagnosis

of juvenile polyps can be difficult due to morphologic similarities with hyperplastic polyps as well as lymphocytic infiltrates and dysplastic portions: a considerable percentage of genetically confirmed cases of juvenile polyposis are initially misdiagnosed as ulcerative colitis or hyperplastic polyposis [377, 378]. Therefore, in case of doubt, a second review of the histologic sample by a gastroenterologically experienced pathologist should be sought.

The disease can already become noticeable in early childhood due to chronic gastrointestinal bleeding or exsudative enteropathy with concomitant delayed development. The cause is germline mutations in the SMAD4- or BMPR1A-gene. The lifetime risk for developing CRC is up to 68%. There is a clear genotype-phenotype-relationship: patients with a SMAD4-germline mutation have a higher risk of developing gastric polyps and stomach cancer as well as hereditary hemorrhagic telangiectasia (Morbus Osler-Rendu-Weber) [378, 379]. In addition, the risk of pancreas cancer may be increased [380-384]. In case of very severe early manifesting courses **juvenile polyposis of toddlers** should be considered [385].

The endoscopic-histologic distinction of juvenile polyposis from the PTEN-mutation-based **Cowden-syndrome** or the presumably non-hereditary Cronkhite-Canada-syndrome can cause problems. It is usually done using primarily the extra-intestinal tumor spectrum and molecular genetics. Cowden-syndrome [386] is especially associated with a higher risk of breast and thyroid cancer. According to recent data, the lifetime risk for CRC also seems to be increased by 28% [387]. Furthermore, increased risks for endometrial and renal cancer as well as melanomas were reported. The Bannayan-Riley-Ruvalcaba-syndrome is viewed as a variant of the Cowden-syndrome. Both are germline mutations associated with the PTEN-gene. They are summarized under the term PTEN-hamartom-tumor-syndrome (PHTS) [388, 389].

Hereditary mixed polyposis syndrome (HMPS) and hyperplastic polyposis syndrome (HPS) are difficult to define entities and there is still little known about their genetics. Both syndromes are associated with an increased - in some cases pronounced - CRC risk [390-394]. However, they are rare and, so far, both clinically and genetically poorly characterized. Thus, the knowledge on tumor risk is only partly conclusive. In some patients with HMPS, mutations were identified in the PTEN- or BMPR1A-genes. These cases should be viewed as (atypical) variants of the Cowden-syndrome or FJP and treated accordingly.

5.48.	Consensus-based Recommendation	2013
GCP	Due to the scarce data, general screening recommendations cannot be given. The monitoring of the patients and persons at risk should be done in cooperation with a qualified center.	
	Consensus	

Background

Valid screening recommendations cannot be given, because of the scarce data available. Specific screening programs were suggested by individual experts for the more frequent syndromes. The published guideline for Peutz-Jeghers-syndrome has methodological deficits and gives only little evidence for most of the recommendations [395]. Patients and persons at risk should, therefore, be monitored in close

cooperation with an experienced center. For some of the syndromes, experts suggested specific age-dependent screening programs (review in [261]). However, the recommendations are contradictory and, due to the few case numbers, the efficacy of the very rare syndromes is difficult to validate.

5.3. Chronic Inflammatory Bowel Diseases

5.3.1. Colitis Ulcerosa

5.49.	Consensus-based Statement	2013
GCP	For patients with ulcerative colitis, the risk of CRC is increased in comparison to the standard population. Specific recommendations are given in the S3-Guideline on Diagnostics and Therapy of Ulcerative Colitis.	
	Strong consensus	

Monitoring Colonoscopy, Time Strategy (excerpt from the S3-LL CU [396])

5.50.	Recommendation	2013
Grade of Recommendation A	Since the colitis-associated colon cancer mortality can be decreased by using endoscopic screening, regular monitoring colonoscopies should be performed.	
Level of Evidence ⁴ 3a	[397, 398]	
	Consensus	

5.51.	Recommendation	2013
Grade of Recommendation A	To determine a monitoring strategy, a control colonoscopy should be performed in all UC-patients no longer than 8 years after symptoms have started. This should be done regardless of the disease activity to assess the disease extent.	
Level of Evidence 4	[399]	
	Consensus	

⁴ In the guideline ulcerative colitis a different level of evidence is used Evidenzgrad (396. Dignass, A., et al., [Updated German guideline on diagnosis and treatment of ulcerative colitis, 2011]. Z Gastroenterol, 2011. 49(9): p. 1276-341. S. 7ff)

5.52.	Recommendation	2013
Grade of Recommendation B	Monitoring colonoscopies should be performed every 1-2 years for extensive UC from the 8th year or for distal UC from the 15th year after initial manifestation.	
Level of Evidence 4	[400, 401]	
	Consensus	

5.53.	Recommendation	2013
Grade of Recommendation A	If PSC is simultaneously present, the monitoring colonoscopies should be performed annually regardless of the disease activity and extent of UC starting from the time PSC was diagnosed.	
Level of Evidence 3a	[402, 403]	
	Consensus	

5.54.	Recommendation	2013
Grade of Recommendation A	After subtotal colectomy, in analogy the same endoscopic monitoring strategy as for UC without resection should be followed.	
Level of Evidence 4	[404]	
	Strong consensus	

Comment

A meta-analysis by Collins from the year 2006 summarizes the direct and indirect evidence on monitoring colonoscopies for ulcerative colitis. The three identified case control studies did not show a statistically significant colon cancer risk reduction. It should be noted that, from a present day perspective, these were small studies with partially inadequate colonoscopy standards. In contrast, the meta-analysis gave clear from indirect evidence that monitoring colonoscopies very likely reduce the risk of dying of a colitis-associated colon cancer [397]. At the same time they are cost effective. This is based on the fact that colitis-associated colon cancer are detected earlier even if they can arise between monitoring intervals [398]. The cancer risk increases with the duration of disease and its extent. This is the reason that patients with pancolitis should begin regular monitoring earlier than patients with distal colitis. An initially distal colitis inflammation can develop into a pancolitis without clinical

evidence. Therefore, a screening colonoscopy should be done within 8 years after the first disease symptoms appeared to check the extent and then to decide on a monitoring strategy. A Dutch study indicates that already up to 22% of patients have developed colitis-associated colon cancer before starting the monitoring colonoscopies recommended so far [399]. If patients with PSC were excluded (who should be monitored from the time of diagnosis), the rate of "missed" cancer was reduced to about 15%.

The screening interval should not exceed 2 years, because interval cancer can already arise in this period [400, 401]. Since for proctitis the risk is only minimally increased at most - if other risk factors are not present - regular surveillance is not necessary. Monitoring of patients with CU and PSC from the time of diagnosis should be done annually independent of its extent, because the cancer risk is increased 5-fold [403] and because cancer arise more frequently on the right side [402].

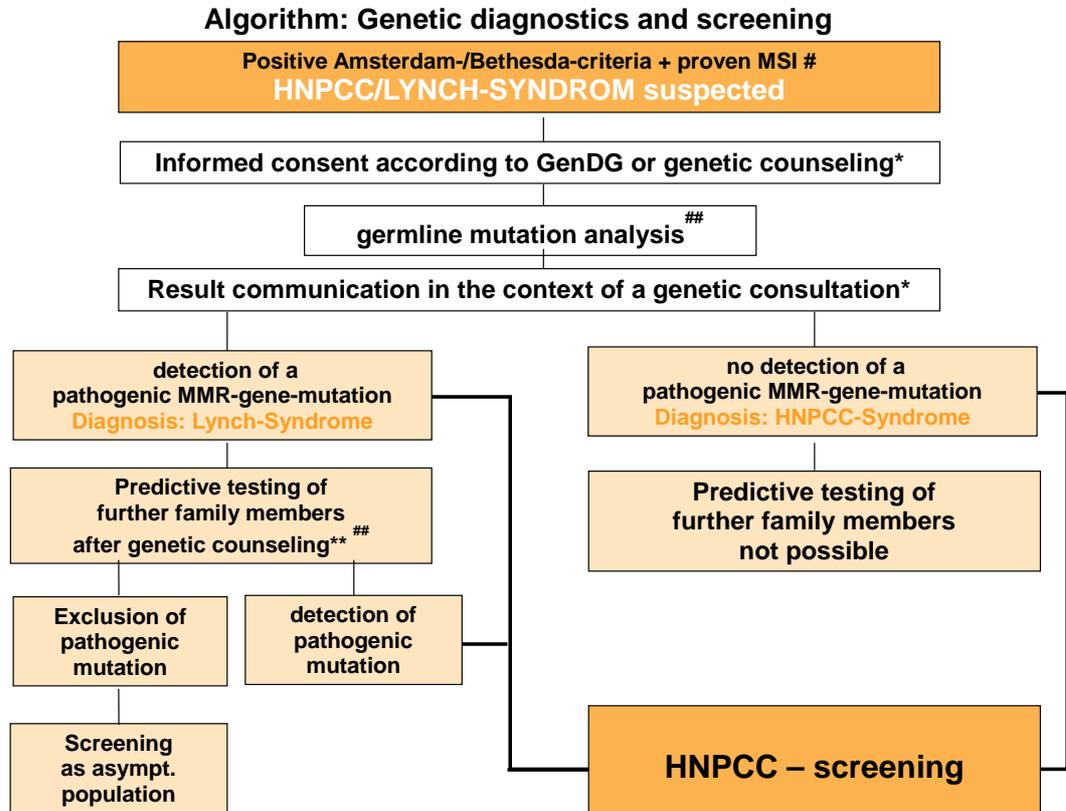
After subtotal colectomy, cancer can occur in the remaining colon, as well as after restorative proctocolectomy in the pouch or depending on the operation technique in the area of the remaining colon mucosa distal to the anastomosis [404]. Therefore, a regular surveillance of the remaining colon or pouch is recommended.

5.3.2. Crohn's Disease

CRC risk in patients with Crohn's disease seems to be higher than in the general population especially if the colon is affected. The benefit of screening programs with ileocolonoscopies to screen for cancer in Crohn colitis is unknown. The data are discussed in the S3-Guideline on Diagnostics and Therapy of Crohn's Disease [405].

5.4. Appendix: Figures and Tables of TK III

5.4.1. Algorithmus: Genetic diagnostics and screening



* A diagnostic germline exam requires informed consent and documentation of contents of the consultation by the initiating physician according to the GenDG . Alternatively, a genetic consultation may be performed. The results must be communicated in a genetic consultation according to the GenDG.

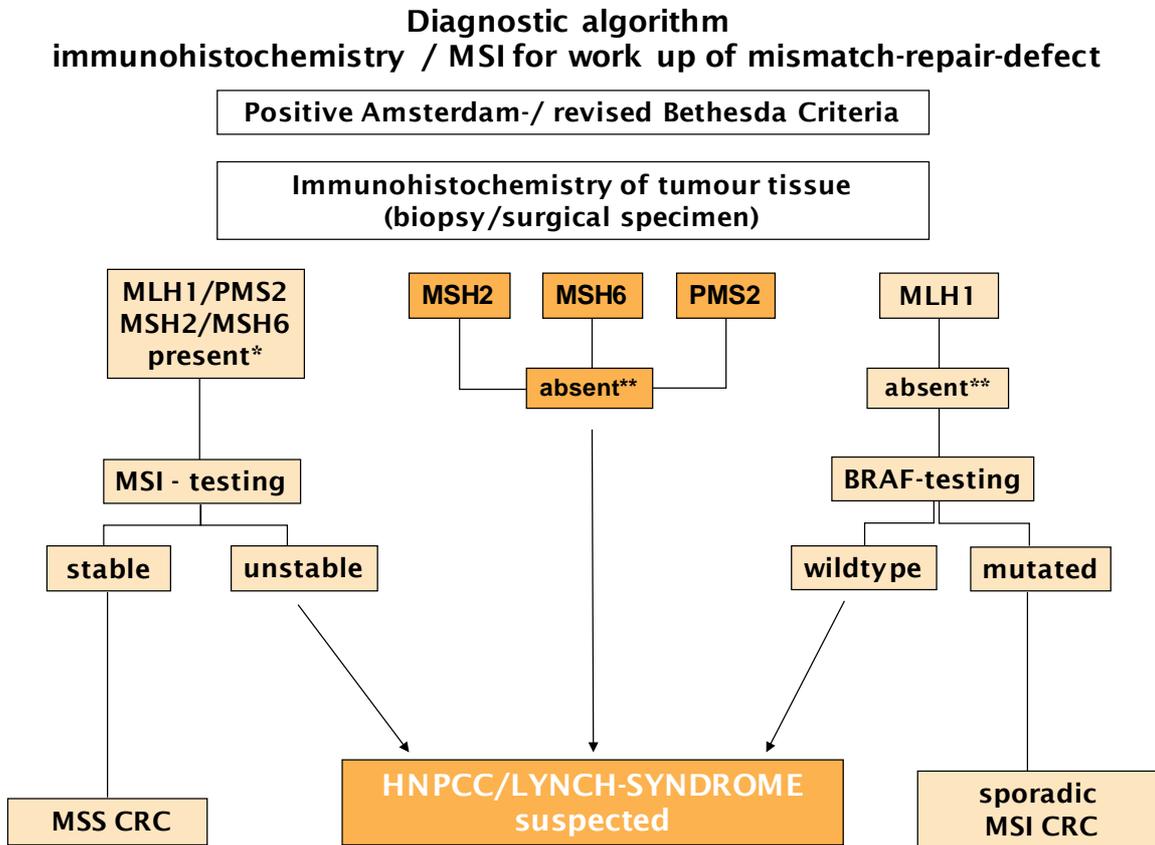
** Predictive genetic germline diagnostics for asymptomatic individuals can only be performed after a genetic consultation according to the GenDG. The results must also be communicated in a genetic consultation according to GenDG.

For high grade suspicion of HNPCC/Lynch-syndrome (e.g. positive Amsterdam-criteria) and absence of tumor tissue, a direct mutation analysis may be performed.

If the patient does not wish to have germline diagnostics, a HNPCC-screening should nonetheless be recommended.

Figure 2: Algorithm on Genetic Diagnostic Procedures in Patients with Hereditary Tumor Disposition Syndrome Using HNPCC-/Lynch-Syndrome as an Example. To identify MSI if HNPCC-/Lynch-syndrome is suspected, please see Figure 3.

5.4.2. Diagnostic algorithm immunohistochemistry / MSI for work up of mismatch-repair-defect



* >10% of tumor cells are nucleus positive in each; ** in <10% of tumor cells are nucleus positive

Figure 3: Algorithm on the Molecular Pathologic Differential Diagnosis Procedures of Mismatch-Repair-Defects if HNPCC-/Lynch-syndrome is Suspected. Please see Figure 2 for possible subsequent genetic diagnostics.

5.4.3. Recommended Screening Programs for HNPCC

Table 6: Recommended Screening Programs for HNPCC

Age	Examination	Interval
From age 25	Physical exam	annually
	Colonoscopy	annually
	Gynecologic exam incl. transvaginal sonography (in women)	annually
From age 35	EGD	regularly
	Endometrial biopsy (in women)	annually

5.4.4. Spigelman-Classification

Table 7: Classification Duodenal Polyposis Characteristics According to the Spigelman-Classification (modified according to [307])

	Number of points		
	1	2	3
Number of polyps	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Histology	tubular	tubular villous	villous
Intra-epithelial neoplasia	low grade	-	high grade
Stage 0: 0 points Stage I: 1-4 points Stage II: 5-6 points Stage III: 7-8 points Stage IV: 9-12 points			

6. Endoscopy: Implementation and Management of Polyps

6.1. Role of Endoscopy in the Diagnostics of Polyps and CRC

6.1.	Statement	2008
Level of Evidence 1b	The complete colonoscopy is the standard procedure for the detection of colorectal polyps and cancer. It has the highest sensitivity and specificity for the detection of CRC and colorectal polyps. The examination quality is crucial for the effectiveness of colonoscopies. The examination quality is influenced by technical factors and the endoscopist.	
	Strong consensus	

6.2.	Recommendation	2008
Grade of Recommendation A	If a colonoscopy was incomplete due to a stenosing tumor, an additional preoperative CT or MR colonography can be performed. A complete colonoscopy should be conducted postoperatively.	
Level of Evidence 4	Strong consensus	

6.3.	Recommendation	2008
Grade of Recommendation B	If a colonoscopy was incomplete due to other causes (e. g. adhesions), a CT or MR colonography should be performed.	
Level of Evidence 4	Strong consensus	

Background

Colonoscopy is the most-reliable procedure for the detection of colorectal cancer and polyps if performed with high quality. Important quality features include a complete examination up to the caecum, optimal preparation with little or no remaining stool remains, as well as the careful inspection of the colorectal mucosa during withdrawal. It was shown that the polyp detection rate correlates with withdrawal time after reaching the caecum. The withdrawal time should be at least six minutes [406-408]. Further quality features include the primary detection of polyps in 20-50% of

examinations (polyp detection rate) [409], as well as missing polyps in less than 10% of patients (polyp miss rate) [410, 411].

However, colonoscopy also has limitations: 4-6% of cancer are missed during the initial exam [412-414]. Also within a time period of three years after a colonoscopy with polypectomy of adenomas, interval cancer appear in up to 1% [415]. These can partly be attributed to missed lesions (see also the section on polyp management, Chapter 6.5).

Sensitivity and specificity of CT colonography has improved in the past few years since the presentation of the last guidelines. In one study, colonoscopy and CT-colonography performed equally in the detection of polyps >5 mm. [410]. However in other studies, this particularly good result was not achieved [416, 417]. Here CT-colonography was clearly inferior to colonoscopy, [418, 419], but was better than double contrast enema [417, 420]. Nowadays, double contrast barium enema of the colon no longer plays a role in screening. For the evaluation of MR colonography for screening, there are too few study results available [421-423].

Diagnostic problems with CT colonography can include remaining stool and poor unfolding of the colorectal lumen. The detection of flat, sunken, and small polyps is more difficult than prominent polyps. Due to missing standardization, the results at this time are strongly dependent on the center performing them. In addition, the high price and the radiation exposure associated with CT colonography have to be considered.

For this reason, for the work-up of a positive fecal occult blood test (FOBT) or in case of a suspected tumor, a complete colonoscopy is regarded as the gold standard. Colonoscopy also allows the possibility of taking biopsies for histological diagnosis as well as performing polypectomy. In case of pathological findings during colonoscopy, a location classification according to endoscopic-anatomical structures or diphanoscopy are insufficient; a statement of distance from the anus in cm should only be used for lesions in the rectum and lower sigma. With findings that are unclear or have a clear surgical indication labeling using a clip (only at a time close to surgery) or India ink should be performed in order to make reidentifying the lesion later on possible.

For patients with stenotic tumors or incomplete colonoscopies for other reasons, in case series proximal tumors or polyps were detected using CT or MR colonography [424-427].

6.1.1. Sigmoidoscopy Versus Colonoscopy

6.4.	Recommendation	2008
Grade of Recommendation A	In case of a positive FOBT, suspicion of a tumor, or sigmoidoscopic evidence of neoplastic polyps a full colonoscopy has to be performed.	
Level of Evidence 2b	Strong consensus	

Background

Work-up of a positive FOBT test and/or suspicion of tumor requires a complete colonoscopy, because this method is able to detect adenomas and cancer in the right hemicolon. Relevant neoplastic lesions proximal to the sigma are found in 25-55% of cases. Screening studies showed that in 30 to 46% of cases with proximal advanced neoplasias in the right hemicolon the rectosigmoid is free of adenomas [107, 127].

A sigmoidoscopy should only be performed as an exception when a complete bowel preparation is not possible. A complete colonoscopy is possible in a high percentage of cases and can also be conducted among older patients with a low rate of side effects [428, 429]. Sigmoidoscopy plays no significant role in Germany as a screening test.

6.1.2. Chromoendoscopy

6.5.	Recommendation	2008
Grade of Recommendation 0	Chromoendoscopy can be performed in patients with inflammatory bowel disease and HNPCC for improved detection of neoplastic lesions. It can in addition be used for a better demarcation of flat and sunken lesions before endoscopic therapy.	
Level of Evidence 1b	Strong consensus	

Background

Among patients with CED or HNPCC an increased detection rate of neoplastic lesions using chromoendoscopy has been shown [430-432]. In studies on patients without hereditary tumor diseases or IBD, a higher detection rate of mostly small adenomas was found [433-435]. However, this was not confirmed in another study [436].

It is currently unclear whether the recognition of an increased rate of primarily smaller lesions is useful for the patient and justifies the greater amount of time required for the examination.

Employing chromoendoscopy with indigo carmine or methylene blue enables a better delimitation of flat and sunken lesions from the surrounding healthy mucosal tissue [437-442]. Chromoendoscopy can, therefore, be used before the endoscopic removal of flat adenomas.

6.1.3. Magnifying Endoscopy

6.6.	Recommendation	2008
Grade of Recommendation 0	The use of magnifying endoscopy with evaluation of lesions according to the “pit pattern” classification is not a standard procedure at this time.	
Level of Evidence 2b	Strong consensus	

Background

The goal of magnifying endoscopy is to differentiate between hyperplastic and neoplastic lesions without histology using the “pit-pattern” classification, and to decide which lesions have to be removed. In some studies this was possible with high sensitivity [434, 443, 444]. In other studies, however, the specificity was not sufficient with 75% [439, 441, 445, 446]. Magnifying endoscopy does not replace histology at this time. It is helpful in the evaluation of polypoidal and flat lesions before polypectomy, but cannot at this time be recommended as a standard procedure.

Procedures such as narrow-band imaging (NBI) or Fuji intelligent chromoendoscopy (FICE) represent further methods for the evaluation of neoplastic lesions. In uncontrolled studies NBI was helpful in the detection of flat adenomas, the detection of intraepithelial neoplasias in patients with ulcerative colitis, as well as differentiating benign and malignant lesions [447-449]. For FICE there are currently no comparable data available. Confocal laser microscopy is a diagnostic procedure that should be further evaluated in clinical trials [450].

6.2. Polypectomy

6.2.1. Removal of Polyps by Snare Versus Forceps

6.7.	Recommendation	2008
Grade of Recommendation A	Polyps should be removed and retrieved with exact recording of the localization of the polyp. In case of multiple polyps the removal of polyps can be performed in more than one session.	
Level of Evidence 1c	Strong consensus	

Background

In order to allow an exact classification, polyps should be individually retrieved for histological processing and their localization recorded. With several polyps in one segment, combined retrieval of these polyps is justified. With this, however, the

oncological resection borders must be respected; labeling the colon segment where the polypectomy has been performed can be useful.

The following endoscopic procedures are available:

- * Polypectomy with a snare
- * Endoscopic mucosa resection (EMR)

Alternative procedures to remove polyps (open or laparoscopic resection, rendezvous procedures, TEM, trans-anal removal) may be considered in individual cases. New therapeutic procedures, such as endoscopic submucosal dissection (ESD) to reach an en-bloc resection are currently being tested. Removed flat and sessile polyps should be marked with the use of a pin or dye. Fixing on a cork plate has also proved to be useful.

A requirement and limitation for an endoscopic removal of larger polyps are the realistic chance of a complete removal of the polyp with low bleeding and perforation risks. The experience of the endoscopist and the localization of the polyp can also be limiting factors. Other factors that should be considered include the increasing rate of cancer with increasing size of neoplastic polyps (up to 15%), the polyp characteristics (sessile or flat vs pedunculated), the general status of the patient, as well as the increased risk of perforation in the proximal colon [451-455]. Flat lesions can be removed using an endoscopic mucosectomy (EMR) [455-457]. Exclusively depressed, flat lesions (IIc) should as a rule be treated surgically and not endoscopically, because most of these lesions do not present so-called 'early invasive T1 cancer' and complete endoscopic removal (RO) is seldom possible. Evidence of this is a non-lifting sign. Independent factors in relation to the risk of perforation are polyp size over 1 cm as well as localization in the right colon, for the risk of bleeding only a polyp size of > 1 cm [458]. The risk of severe bleeding (requiring transfusion, surgical intervention, recurrent bleeding) is 0.9%; risk of perforation in the right colon 1.2%, in the left colon 0.4%. A prophylactic injection of NaCl or adrenalin into the base or the shaft of the polyp or the use of an endoloop reduces early-onset bleeding with the removal of larger polyps >1 cm [459-462]. However, the rate of late-onset bleeding is not reduced [368].

A polypectomy can also be carried out in patients who are taking a platelet-aggregation inhibitor [464-466], the combination of aspirin and clopidogrel, however, increases the risk of bleeding and should be avoided [467]. The complete removal of a polyp is always required, because the remaining rest of an incompletely removed polyp can still contain a high-grade intra-epithelial neoplasia or a cancer. The size of the removed polyp, the histological type of adenoma, and the degree of severity of the intraepithelial neoplasias specifies the degree of risk for local recurrence and metachronous polyps. With polyps >2 cm the local recurrence rate is 8-20% [468]. The recurring polyp can as a rule also be removed endoscopically.

If surgical treatment is expected to be necessary or possible, pre-operative labeling of the polyp area with clips or ink must be performed to help localize the lesion (exception: coecum and distal rectum). An alternative to find the polyp or removal site is an intra-operative colonoscopy. In cases of difficult localization (with a decreased chance of finding the area again during repeated or surveillance examinations) a polypectomy area should also be marked after endoscopic interventions.

6.8.	Recommendation	2008
Grade of Recommendation A	<p>To obtain a representative histological specimen and achieve a definitive therapy, polyps >5 mm should be completely removed using a snare. Polyps ≤5 mm should be completely removed, in general with biopsy forceps.</p> <p>In general, diagnostic colonoscopies should only be performed if the possibility of performing a polypectomy using a snare is given.</p>	
Level of Evidence 3b	Strong consensus	

Background

To prevent double examinations, a colonoscopy should only be performed if the possibility of performing interventions is given. If the removal of a lesion is not possible or does not make sense (risk situation in an out-patient setting, inadequate expertise with larger polyps), the lesion should be marked and the patient should be referred to an expert center. A biopsy of polyps does not make sense if removal is technically possible. In addition, the result of such a biopsy is unreliable [469]. Furthermore, extensive biopsies can cause scarring which can make it more difficult to perform subsequent endoscopic removal. Biopsies are obligatory when clear malignancy criteria are met with a primary indication for surgery. For polyps ≤5 mm adenomas with invasive cancer are rarely seen, with polyps ≤1 cm the rate is <1%. The goal of a colonoscopy must be to achieve a polyp-free colon (clean colon). For polyps ≤5 mm a complete removal using biopsy forceps is required in order to histologically classify the lesion. Small (≤5 mm) polyps in the rectum with typical macroscopic appearance of hyperplastic polyps do not have to be removed. In recent years evidence has accumulated that, in addition to the adenoma-carcinoma sequence, a further pathway to colorectal cancer the so-called “serrated pathway” exists (see below).

In case of a diagnosis of a so-called hyperplastic polyposis, the suspected higher colorectal cancer risk should be considered when determining the surveillance intervals.

Hyperplastic polyposis is defined (according to the WHO) by:

- at least 5 hyperplastic polyps proximal to the sigmoid colon, whereby two should be larger than 1 cm;
- the appearance of hyperplastic polyps proximal to the sigmoid colon, independent of the polyp number and size, if a first-degree relative (parents, children, siblings) has been diagnosed with a hyperplastic polyposis;
- if more than 30 hyperplastic polyps of any size appear proximal to the sigmoid colon [470-476].

6.3. Histologic Examination

6.9.	Recommendation	2008
Grade of Recommendation A	The histological examination of each polyp is obligatory. The histological reporting of polyps should follow WHO criteria [477] with a statement about the completeness of the removal. Conventional adenomas are classified according to histological type of growth (tubular, tubulovillous, and villous) and the level of intra-epithelial neoplasia (low- and high-grade intra-epithelial neoplasias); serrated lesions are subclassified as hyperplastic polyps, sessile serrated adenomas, mixed polyps (with IEN grade) and traditional, serrated adenomas (with IEN grade) [478, 479].	
Level of Evidence 3b	Strong consensus	

Background

About 8% of the polyps classified as hyperplastic are sessile serrated adenomas (SSA) according to new findings. These adenomas possess a potential to progress to cancer, especially if their size is greater than 1 cm and they are located on the right side of the colon. Also mixed mucosal polyps (mixed polyps) may occur. In addition, 2% of all colorectal polyps are traditional serrated adenomas (TSA). All of these variants demonstrate a similar molecular pathway on their progression to cancer.

6.10.	Recommendation	2008
Grade of Recommendation A	In case of a cancer, the histology report has to contain the following characterizations [480]: <ul style="list-style-type: none"> • a measure of the depth of infiltration (pT category), with sessile polyps the invasion measurement in μm, • the histological differentiation grade (grading), • presence or absence of lymph vessel invasion (L classification), and • the judgment of the resection borders (R classification with regard to the local removal in healthy tissue (for depth and on the sides). 	
Level of Evidence 2b	Strong consensus	

6.11.	Recommendation	2008
Grade of Recommendation A	Because of the therapeutic consequences for completely removed pT1 cancer, a classification into “low-risk” (G1, G2, and no lymph vessel invasion (L0)) or “high-risk” (G3, G4, and/or lymph vessel invasion (L1)) should be performed.	
Level of Evidence 2b	Strong consensus	

Background

The necessity of a statement on the distance of the tumor from the lateral resection margin in patients with pT1 cancer is unclear.

6.4. Approach for pT1 Cancer

6.12.	Recommendation	2008
Grade of Recommendation A	In the context of an endoscopically R0-removed polyp with a pT1 cancer, no additional oncological resection should be performed if there is a low-risk situation with a cancer-free polyp base (R0) [481-484]. In the high-risk situation, radical surgical therapy is required, even if the lesion has been completely removed.	
Level of Evidence 3a	Consensus	

6.13.	Recommendation	2008
Grade of Recommendation A	With incompletely removed low-risk pT1 cancer, a complete endoscopic or local surgical removal has to follow [485]. If an R0 situation cannot be achieved or it is doubtful that a pT1 situation exists, an oncological-surgical resection is necessary.	
Level of Evidence 3a	Strong consensus	

Background

The prognosis of pT1 cancer can vary widely. The major determinant of a risk stratification is the probability of lymph node metastases. Overall the group of T1 cancer shows a lymph node metastasis rate (N+) of 0-20% [482, 486-488]. For the estimation of the rate of lymph node metastases, there are qualitative and quantitative prognostic criteria [488, 489].

Qualitative criteria are: Grading (G1—well differentiated, G2—moderately differentiated, G3—poorly differentiated, G4—undifferentiated) and the invasion of

lymph vessels (L classification) of the polyps. Quantitatively, the submucosal invasion of the surgical and endoscopically removed specimen can be measured. A proven method involves differentiating the submucosa into three layers. In case of endoscopic removal of a sessile polyp the measurement of the submucosal invasion depth in μm makes more sense, because the submucosa is not available as a total layer and/or no muscularis propria is present. The so-called early invasion forms (sm1, sm2, and/or submucosa invasion $\leq 1000 \mu\text{m}$) have a low N+ risk of 0-6% [489, 490]. In contrast, the risk of lymph node metastasis for sm3 cancer is about 20% [490, 491]. Cave: The measurement of submucosal thickness for stalked polyps in μm is not helpful and/or can lead to false conclusions, because the submucosal thickness depends upon the length of the stalk; this means that the stalk is always level sm1. The presence of vein invasion (V classification) should be mentioned, but the value for local therapy is currently unknown.

Additional comments:

As a rule endoscopic cancer therapy in the context of a polypectomy is performed without prior knowledge of the cancer diagnosis. Care should be taken with sessile lesions if a diagnosis of cancer was made by biopsy. Frequently in this case a situation is present in which the lesion cannot be treated adequately using endoscopic means.

Warning signs are: presence of ulcerations, depressed lesions, contact bleeding, and the lack of a lifting sign when injecting under the lesion. Proof of having achieved a R0 situation is mandatory; the necessity of a safety margin of 1mm from the base is controversial [489]. An endoscopic removal as an en-bloc resection is optimal. Removal using a piecemeal technique appears adequate. With this, evaluation of lateral R0-margins is done macroscopically during endoscopy, evaluation of vertical infiltration and complete removal is performed histologically (basal R0). In any case, an early (2-6 months) endoscopic re-examination of the resection site is necessary. According to available data in a low-risk situation [482, 484, 488-490, 492], the post-interventional rate of metastases and/or local recurrence is 0-5%, whereby the concept of early invading submucosal cancer is only addressed in the newer studies. Local endoscopic therapy of early colorectal malignant neoplasias is a safe and effective therapy in specialized centers, and is considered to be the standard procedure if all low-risk criteria are present. In this situation a radical surgical resection according to oncological criteria is not necessary.

6.14.	Recommendation	2008
Grade of Recommendation A	After complete removal (R0) of low-risk (pT1, low-grade (G1, G2, L0)) cancer, endoscopic surveillance examinations of the local resection site should be performed after six months and after two years.	
Level of Evidence 4	Strong consensus	

Background

The recommendations are made to enable the recognition of local recurrences, and consist of inspection of the former lesion site. A colonoscopy of the whole colon for

the early detection and treatment of recurrences should be performed according to the recommendations for adenoma surveillance.

6.5. Polyp Management (Follow-Up)

6.15.	Recommendation	2008
Grade of Recommendation B	After removal of small single, non-neoplastic polyps, there is no necessity for endoscopic surveillance.	
Level of Evidence 3b	Strong consensus	

Background

Patients with small (<1 cm) hyperplastic polyps and negative family history, do not seem to have an increased colorectal cancer risk. Here the general recommendations for CRC screening apply, i.e. a screening colonoscopy every 10 years. Exceptions are non-neoplastic polyposis syndromes (hyperplastic, juvenile, Peutz-Jeghers) with an increased CRC-risk [496].

6.16.	Recommendation	2008
Grade of Recommendation B	After complete removal of neoplastic polyps (adenomas), a surveillance endoscopy is necessary. The time point of the surveillance endoscopy should depend on the number, size, and histology of the removed adenomas. For patients with 1 or 2 adenomas <1 cm without high-grade intra-epithelial neoplasia a surveillance colonoscopy after five years is sufficient.	
Level of Evidence 2b	Strong consensus	

6.17.	Recommendation	2008
Grade of Recommendation B	For patients who have 3-10 adenomas, or at least one adenoma that is 1cm or larger, or an adenoma with villous histology, the first control colonoscopy should follow after 3 years.	
Level of Evidence 1b	Strong consensus	

6.18.	Recommendation	2008
Grade of Recommendation B	For patients with adenomas with high-grade intra-epithelial neoplasia and histologically-confirmed complete removal, a surveillance colonoscopy after three years is sufficient.	
Level of Evidence 1b	Strong consensus	

6.19.	Recommendation	2008
Grade of Recommendation B	With histologically non-confirmed complete removal, even if macroscopically the removal was complete, an early (2-6 months later) control should be performed.	
Level of Evidence 3b	Strong consensus	

6.20.	Recommendation	2008
Grade of Recommendation B	In case of more than 10 adenomas, the control interval should be shorter than 3 years and should be defined under consideration of individual criteria (family history).	
Level of Evidence 3b	Strong consensus	

6.21.	Recommendation	2008
Grade of Recommendation B	After removal of large, flat, or sessile adenomas in piecemeal technique, a short-term control of the removal area should follow after 2-6 months.	
Level of Evidence 3b	Strong consensus	

6.22.	Recommendation	2008
Grade of Recommendation B	After an unremarkable surveillance endoscopy, further controls are indicated every five years. After complete removal of a traditional serrated adenoma, mixed mucosal membrane polyps, or a sessile serrated adenoma, due to the potentially increased risk of cancer and independent of an IEN grade, a control surveillance should follow after three years.	
Level of Evidence 4	Strong consensus	

Background

The recommendations for post-polypectomy management should be influenced by the individual risk of the respective patients (family history, comorbidities, diverticulosis [497]) and the cleanliness of the colon during the last colonoscopy. The recommendations made above rely on a high-quality baseline colonoscopy (see above). After diagnosis and removal of adenomas, interval cancer are diagnosed in 0.7 to 0.9% of patients within 3 years [415]. This is caused by missed lesions (miss rate), incomplete polypectomies, as well as the occurrence of tumors with a faster progression rate [410, 411, 413, 498]. An underlying principle for the establishment of surveillance recommendations after polypectomy is a patient risk stratification according to the low-/high-risk adenoma concept. The patients are classified into these risk groups according to the number, size, and histology of the removed adenomas during the baseline colonoscopy.

According to this classification, a low-risk adenoma situation is defined as follows: 1-2 tubular adenomas, each <1cm, only LGIEN, exclusion of HGIEN, and villous components.

A high-risk adenoma situation (so-called advanced adenomas) is defined as follows: ≥ 3 tubular adenomas, ≥ 1 adenoma with ≥ 1 cm, adenoma with tubulovillous or villous structure, ≥ 1 adenoma with HGIEN, ≥ 10 adenomas independent of size or histology [499].

Flat or sessile adenomas which were removed using the piecemeal technique also belong to this high-risk group.

A surveillance interval of five years for the so-called low-risk adenoma group seems reasonable. If no adenomas are detected during the surveillance colonoscopy the colonoscopy should be repeated after 5 years.

For the so-called high-risk adenoma groups, the control interval should be three years provided that there is histological proof of complete removal of the lesion. If the surveillance colonoscopy is without adenoma detection, the next colonoscopy can follow after 5 years.

After removal of flat or sessile adenomas in piecemeal technique, the recurrence rate is significantly increased, especially with larger adenomas (9-28%) [468, 500-503]. The use of argon plasma coagulation to remove remaining tissue to ensure complete removal can be helpful [501, 503]. In this case, however, a complete histological

examination cannot be done. The special group of patients with removal of flat or sessile adenomas using the piecemeal technique should undergo surveillance colonoscopies after a short period of time (2-6 months), due to the higher rate of metachronous lesions. Later the monitoring should be after three years and then after five years; in some cases, if necessary, even sooner. In cases of larger ≥ 1 cm and especially right-sided sessile serrated adenomas (earlier classified as hyperplastic polyps), a potentially accelerated progression risk for cancer appears to be established (via the serrated pathway), so that in these cases a complete removal and a short control interval are recommended (according to the current level of understanding, after three years).

Also after the removal of TSA, which predominantly occurs in the left colon and has an increased risk of progression, surveillance in the same way as SSA is indicated.

For recommendations for surveillance of patients with HNPCC, FAP, and CED see Section 10.6.

6.6. Medical Secondary Prevention of Adenomas

6.23.	Recommendation	2008
Grade of Recommendation B	Medical secondary prophylaxis should not be given after polypectomy, except in the context of clinical studies.	
Level of Evidence 1b	Strong consensus	

Background

Even though a small preventative effect has been demonstrated for aspirin in several prospective randomized studies with high levels of evidence (1b) [504, 505], it cannot be recommended due to the small effect (reduction of the recurrence rate by a maximum of 35%) and its known side effects [506]. The same is true for COX-2 inhibitors, for which a reduction in the adenoma recurrence rate of 24 to 45% has been shown [79-81]. They are associated, however, with a significantly increased rate of cardiovascular side effects [507, 508] which outweigh their potential benefit [509]. The reduction of the adenoma recurrence rate of 12% with calcium appears to be too low to recommend long-term administration for this indication [510].

7. Pre-operative Diagnostics and Surgery

7.1. Introduction

In the following the general principles of diagnosis and therapy will be shown in a summary fashion for both entities, as long as they apply to both colon and rectal cancer. Unique diagnostic and therapeutic aspects will be listed separately.

The therapy of colorectal cancers should always be planned on the basis of a histopathological examination. A colorectal cancer is defined by atypical epithelial formations infiltrating the submucosa (pT1 or more). Not included are the so-called mucosal cancer or intraepithelial cancer (pTis) that have no metastatic potential and can be treated by local excision alone.

7.2. Definition of Colon and Rectal Cancer

The border between the colon and rectum has been defined differently. The intra-operative assessment using the end of the taeniae or the peritoneal fold is different for each individual and depends upon age, sex, and other factors. The pre-operative determination of the distal tumor margin with a flexible endoscope is unreliable. This is done more reliably by rigid rectoscopy. The anocutaneous line serves as the distal reference point. According to the international documentation system [511, 512] rectal cancer have aboral borders of 16cm or less from the anocutaneous line as measured by rigid rectoscopy.

According to UICC 2003, rectal cancer are subdivided according to the distance from the anocutaneous line into cancer of the upper rectal third (12-16cm), the middle rectal third (6-<12 cm), and the lower rectal third (<6cm) [513].

In contrast, in the US [514, 515], colon cancer have by definition a distal margin of more than 12 cm and rectal cancer a distal margin of less than 12 cm from the anocutaneous line. This is based on the significantly higher local recurrence rate of tumors with less than 12cm distance from the anocutaneous line [516].

7.3. Definition Interdisciplinary Tumor Conference

7.1.	Consensus-based Recommendation	2013
GCP	<p>All CRC patients should be presented in an interdisciplinary tumor conference after they have completed their primary therapy (e.g. operation, chemotherapy).</p> <p>Patients with the following constellations should already be presented before therapy:</p> <ul style="list-style-type: none"> - every rectal cancer - every stage IV colon cancer - metachronic distant metastases - local recurrence - before every local ablative procedure, e.g. RFA/LITT/SIRT 	
	Consensus	

Background

Because of the complexity of the colorectal cancer therapy, patients should be discussed in an interdisciplinary tumor conference. Members of the conference should include the following experts: a gastroenterologist, a hematologist/oncologist, a visceral surgeon, a radiotherapist, a radiologist, and a pathologist. To evaluate the primary or secondary resectability of liver metastases, an experienced liver surgeon should be consulted. If one is not available on site, an external second opinion by an expert should be sought.

In certain cases, a presentation at the tumor conference is necessary before therapy has been initiated. For example, for patients with rectal cancer it must be decided upon whether a neoadjuvant therapy should be performed. A study showed that the presentation at a tumor conference and the interdisciplinary determination of a therapy concept significantly reduced the rate of involved circumferential resection margins in the surgical specimen [517]. If distant metastases are present, it must be determined whether a purely palliative concept should be followed or whether the patient can be cured by primary or secondary resection of metastases (especially liver metastases). The frequent presentation of patients with stage UICC IV at the tumor conference has led to an increase in metastasis surgery [518].

Also patients with distant metastases or local recurrences during the disease course should be presented first to the conference to decide on further concepts. Patients with a planned local ablative procedure should also be presented to discuss alternative treatment options.

For colon cancer without distant metastases, an oncologic resection of the cancer is usually done as primary treatment. In this case a pre-operative presentation is not necessary.

A presentation is necessary for all patients after therapy has been completed e.g. following a colorectal cancer operation to discuss the indication for adjuvant therapy. In a British study this procedure led to a higher rate of adjuvant chemotherapy and a significant increase in patient survival [519].

Also patients with distant metastases who have begun primary chemotherapy should be presented again to a tumor conference (with consultation of an experienced liver or lung surgeon) during the course of therapy. A possible secondary resectability should be discussed.

7.4. Pre-Operative Evaluation

Table 8: Staging of Colorectal Cancer

Examination	ColonCa	Rectal Ca
Complete colonoscopy	X	X
CEA	X	X
Abdominal ultrasound	X	X
Chest x-ray	X	X
Rigid rectoscopy		X
Pelvis MRT (CT) with statement on distance between tumor and mesorectal fascia		X
Rectal endosonography for localized tumors		X

7.4.1. Endoscopic Diagnostics

7.2.	Recommendation	2008	
Grade of Recommendation	The following examinations should be obligatory components of a pre-operative evaluation of patients with colorectal cancer:	Level of Evidence	Evidence basis
B	<ul style="list-style-type: none"> Digital-rectal examination 	5	[520-522]
A	<ul style="list-style-type: none"> Complete colonoscopy with biopsy 	4	[520-522]
A	<ul style="list-style-type: none"> In the case of an endoscopically non-transversible stenosis, complete colonoscopy 3-6 months postoperatively 	3b	[520-522]
Strong consensus each			

Background

The digital-rectal examination allows an initial judgment of the sphincter function as well as the depth of infiltration with deep-located rectal cancer and allows an assessment of the possibility of sphincter retention.

Before therapy of a patient with a colorectal cancer, a colonoscopy with a biopsy has to be performed. In up to 5% of colorectal cancer synchronous tumors are present. Since these can be missed during intra-operative evaluation, a colonoscopy of the entire colon should be performed [520-522]. If for technical reasons a complete colonoscopy is not possible, an alternative radiological procedure should be used (see Chapter 6.1).

Relevance of Virtual Colonoscopy (for stenosing tumors and incomplete colonoscopies)

7.3.	Recommendation	2008
Grade of Recommendation O	If a colonoscopy is not complete due to stenosing tumors additionally, a CT- or MRcolonography can be performed pre-operatively. A complete colonoscopy should be performed postoperatively.	
Level of Evidence 4	[426]	
	Strong consensus	

7.4.	Recommendation	2008
Grade of Recommendation B	If the colonoscopy is incomplete for other reasons (e.g. adhesions), a CT- or MR-colonography should be performed.	
Level of Evidence 4	[426]	
	Strong consensus	

Background

In this case a virtual colonography is a promising alternative [426]. If a complete colonoscopy is not possible due to a stenotic process, a colonoscopy should be done 3 to 6 months after resection. A pre-operative colon contrast enema is of little value and in the case of stenoses has the danger of causing an ileus. Therefore, it is not recommended.

7.4.2. Imaging Procedures

7.4.2.1. The Relevance of Individual Imaging Procedures (except PET) for the Evaluation of Distant Metastases in the Primary Treatment of CRC

7.5.	Consensus-based Recommendation	2013
GCP	<p>An abdominal ultrasound and a conventional chest x-ray in 2 levels should be the basic examination for pre-operative staging of CRC.</p> <p>If the result is not clear or if distant metastases or infiltration of adjacent organs or structures is suspected, a multi-slice CT of the abdomen and pelvis should be performed. If lung metastases are suspected, a CT of the chest should be performed.</p>	
	Consensus	

Background

The goal of pretherapeutic imaging is to clarify whether distant metastases are present. At the time of initial diagnosis of colon cancer, 25% of patients have distant metastases: in 13% limited to one organ (M1a), in 12% more than one organ or in the peritoneum are involved (M1b). Liver metastases are found in 19%, lung metastases in 3%, and peritoneal metastases in 9%. Other distant metastases located in non-regional lymph nodes (2%), the skin (2%), the ovaries (1%), the bones (<1%), or other locations (2%) are rare.

The incidence of distant metastases for rectal cancer at first diagnosis is 18%: in 12% limited to one organ (M1a), in 6% more than one organ or in the peritoneum are involved (M1b). Distant metastases in the liver are found in 15% and lung metastases in 4%. Other distant metastases are in the peritoneum 3 %, in non-regional lymph nodes 2 %. Distant metastases in skin, bone, brain, ovaries, or other locations are found in less than 1% of patients [Data from the Clinical Cancer Registry of the Surgical University Clinic Erlangen-Nürnberg].

A primary abdominal ultrasound should be used to evaluate the presence of liver metastases (sensitivity 63-86%, specificity 98%) [523-525]. If the results are suspicious, if the liver can only be poorly evaluated, or if there is clinical suspicion of liver metastases, a multi-slice CT of the abdomen should be performed (sensitivity 75-83%, specificity 95-98%) [523, 526]. A multi-slice CT is also best to attribute metastases to the liver veins, the hilus structures, as well as the vena cava. This is necessary to evaluate the resectability of liver metastases (see Chapter 7.7.5). The extent of liver metastases can be best assessed using MRI (sensitivity and specificity: MRI 80-88% and 93-97%, CT 74-84%, and 95-96%) [523, 526].

Contrast-enhanced sonography of the liver and MRI have nearly equal performance characteristics (sensitivity 83-86%, specificity 94-98%). However, it requires adequate quality standards (technical equipment and experience of the examiner) [524, 525, 527].

Since the multi-slice CT also gives information on the local tumor extension (see below), there is a tendency to implement a primary abdominal CT instead of or in addition to an abdominal ultrasound. However, studies show that only few patients with colon carcinoma who routinely had pre-operative abdominal CTs had a change in further procedures [528, 529].

7.4.2.2. Relevance of Pre-Operative Local Staging Using CT (MRI) for Colon Cancer with Regard to Local Spread

7.6.	Consensus-based Statement	2013
GCP	A pre-operative staging CT can differentiate between tumors that are limited to the bowel wall and those that have penetrated the wall. However, the evaluation of the nodal status is significantly less reliable. The best results are achieved with multi-slice CTs (MSCT).	
	Consensus	

Background

Neoadjuvant therapy for colon cancer without extensive distant metastases is currently only considered in exceptional cases (e.g. distal sigmoid cancer with very extensive regional lymphogenic metastazation or deep tumorinfiltration reaching the probable conceivable resection margins). However to optimize the therapy algorithm for patients, the use of corresponding pre-operative imaging procedures is increasingly being discussed, e.g. selection for laparoscopic resections or transferal of patients with predictable multi-visceral resections to experienced centers.

The validity of pre-operative abdominal ultrasound examinations is insufficient in this respect. Data on the sensitivity of CTs for local colon cancer staging do not exist. The modern multi-slice CT (MSCT) reaches a high sensitivity (86%) and specificity (78%) with regard to local tumor expansion. However, the detection of local lymph node metastases is much less sensitive (70%) with the same specificity (78%) [530].

7.4.2.3. Relevance of PET-CT

7.4.2.3.1. For Primary Diagnosis of Colorectal Cancer

7.7.	Statement	2013
Level of Evidence 2b	PET/PET-CT has no relevance in the diagnostic work up of newly diagnosed CRC.	
	De Novo: [531-546]	
	Strong consensus	

Background

15 prospective and 5 retrospective cohort studies and case series were identified in the literature search. 13 Studies included patients with colon and rectal carcinomas and 7 trials only rectal carcinoma patients. 14 studies included all patients, 2 retrospective

studies only patients with locally advanced rectal cancer, and 1 study included only patients with increased CEA or inconclusive CT imaging. In the studies that were included 10 cases used PET, 6 PET-CT, and 4 PET-CT with CT-colonography. PET was compared to CT +/- other modalities in 14 studies, and with MRI in 3 studies. In 4 studies there was no comparison. 18 cases used histology and clinical course as references and in 2 cases clinical staging was done using the examinations that had been performed.

The sensitivity of PET for distant metastases was high (75-100%) and in a number of cases superior to the method that it was compared [531, 536]. In some cases it was not better [532-534, 539]. The quality of the method used for comparison is not known. In recent studies with multidetector spiral CT there was no significant detectable difference [532, 533].

The sensitivity for lymph node metastases was mainly low (29-85%), in 2 retrospective rectal cancer studies 44 and 85% and not better than comparison studies (CT or MRI) [531-539].

In the studies the use of PET or PET-CT led to changes in therapeutic procedures in 2-27% of the cases [532, 533, 536, 539-546].

Overall, the data show no conclusive additional benefit of PET for the primary diagnosis of CRC.

7.4.2.3.2. Before Resection of Colorectal Liver Metastases

7.8.	Recommendation	2013
Grade of Recommendation 0	A PET-CT can be performed in patients with resectable liver metastases of CRC to avoid an unnecessary laparotomy.	
Level of Evidence 2b	De Novo: [547, 548]	
	Consensus	

7.9.	Recommendation	2013
Grade of Recommendation A	A PET-CT shall not be performed within 4 weeks after systemic chemotherapy or antibody therapy, because it this significantly reduces its sensitivity.	
Level of Evidence 2b	De Novo: [549-551]	
	Strong consensus	

Background

A preliminary report on the benefit of PET/PET-CT for relapse diagnostics and relapse staging in CRC patients was presented by the IQWiG (Institute for Quality and Economics in Health Care) in August 2011 [552]. Aside from the evaluation of the patient relevant benefit, a systematic evaluation of the prognostic and diagnostic quality of the PET/PET-CT was done. The literature search included a period up to August 2009. More recent publications were mentioned in the text. The guideline recommendations given here are based on the evidence evaluation of the IQWiG report. The Grade of Recommendation was developed under additional inclusion of the clinical evaluation of the procedure. Furthermore, in a more recent literature search from August 2009 – December 2011, a RCT in abstract form [548], 2 systematic reviews [553], [526], a prospective case control study [549], and a retrospective case series [551] were identified. They were also included in the evaluation (for details see evidence report). The previous recommendation of Grade B from the last guideline update in 2008 (9.1.2.1) for PET/PET-CT examinations before resection of colorectal liver metastases with a FONG score > 2 was changed, because the study that led to this recommendation has still not been published as a full article [554].

So far, a RCT as a full publication and 1 RCT in abstract form have been published on the issue of patient-relevant benefit of PET/PET-CT. For patients before resection of CRC liver metastases, a supporting PET/PET-CT has no effect on disease-free or total survival of the patient. Whether supplemental PET-CT examinations help to avoid futile laparotomies as clinical endpoints is not completely resolved. The consensus recommendation here is especially supported by the full published study by Ruers [547] which has, however, methodological weaknesses. In this study 150 patients with colorectal liver metastases who were planned to undergo resections were randomized to 2 study arms (CT or CT plus 18F-FDG PET). The primary study objective was reported in the publication as rate of futile laparotomies that were avoided as a result of the PET examination. This endpoint is relevant for the patient. The study reported no significant difference in survival in the PET-arm. However, a significantly reduced number of "futile laparotomies" was seen in this study arm. The rate of futile laparotomies was 45% in the control arm and 28% in the PET-arm. This corresponded to a risk reduction of 38% with a very large confidence interval (95% CI, 4-60%, $p=0.042$). The authors concluded that in one in six patients a laparotomy can be avoided with an additional PET before liver metastasis resection. The secondary endpoint DFS and OS were as follows: DFS: 35.5% versus 29.8 % (p -value = 0.194); OS: 61.3% versus 65.8 % (p -value = 0.378). The study's evidence level was downgraded by the consensus conference (see also IQWiG-report, degrading from Ib to II), because the primary study endpoints mentioned in the study plan were different from the ones in the publication (original endpoint: rate of patients who were disease-free after 9 months).

Another multicenter randomized study that has so far been published as an abstract at the ASCO annual meeting 2011 also investigated this issue [548]. Endpoint of this study was the change in patient management after PET-diagnostics (no operation because of additional results or expansion of surgery compared to the intention without/before PET-diagnostics) in a 2:1 randomization design in CRC patients who seemed suitable for liver resection for liver metastases. 404 patients were randomized (270 patients in the PET/CT-arm, 134 patients without PET). There was no difference in management change between both study arms. Thus, the endpoint was not reached. However, as far as could be deduced from the presentation, about 70% of patients had chemotherapy before PET diagnostics. This significantly reduces the sensitivity of the

examination method (see below). It should also be critically noted that the endpoint "change in patient management" in contrast to "reduction of futile operations" was not considered patient relevant.

Several studies point out that the sensitivity of PETs is significantly reduced if they are done within 4 weeks after chemotherapy (evidence level IIa-III). Therefore, a PET is not recommended during this time, because too many false negative cases occur. The issue was not evaluated by the IQWiG report. A larger case control study without randomization was published in 2010 which investigated the sensitivity of PET after chemotherapy [549]. The study found a negative predictive value of only 13.3% and a positive predictive value of 94% with a specificity of 22.2% at an accuracy of 85% if the PET was done within 4 weeks after the end of chemotherapy. The authors concluded that diagnostic PET examinations shortly after chemotherapy administration are not useful. A retrospective study from Australia evaluated PET-results of patients with liver metastases before liver resection [555]. This study was small and heterogeneous. 21 patients were systematically treated before surgery, 53 were not. Correct results were determined using PET for 29% of patients after chemotherapy and 53% without chemotherapy. Underestimated results were observed in 52% in the chemotherapy group and only 34% in the group without chemotherapy. This study underscores that PET examinations shortly after chemotherapy are not useful. Another prospective trial [550] and a retrospective study [551] reached similar results.

7.4.3. Tumor Markers

7.10.	Consensus-based Recommendation	2013
GCP	The CEA-value should be assessed pre-operatively.	
	Strong consensus	

7.11.	Consensus-based Statement	2013
GCP	CA 19-9 does not increase the conclusiveness of a relapse compared to determining only the CEA-value.	
	Strong consensus	

7.12.	Consensus-based Statement	2013
GCP	The relevance of CA 125 to diagnose ovarian metastases and as a course parameter for further treatments of confirmed peritoneal carcinosis is unknown.	
	Strong consensus	

Background

In about 30% of all CRCs the tumor marker CEA is increased at the time of first diagnosis [data from the Clinical Cancer Registry of the Surgical University Clinic Erlangen-Nürnberg]

This tumor marker is especially reliable as an indicator for tumor relapse. It is also an independent prognostic factor for liver metastases.

Other tumor markers under discussion are CA 19-9 and CA 125, the latter being a marker for peritoneal cancer [556-558].

The detection of circulating DNA and so-called circulating tumor cells in peripheral blood as well as bone marrow has no consequences.

7.4.4. Specific Diagnostics for Rectal Cancer

7.13.	Consensus-based Recommendation	2013
GCP	The prediagnostic work up of a patient with rectal cancer should include a rigid rectoscopy with a statement on the distal tumor or margin.	
	Strong consensus	

Background

Rigid rectoscopy allows an exact determination of the distance of the distal tumor margin from the dentate line and is of major importance for determining further therapy.

7.14.	Recommendation/Statement	2013
Grade of Recommendation B	Local staging of rectal cancer should preferably be performed using MRI. If a T1-cancer is suspected, an endoscopic ultrasound should be performed.	
Level of Evidence 2b	De Novo:[559-567]	
	Strong consensus	

7.15.	Statement	2013
Level of Evidence 3	CT is not suitable for staging of T1-cancer.	
	De Novo:[559-567]	
	Strong consensus	

7.16.	Statement	2013
Level of Evidence 2b	The accuracy of all imaging procedures for the evaluation of the lymph node status is very questionable.	
	De Novo:[561, 562]	
	Strong consensus	

7.17.	Recommendation	2013
GCP	The report should include information on the distance of the tumor to the mesorectal fascia.	
	Strong consensus	

Background

In rectal cancer local staging is essential for further therapy planning. While local removal is sufficient for low-risk T1-carcinomas, for high-risk T1 and T2-cancers a resection according to oncologic criteria is necessary. In Germany, neoadjuvant therapy is recommended if tumor infiltration in the mesorectum (T3) has been identified. If neighboring organs have been infiltrated (T4), neoadjuvant radiochemotherapy is recommended. For T3-cancers there are data which indicate that the extent of the mesorectal infiltration especially the distance from the mesorectal fascia are of important prognostic relevance [559]. This level is the circumferential resection margin (CRM) in the TME. If the mesorectal fascia is infiltrated by the tumor or the distance between the tumor and the fascia is less than 1 mm (CRM+), the local recurrence risk is significantly increased [560]. Another prognostic factor is affected lymph nodes [559].

A number of studies on the value of different methods for local staging of rectal cancer had to be excluded in the literature search, because study collectives also included patients who had had radio-or radiochemotherapy. For further details see the evidence report.

The accuracy of individual diagnostic methods depends on the technical characteristics of the equipment (e.g. multidetector spiral-CT vs. single-slice CT) and the local expertise. An endosonography is often technically not possible if high-grade stenoses are present or the tumors are localized in the proximal rectum.

A meta-analysis which analyzed data on endosonography, MRI, and CT up to 2002 showed that endosonography demonstrated the highest accuracy for T1-cancers [561]. Its high sensitivity and specificity was confirmed in a more recent meta-analysis [562]. MRIs with endorectal spools are a possible alternative for EUS. However, they are more costly, are considered unpleasant by patients, and are established at very few sites. CTs are not suited for diagnosing T1-cancers.

However, to differentiate T2 and T3-cancers, the endosonography was more sensitive than MRI and CT with comparable specificity [561]. For T4-cancers the meta-analysis showed no significant differences between the procedures. Recent individual cohorts demonstrated a higher sensitivity for MRI and occasionally spiral-CT for tumors with

mesorectal infiltration (> T2) [563-567]. However, the accuracy of the CT was significantly lower in the lower third than in the upper two thirds [568]. If it is necessary to show the mesorectal fascia and its association with the tumor, the MRI is currently the most sensitive method [563]. The fascia cannot be demonstrated by endosonography.

When evaluating lymph nodes the sensitivity (55-73%) and specificity (74-78%) of all methods are currently insufficient [561, 562]. The reasons include, on the one hand, reactive lymph node enlargement and, on the other hand, lymph nodes 5mm and smaller that may contain metastases. Therefore, the indication for neoadjuvant therapy should be made very carefully if it is solely based on suspected lymph nodes seen in pretherapeutic imaging.

Furthermore, it must be considered that the accuracy of the individual methods depends greatly on the local expertise. This is especially true for CTs.

Considering especially the possibility of depicting the mesorectal fascia, many experts currently prefer MRIs for local staging of rectal cancers (with the exception of early cancers).

Excluding short term radiation, neoadjuvant therapy impairs the accuracy of individual diagnostic procedures (see evidence report).

7.18.	Recommendation/GCP	2008
Grade of Recommendation	In individual cases the following examinations may be useful:	Level of Evidence
0	<ul style="list-style-type: none"> Sphincter manometry 	4
GCP	<ul style="list-style-type: none"> Gynecologic examination 	
GCP	<ul style="list-style-type: none"> Cystoscopy 	
Strong consensus each		

Background

In general, sphincter manometry has no relevance for therapy decisions beyond the result of the rectal-digital examination and the differential medical history. In unclear cases, it can make the decision on sphincter retention easier.

If bladder infiltration is suspected, a cystoscopy can be helpful. If the infiltration of the vagina, uterus, or adnexa is suspected, a gynecologic exam should be done. In contrast to the previous guideline, a urine sediment is no longer recommended for rectum or sigma cancers, because the test is too unspecific.

7.5. Surgical Therapy with Curative Intention

7.5.1. Intraoperative Staging

7.19.	Consensus-based Recommendation	2013
GCP	<p>An intraoperative inspection and, in case of open surgery, palpation of the liver should be performed in every case, i.e. also in case of an inconspicuous preoperative evaluation.</p> <p>If the pre-operative diagnostics are sufficient, the diagnostic benefit of intra-operative ultrasound to look for further metastases does not justify its effort.</p>	
	Consensus	

Background

Due, nowadays, to the quality of magnetic resonance imaging and computer tomography, during a laparotomy usually only subserosal liver metastases (< 2mm) are additionally detected by intra-operative inspection and palpation.

However, the sensitivity and the positive predictive value of the intra-operative ultrasound examination with contrast medium is very high (in a single series with 24 patients at 100 % each) [570].

7.5.1.1. Intra-Operative Pathological Examination

In general, rapid sections should be used only if this has direct consequences. The most frequent indication is the evaluation of metastatic spread, e.g. in the peritoneum, in the liver, or in non-regional (e.g. peri-aortal) lymph nodes.

With local surgical excision (full wall excision), the important question is whether a cancer proven by previous biopsy was excised with tumor-free margins.

However, this cannot be adequately determined intra-operatively using rapid sections.

In the case of a deep-seated rectal cancer, rapid section examination of the aboral resection margin can help to decide whether total rectal extirpation should be performed.

With segmental resections of large colon polyps, especially of villous histology, in which pre-operative evaluation failed to confirm an invasive neoplasm, an assessment of malignancy using rapid section is frequently not possible due to technical reasons (examination of multiple tissue blocks!). Therefore in these cases, the use of standard oncological resection is recommended.

In case of adherence of a tumor to neighboring organs it is not possible to determine macroscopically whether an infiltration of the neighboring organs or only a peritumorous inflammatory reaction is present. In such cases, biopsies with rapid sections should be strictly avoided, because of possible local tumor cell dissemination, which can be associated with reduced survival [571]. This is the reason for the en-bloc resection in all cases of tumor adherence to neighboring organs or other structures (see section 7.7.2 on therapy and multivisceral resection).

7.20.	Consensus-based Recommendation	2013
GCP	If the etiology of a focal liver lesion remains unclear, histological examination should be performed.	
	Consensus	

Background

In case of unclear liver lesions (see below) with therapeutic consequences, a histologic work up preferably with a needle biopsy passing through the healthy liver parenchyma should be performed. Incision biopsies should be strictly avoided. Smaller lesions can be completely excised in form of an excision biopsy.

7.21.	Consensus-based Statement	2013
GCP	The sentinel-node-biopsy has no relevance for CRC.	
	Consensus	

Background

In malignant melanomas and breast cancers sentinel-node-biopsies are performed. This is done to avoid more extensive dissection that would result in increased morbidity rates in patients with histologically negative sentinel lymph nodes.

With the introduction of laparoscopic surgery methods, it was discussed whether limited resection methods can also be used for CRC if the sentinel-node-biopsy was negative.

In addition, it was questioned whether ultra-staging (immunohistochemical preparation) of the sentinel lymph node would change the tumor stage with the corresponding need for adjuvant therapy [572, 573].

7.5.2. Radical Surgical Therapy of Colon Cancer

7.5.2.1. Extent of Lymph Node Dissection:

If there is lymphogenic metastazation of the colon cancer, it occurs according to a regular metastazation pattern. At first, it metastasizes longitudinally to both sides of the tumor into the paracolic lymph nodes, then to the intermediary lymph nodes along the radial arteries to the central lymph nodes at the origin of the supplying arteries. The paracolic metastazation never exceeds a distances of more than 10 cm [574-576].

The extent of the colon resection is defined by the transection of the central arteries. Cancer lymph node metastases at the terminal ileum on the right side, however, seldom occur and if so, only in very advanced cancer [577]. Therefore, a resection of the terminal ileum of maximally 10 cm is sufficient for right hemicolectomies.

Oncologic Principles

In colon cancer surgery, the lymph node yield also correlates with the prognosis in nodal negative cancer (UICC II) [578, 579].

Resection of cancers of the Coecum and the Ascending Colon

Cancers in this area metastasize centrally via the ileocolic artery and the right colic artery. Accordingly, both vessels must be centrally ligated. However, a real colic artery originating from the superior mesenteric artery is present in less than 15 % of all cases [580]. Accordingly if the vessel is not present, branches leading to the right from the origin of the middle colic artery are centrally ligated. Parts of the major omentum only have to be resected if there is direct tumor contact.

Resection of cancers of the Right Colonic Flexure and Proximal Transverse Colon

For the extended hemicolectomy, the ileocolic artery, the right colic artery (if present), and the middle colic artery are centrally ligated. Accordingly, the distal resection margin is in the area of the left transverse colon. In this tumor localization a lymphogenic metastasization also takes place via the major omentum in the direction of the gastric antrum and on to the pancreatic head [575]. Thus, aside from skeletonizing the greater gastric curvature and resecting the gastroepiploica-dextra-arcade and, thus, parts of the right-sided omentum, the lymph nodes cranial of the pancreatic head should also be dissected.

Resection of cancers of the Middle Transverse Colon

These tumors metastasize via the middle colic artery centrally toward the superior mesenteric artery, and via the left colic artery toward the inferior mesenteric artery. A transverse colon resection includes both colon flexures. If metastasization towards the greater gastric curvature via the major omentum has occurred, a omentum resection corresponding to the tumor site as well as skeletonizing of the greater gastric curvature with removal of these lymph nodes must also be performed. The arcade principle must be observed for the omentum resection (inclusion of the omentum artery within an arcade of 10 cm to both sides of the cancer).

Resection of cancers of the Distal Transverse Colon and Left Colonic Flexure

Here the tumor metastasizes to the right via the middle colic artery and to the left via the left colic artery. Thus, the middle colic artery is centrally ligated and the left colic artery is cut descending from the inferior mesenteric artery. An advantage of the greater radicality of removing the inferior mesenteric artery has not been confirmed. An ascendo-sigmoideo-stomy can be done to restore the continuity. Due to metastasization via the major omentum towards the greater gastric curvature, the left sided parts of the omentum with dissection of the arcade at the greater gastric curvature must also be removed. If the tumor is advanced in this region, the lymph nodes at the left pancreas lower margin may also be affected. These must also be dissected from the isthmus to the pancreas tail.

Resection of cancers of the Colon Descendens

In this case a left hemicolectomy with central ligature of the inferior mesenteric artery is necessary. The distal resection margin lies in the upper third of the rectum, the proximal one in the left flexure region. Accordingly, it may be necessary to resect possible adherent parts of the omentum.

Resection of cancers of the Sigmoid Colon

These tumors metastasize via the sigmoid branches to the origin of the inferior mesenteric artery . The proximal transection of the bowel is performed in the descending colon with central ligation of the inferior mesenteric artery. For the distal bowel dissection the guidelines for rectal cancers in the upper third of the rectum also apply. However, a distal safety distance of at least 5 cm distal safety distance from the tumor margin must be observed .

Background: For 2 - 4 % of patients lymph node metastases are found close to the origin of the inferior mesenteric artery [581, 582].

7.5.2.2. Complete Mesocolic Excision (CME)

7.22.	Consensus-based Recommendation	2013
GCP	Surgical therapy for colon cancers should include the complete mesocolic excision.	
	Consensus	

Background

Analogous to the mesorectum, a mesocolon exists which covers the lymph nodes of the supplying arteries like envelopes.

Analogous to TME for rectal cancer, CME is used for colon cancer surgery. This is done to achieve maximal local radicality with the greatest possible lymph node yield by preparation in predefined anatomical layers with central ligation of the supplying vessels without breaching of the visceral fascia layer. .

For colon cancer a complete mesocolic excision is suitable to achieve maximal local radicality with high lymph node yield.

It leads to high quality preparations [583, 584]. The higher radicality does not seem to be associated with an increased complication rate [585]. Previous data indicate an improvement of survival rate if CME is consistently performed [583].

The morphometric examination of the colon specimen can be used in the future to objectively evaluate colon cancer specimen.

7.5.2.3. Local Ablative Therapies for Liver Metastases

7.5.2.3.1. Radio-Frequency Ablation (RFA)

7.23.	Recommendation	2013
Grade of Recommendation 0	An RFA can be performed if non-resectable liver metastases are present or if the general health of the patient does not allow resection, especially following previous liver resection.	
Level of Evidence 3a	De Novo: [586-588]	
	Strong consensus	

Background

The present evidence on the safety and efficacy of radio frequency ablation for colorectal liver metastases is sufficient to recommend this method for patients who either have non-resectable liver metastases, whose health status does not allow resection, or who have previously had a liver resection [586].

The RFA can also primarily be performed in combination with surgical resection.

Recent studies suggest that solitary liver metastases <3cm can be treated using RFA with similarly good results as with resections [587, 588]. However, present data on this subject are contradictory and comparative controlled randomized studies still do not exist.

7.5.2.3.2. Selective Internal Radiation Therapy (SIRT)

7.24.	Recommendation	2013
Grade of Recommendation B	SIRT to treat disseminated liver metastases of CRC should only be performed in patients who have no other therapy option and only as part of a clinical study.	
Level of Evidence 2a	De Novo: [589, 590]	
	Consensus	

Background

Patients with absent or limited extrahepatic metastazation, and without options of further systemic chemotherapies show a prolonged median survival and longer interval to progression of liver metastases in individual studies using SIRT (also called radioembolization). There are too few data for a conclusive evaluation especially on survival and quality of life. Therefore, patients who are eligible for SIRT should only be treated as part of clinical studies [589, 590].

7.5.2.3.3. **Laser Induced Interstitial Thermotherapy (LITT)**

7.25.	Recommendation	2013
Grade of Recommendation B	A LITT for the treatment of CRC liver metastases should only be performed as part of a clinical trial.	
Level of Evidence 4	De Novo: [591, 592]	
	Strong consensus	

Background

The interstitial laser thermo-ablation was a safe and effective method in individual case-series for patients with inoperable CRC liver metastases [591, 592]. Data comparing it to percutaneous radiofrequency ablation do not exist. The data are not sufficient for conclusive evaluation especially of survival and quality of life. Therefore, patients who are eligible for LITT should only be treated as part of clinical studies.

7.5.3. **Radical Surgical Therapy of Rectal Cancer**

As a general rule the curative therapy of rectal cancers requires, in addition to the complete resection of the primary tumor, the partial or total removal of the mesorectum including the regional lymph drainage area (so-called radical resection according to the international documentation system for colorectal cancer) [511, 512]. Only in strictly selected cases a curative resection is possible using local measures. The following operative procedures are considered equivalent the criteria of oncological surgery are taken into account. The individual indication is dependent on tumor localization, especially the relation to the dentate line and the levator muscle, the depth of infiltration and the anal sphincter function:

- (deep) anterior rectal resection
- abdominoperineal rectal extirpation
- intersphincteric rectal resection (also described as an abdominal-perianal rectal resection). This operation requires special experience.

It must be noted that for the deep anterior rectal resection an intersphincteral preparation is also frequently necessary to achieve a sufficient safety distance to aboral. This operation method should, however, not be confused with an abdominal peranal preparation.

If at all possible, a continence-preserving procedure should be chosen with regard to the future quality of life. With poor sphincter function, instead of a deep resection a permanent colostomy should be preferred which depending on the safety margin to the pelvic floor should be performed in form of a rectal exstirpation or preserving the pelvic floor.

7.5.3.1. **General Oncologic Principles**

Surgical therapy should adhere to the following principles:

Removal of the regional lymph drainage areas with resection of the inferior mesenteric artery at least distal to the origin of the left colic artery. The central dissection of the inferior mesenteric artery close to its origin has no prognostic significance; however, it is often necessary due to technical reasons for the mobilization of the left hemicolon used for reconstruction [593]. However, anatomical studies show that in many cases a deep anastomosis is also possible without central ligation [594]. A benefit of lymph node dissection at the origin of the inferior mesenteric artery proximal to the exit of the left colic artery has not been shown (level of evidence: 2b) [595-598].

- The complete removal of the mesorectum for cancers in the middle and lower part of the rectum and the partial mesorectal excision for cancers in the upper third of the rectum through sharp dissection along the anatomical structures between the fascia pelvis visceralis and parietalis (total mesorectal excision TME) [599, 600].
- The observance of an appropriate safety distance (see below).
- As a rule, the en-bloc resection of tumor-adhering organs (multivisceral resection) to prevent local tumor cell dissemination [601].
- Protection of the autonomic pelvic nerves (hypogastric nerves, inferior and superior plexus [602, 603].

7.26.	Recommendation	2013
Grade of Recommendation A	The systematic dissection of lateral lymph nodes along the internal iliac artery and its branches should not be done without justified suspicion of metastases. It increases the perioperative morbidity without confirmed oncologic benefit.	
Level of Evidence 1b	De Novo: [604-607]	
	Strong consensus	

7.5.3.2. Approach to Tumors of the Upper Third of the Rectum

7.27.	Recommendation	2013
Grade of Recommendation B	With tumors of the upper third of the rectum, resection of the rectum with partial mesorectal excision 5 cm distal to the macroscopic tumor border, measured in-vivo should be performed. The mesorectum should be dissected horizontally without proximal thinning (no coning).	
Level of Evidence 3b	De Novo: [599, 608-612]	
	Strong consensus	

Background

The reason for this procedure [611, 612] is that with T3 and T4 tumors rarely satellite nodes or lymph node metastases occur up to 4 cm distal to the macroscopic tumor margin as measured using the histological slice after fixation of the non-stretched surgical specimen preparation.

7.5.3.3. Approach to Tumors of the Middle and Lower Third of the Rectum

7.28.	Recommendation	2008
Grade of Recommendation A	With tumors of the middle and lower third of the rectum, a total mesorectal excision (TME) should be performed up to the pelvic floor, preserving the superior and inferior hypogastric plexus and the hypogastric nerves.	
Level of Evidence 1b	[602, 613, 614]	
	Strong consensus	

7.29.	Recommendation	2008
Grade of Recommendation B	For low-grade tumors with high or moderate differentiation in the lower third of the rectum, a safety margin of 1-2cm in-situ is sufficient. With high-grade tumors (G3/4), a larger safety margin must be attempted.	
Level of Evidence 2b	[600, 615-618]	
	Strong consensus	

7.30.	Recommendation	2013
Grade of Recommendation B	After neoadjuvant radiochemotherapy, an aboral distance of 0.5cm may also be acceptable to avert an otherwise necessary extirpation. Intraoperative frozen sections should confirm that the aboral resection margin is tumor-free.	
Level of Evidence 2b	de Novo: [619, 620]	
	Consensus	

Background

For cancers of the lower third (as an alternative to the otherwise recommended rectal extirpation) an intersphincteric rectal resection can be performed (also called the abdominal-perianal rectal resection), if - under observance of the above-mentioned safety margins - the puborectal loop is not infiltrated. This operation requires special experience.

7.5.3.4. Reconstruction After Total Mesorectal Excision

After total mesorectal resection with an anastomosis near the anal sphincter, significant functional disorders can occur. These are dependent on the choice of the reconstruction method. Some possibilities available include:

- a straight colo-anal anastomosis
- a colon-J-pouch
- a transverse coloplasty
- a side-to-end anastomosis

7.31.	Recommendation	2013
Grade of Recommendation A	For reconstruction after deep anterior resection, a straight colo-anal anastomosis should usually not be used (if anatomically possible) because of the better functional results.	
Level of Evidence 1a	de Novo: [621]	
	Strong consensus	

7.32.	Statement	2013
Level of Evidence 1a	Of the different reconstruction forms, the advantages of the functional results of a colon-J-pouch are best confirmed.	
	de Novo: [621, 622]	
	Majority consensus	

7.33.	Statement	2013
Level of Evidence 1b	Under functional aspects, the transverse coloplasty is inferior to the colon-J-pouch.	
	de Novo: [622, 623]	
	Majority consensus	

7.34.	Statement	2013
Level of Evidence 2a	The side-to-end anastomosis may be as good as the colon-J-pouch.	
	de Novo: [624]	
	Strong consensus	

Background

The disadvantages of a straight colo-anal anastomosis have been clearly shown. Especially in the first two postoperative years, they result in an increased stool frequency as well as poor continence and quality of life [621]. When constructing a J-pouch the loop length should not exceed 6 cm to prevent emptying problems [625]. The only larger prospective randomized study on the differential use of different reconstructions shows that a J-pouch construction was technically possible in 74% of patients. Compared to a transverse coloplastic, the J-pouch in this study was better with respect to stool frequency and incontinence score. Although a meta-analysis including the Fazio-study put the conclusion on stool frequency into perspective, it considered neither the long-term results of the Fazio-study nor the data on incontinence [623]. Since studies with sufficient case numbers are still missing, definite conclusions on the role of side-to-end anastomosis cannot be made [624].

7.5.3.5. Decision to Preserve the Sphincter

7.35.	Consensus-based Recommendation	2013
GCP	Even in cases in which sphincter preservation was initially regarded as impossible, a sphincter preserving rectal resection may become possible using neoadjuvant radiochemotherapy. Therefore, a re-evaluation should be performed no earlier than 6 weeks after completion of radiochemotherapy.	
	Strong consensus	

Background

A reduction of tumor mass especially for low tumors is one important aspect for sphincter preservation. There seems to be an advantage for neoadjuvant radiochemotherapy. However, its effects do not become identifiable until several weeks after completion. This means that the surgery method cannot be chosen until the time of surgery after neoadjuvant radiochemotherapy has been completed [626]. Imaging procedures are not helpful in evaluating the response [627].

7.5.3.6. Approach in Case of Complete Response after Neoadjuvant Therapy

7.36.	Consensus-based Recommendation	2013
GCP	In rare cases in which after neoadjuvant radiochemotherapy a tumor is no longer detectable clinically, endoscopically, or with imaging procedures (endosonography and MRI, alternatively also CT), it can be considered not to perform a resection. Detailed information on the poor validation of this approach and the willingness of the patient undergo regular follow up at short intervals to have very close knit follow-ups for at least 5 years is required.	
	Consensus	

Background

A Brazilian study in 265 patients with rectal cancer showed that after neoadjuvant therapy a tumor was no longer detectable in 26.8% of the patients. These patients had no surgery and underwent follow-ups [628]. After a median follow-up of 57.3 months, two patients (2.8%) had an endoluminal relapse and in three patients (4.8%) systemic metastases were found. The authors postulated that for patients with complete response after neoadjuvant radiochemotherapy a follow-up without surgery may be sufficient. However, it must be considered that this was not a randomized study. Furthermore, it is not known if these results can also be achieved outside of Brazil.

7.5.3.7. Rectal-Exstirpation

7.37.	Recommendation	2013
Grade of Recommendation B	For low tumors with infiltration of the anal canal/sphincter which cannot be operated with sphincter preservation, an abdomino-perineal extirpation in the form of "cylindrical" resection including the levator ani should be performed.	
Level of Evidence 3b	de Novo: [584, 629, 630]	
	Consensus	

Background

In rectal-exstirpation the preparation rate with insufficient lateral safety margins is classically increased [629]. The oncologic results are poorer compared to sphincter preserving interventions with comparable tumor stages [630]. The extralevatoric "cylindrical" resection leads to better safety margins and should be viewed as the superior method even without randomized studies [584].

7.38.	Recommendation	2013
Grade of Recommendation O	After neoadjuvant radio-(chemo-)therapy and/or with larger perineal defects, perineal wound healing disorders can be reduced using primary plastic reconstruction with a myocutaneous flap.	
Level of Evidence 3b	de Novo: [631]	
	Consensus	

Background

The rate of perineal wound healing disorders is high especially after neoadjuvant radiation and with larger defects. However, the use of different plastic reconstruction methods remains an individual decision, which must take the special anatomical availability, the chance of secondary morbidity of the donor site defect, the surgical complexity, and the available surgical expertise into consideration [631].

7.5.4. Stoma-Construction

7.39.	Consensus-based Recommendation/ Consensus-based Statement	2013
GCP	A temporary deviation stoma should be performed for radical surgery of rectal cancer with TME and deep anastomosis.	
	Strong consensus	

7.40.	Consensus-based Statement	2013
GCP	Colostomies and ileostomies are equally good as deviation stomas.	
	Strong consensus	

Background

A protective stoma can reduce the morbidity especially of clinically relevant anastomosis insufficiencies and urgent relaparotomies [632]. If primary deviation stomas are avoided, the long-term rate of permanent stomata is by no means lower [633]. There are arguments for both types of protective stomas, even if recent meta-analyses favor ileostomies [634, 635].

7.41.	Consensus-based recommendation	2013
GCP	Stoma construction should be discussed and planned with the patient as early as possible before the operation.	
	Strong consensus	

7.42.	Recommendation	2013
GCP	The stoma position should be marked pre-operatively.	
	Consensus	

7.43.	Recommendation	2013
GCP	An ileostomy should be constructed prominently (> 1 cm). A colostomy should be constructed with slight elevation.	
	Strong consensus	

Background

The pre-operative information on the stoma construction should be given by the treating physician and a correspondingly trained nurse (stoma therapist). A meeting with an affected person from a self-help group - if available - should be offered. The stoma marking can be done by a trained nurse/stoma therapist. However, the doctor is responsible for the correct marking of the stoma and, thus, the correct construction. To determine the best position, it is necessary to mark the stoma position while lying down, sitting, and standing.

A postoperative stoma therapy should ensure that patients or if they are not able, their family or caregivers can independently perform the stoma care (base plate change, stoma bag emptying and change), that the supply with stoma material is ensured, and that if necessary, a stoma therapist is available. An irrigation should be offered to the colostomy carrier. In individual studies pre-operative stoma marking and the implementation of stoma therapists reduced the postoperative stoma complication rate [636, 637]. Furthermore, a prospective study reported that pre-operative stoma counseling makes postoperative care easier [638].

7.5.5. Local Excision of Rectal Cancers

7.44.	Statement	2008
Level of Evidence 1b	Local surgical excision of rectal cancers (full wall excision) as the only treatment is only recommended for pT1 cancers with a diameter up to 3cm, good or moderate differentiation, without lymph vessel invasion (low-risk histology). However, complete resection (R0) is required.	
	[639-642]	
	Strong consensus	

Background

Also in low-risk cases, the risk of local recurrence is higher compared to radical surgery, but local therapy is associated with reduced morbidity, mortality, and better functional results is higher compared to radical surgery. Therefore, the risk-benefit must be considered individually for each patient [643, 644]. There is much to suggest that for local excision the transanal endoscopic microsurgical methods are superior to open transanal excision using a spreader [645, 646].

There was no agreement on the relevance of sm-classifications to assess "low-risk" or "high-risk". T1-cancers with deep submucosal infiltration (sm3, according to some series even sm2) are considered by other authors and guidelines as high-risk constellations that should be treated with radical surgery [647-650].

7.45.	Recommendation	2008
Grade of Recommendation B	With T1 high-risk cancers (G3/4 and/or lymph vessel invasion) and with T2 cancers, the probability of lymphatic spread is around 10-20%, so that in general local excision alone cannot be recommended. (see also section 6.4)	
Level of Evidence 3b	[647, 651]	
	Strong consensus	

Background

If a "high-risk" constellation is known before treatment, the primary operation should be radical. If a high-risk constellation does not become apparent until transanal full wall resection, the secondary radical revision surgery within one month is not associated with a poorer prognosis than with a primary radical procedure [647, 651]. If the patient refuses radical revision surgery in this situation, an adjuvant radiotherapy may be considered.

7.6. Laparoscopic Surgery

7.46.	Recommendation	2013
Grade of Recommendation A	Laparoscopic colon and rectal cancer resections can be performed with comparable results to open surgical techniques if the surgeon has appropriate expertise and the selection is appropriate. ⁵	
Level of Evidence 1a	de Novo: [652-656]	
	Strong consensus	

7.47.	Consensus-based Recommendation	2013
GCP	The quality of the surgical specimen should be documented by the pathologist.	
	Strong consensus	

Background

Even if laparoscopic colorectal resections take more time to perform, numerous randomized studies indicate that in the short-term peri-operative surgical morbidity is lower than after conventional operations with unchanged overall morbidity and mortality [652]. In the incisional hernias, adhesion-related revision operations, or regional and systemic tumor relapses [653, 654]. Systematic reviews and meta-analyses show equivalent oncologic long-term results especially for colon cancer. The data on rectal cancer were still insufficient. However, in the meantime, robust long-term results of the British CLASICC-study have been published despite initial problems with surrogate-parameters in the rectal cancer subgroup [655]. This study demonstrates oncologic safety of laparoscopic surgery for both colon and rectal cancer [656]. No strict criteria have been validated for defining special laparoscopic expertise that is without doubt necessary.

7.48.	Consensus-based Recommendation	2013
GCP	Recent operation procedures (e.g. robotics, NOTES) cannot be recommended, because of insufficient data outside of studies.	
	Strong consensus	

⁵ The word "may" is not contradictory to the recommendation grade A, as the recommendation grade refers to the equivalency of both methods.

Background

The DaVinci-telesystem - the only "robot" established in clinical routine - has been used in several series for laparoscopic total mesorectal excisions [657, 658]. Since neither short-term benefits nor long-term oncologic equivalency have been proven, this method must still be viewed as experimental. The same is true to an even greater extent for transgastral, transvaginal, or transanal access and specimen extraction.

7.7. Special Situations

7.7.1. Surgical Therapy of Peritoneal Carcinomatosis

7.49.	Recommendation	2013
Grade of Recommendation 0	<p>For patients with isolated and limited peritoneal carcinosis a cytoreductive operation with subsequent hyperthermal intraperitoneal chemotherapy (HIPEC) can be performed done if the following criteria are fulfilled:</p> <ul style="list-style-type: none"> - PCI (peritoneal cancer index) < 20 - No extraabdominal metastases - Possibility of macroscopic complete removal or destruction of all tumor manifestations - Therapy at a specialized center <p>These procedures should preferably be performed as part of a trial</p>	
Level of Evidence 2a	de Novo: [659-662]	
	Strong consensus	

Background

So far, there is only one completed randomized study comparing systematic chemotherapy and cytoreductive surgery with HIPEC [660]. This study demonstrated also long-term that surgical therapy of peritoneal carcinosis leads to significantly better disease-specific survival [661]. If macroscopic tumor eradication was achieved, the 5-year-survival was 45%. It must be noted that the control arm only received a 5-FU-based systemic therapy. Thus, despite numerous non-randomized studies [662] with promising results, it has not been conclusively defined which patients benefit from surgical therapy with HIPEC compared to modern systemic polychemotherapy.

7.7.2. Multivisceral Resection

In the case of adherence of a tumor to neighboring organs it is not possible to determine macroscopically whether an infiltration of the neighboring organs or only a peritumorous inflammatory reaction is present. In such cases, biopsies and frozen sections should be strictly avoided, because of the possibility of local tumor cell dissemination, which can be associated with reduced survival [571]. This is the basis for performing an en-bloc resection in all cases of tumor adherence to neighboring

organs or other structures (multivisceral resection). In the case of rectal cancer total pelvic exenteration can be necessary.

7.7.3. Multiple Cancers of the Colon and Rectum

In these cases a colectomy should not always be performed, instead the procedure should take into account the requirements of each individual tumor. This might require the construction of several anastomoses.

7.7.4. Emergency Surgery

In the setting of ileus, tumor perforation, or colorectal perforation with a stenotic tumor the procedure performed depends on the individual situation. If possible, the preferred surgical option is a radical resection according to the standard oncological procedures. In appropriately selected cases of ileus due to colorectal cancer, the placement of an endoluminal stent can be discussed [663]. An ileus usually accompanies a rectal cancer only in very advanced cases, so that nearly always a neoadjuvant radio/chemotherapy should be undertaken. Therefore, in this situation a colostoma of the right transverse colon is often constructed. Tumor-associated bleeding is only rarely relevant for further decisions regarding therapy.

7.7.5. Resection of Liver Metastases

7.50.	Consensus-based Statement	2013
GCP	Compared to a two-stage procedure, the simultaneous resection of liver metastases most likely does not have an influence on the long-term survival if suitable patients are selected.	
	Strong consensus	

7.51.	Consensus-based Statement	2013
GCP	In case of certain comorbidities and older age (>70 years), the simultaneous resection of the primary tumor and liver metastases may lead to higher postoperative mortality.	
	Consensus	

7.52.	Recommendation	2013
GCP	A multimodal two-stage procedure should be chosen in case of multiple synchronous liver metastases.	
	Consensus	

Background

The decision to perform simultaneous resection of liver metastases on top of resection of the primary tumor must be considered under several aspects:

- If it is a right-sided colon resection, the liver is usually easily accessible due to the positioning of the patient and the incision path (except for very obese patients, a very large fatty liver). In case of a left-sided colon and rectal operation with the according patient positioning the liver access is much more difficult.
- Resection of individual peripheral metastases may also be performed without substantial difficulty if the patient is positioned as done for left-sided resections. Especially formal right-sided resections (e.g. right hemihepatectomy) are only acceptable with right-sided resections, because of the corresponding access.
- Especially small individual metastases are often followed by an advanced metachronic metastazation. Therefore, it is also justified, despite technical resectability, to wait and see if liver metastazation progresses and if necessary to perform systemic chemotherapy in the meantime.

Furthermore for rectal cancer, individual surgeons advocate the concept of primary liver resection without resection of the primary tumor or other preceding procedures such as neoadjuvant chemotherapy or neoadjuvant radiochemotherapy.

7.7.6. Extensive Distant Metastazation and Asymptomatic Primary Tumor

7.53.	Recommendation	2013
Grade of Recommendation 0	Stage IV patients with extensive liver metastazation ("metastasis liver") and asymptomatic primary tumor (no stenosis symptoms, no bleeding that needs transfusions) may undergo primary chemotherapy without resection of the primary tumor.	
Level of Evidence 4	de Novo: [664, 665]	
	Strong consensus	

Background

Extensive non-resectable distant metastases usually determine the prognosis of patients with this type of metastazation. If ileus symptoms are present due to the primary tumor or if transfusions are necessary due to bleeding, prompt resection of the primary tumor (with few exceptions) is essential. If the primary tumor is asymptomatic it is, however, still not clear whether resection has a benefit for the patient. The start of chemotherapy has to be postponed because of the operation. A meta-analysis of 8 retrospective descriptive studies (from 1985-2005) showed prolonged survival for patients with resection of their primary tumor in 7 studies [664]. However, these studies were not randomized i.e. the reason for the allocation of patients to primary surgery or primary chemotherapy groups remains unknown. Furthermore, the median survival of 6 months found in some chemotherapy groups seems lower than would be expected with the chemotherapy protocols available today. The risk that during the course of primary chemotherapy surgery due to ileus or perforation becomes necessary is small according to current data (about 7%) [665]. The initiation of chemotherapy with retention of the asymptomatic primary tumor with

extensive distant metastazation, thus, seems justified. The role of resection of primary tumors with extensive distant metastazation is currently being studied in a randomized study (Synchronous-study, study number ISRCTN30964555).

7.7.7. Patients with HNPCC (Hereditary Non-Polyposis Colorectal Cancer)

7.54.	Consensus-based Recommendation	2013
GCP	Prophylactic colectomy or proctocolectomy in HNPCC mutation carriers shall not be performed. A subtotal colectomy in patients with a cancer should not generally be done, but should be discussed individually with the patient.	
	Strong consensus	

7.55.	Recommendation	2008
Grade of Recommendation A	After cancer resection in addition to the usual follow-up-colonoscopy must be performed in the same interval as preoperatively. (see also Chapter 5.2.2.1)	
Level of Evidence 2a	Evidence from update literature search:[272, 273, 287-290]	
	Strong consensus	

Background

Since regular screening nearly always detects cancers in stage UICC I/II or even as premalignant adenomas [272, 273] and there is incomplete penetrance of the disease, a prophylactic colectomy or proctocolectomy is not recommended.

If a cancer is detected, patients will have oncologic resections. The risk of CRC in the remaining colon and the risk of extracolonic neoplasia is, however, increased. Thus, these patients must undergo an intensive postoperative follow-up. The usual follow-up for sporadic CRC should be combined with a HNPCC-specific prevention program for CRC and extracolonic tumors. It is currently not known whether an extended prophylactic resection for the prevention of metachronic CRC is better than continuous surveillance. Previous data from retrospective case series are insufficient and due to national differences in screening intervals not applicable to Germany (for further information see Chapter 5.2.2.1).

7.7.8. Cancers in Familial Adenomatous Polyposis (FAP)

7.56.	Recommendation	2008
Grade of Recommendation B	The procedure of choice for FAP patients is a proctocolectomy with ileo-anal pouch including a lymph node dissection depending on the localization of the carcinoma and the resulting consequences (e.g. radial vessel cutting, total mesorectal excision). Depending on anal sphincter function or an incurable tumor stage, a proctocolectomy or a limited resection can be carried out. In attenuated FAP with only minimal involvement of the rectum, an ileorectostomy is recommended (see also 5.2.2.2)	
Level of Evidence 3b	[305]	
	Strong consensus	

7.7.9. Cancers in Ulcerative Colitis

7.57.	Statement	2008
Level of Evidence 3b	The preferred procedure is a proctocolectomy with an ileo-anal pouch (IAAP), if sensible according to oncological or functional considerations.	
	Strong consensus	

For further recommendations and information e.g. on the procedures for surveillance colonoscopies, see the *S3 Guideline Diagnostics and Therapy of Ulcerative colitis* [396].

7.8. Postoperative Histopathological Examination

7.58.	Recommendation	2008
Grade of Recommendation	The following data are obligatory components of the pathology report:	Level of Evidence
A	Tumor type according to WHO classification	1c
	• Tumor invasion depth (pT-classification)	1c
	• Regional lymph node status (pN classification)	1c
	• Number of lymph nodes examined	2a
	• Minimum number of lymph nodes to be examined:12	2a
	• Grading	2a
	• Distance from the resection margins (with rectal cancer, circumferential)	2a
	• R-Classification	1c
Sources for all specifications: [477, 579, 666-678]		

Background

Increasingly and especially after neoadjuvant radiochemotherapy, the degree of remission achieved is histologically classified according to Dworak [678].

7.59.	Consensus-based recommendation	2008
GCP	Testing for microsatellite instability may be performed in case of suspected HNPCC.	

7.8.1. Cancer-Grading Based on MSI-H

7.60.	Consensus-based recommendation	2013
GCP	Poorly differentiated adenocarcinomas including mucinous adenocarcinomas and undifferentiated cancers should be tested immunohistochemically for the expression of hMLH1 and hMSH2. If there is no hMLH1 or hMSH2 expression, they should be classified as low-grade.	
	Consensus	

Background

CRCs with high-grade microsatellite instability (MSI-H) have a significantly better prognosis and lower distant metastazation rate than CRC with microsatellite stability (MSS) or low-grade microsatellite instability (MSI-L) [679-682]. Furthermore, it was shown that poorly differentiated (G3) adenocarcinomas and also mucinous adenocarcinomas which have been graded as G3 have a significantly better prognosis if MSI-H is present than if MSS or MSI-L are found [683, 684]. Therefore, if there are indications for MSI-H, poorly differentiated adenocarcinomas including mucinous adenocarcinoma and undifferentiated colon cancer should not be graded as high-grade but as low-grade.

The immunohistochemical evidence of lack of hMLH1 or hMSH2 expression is as important for the prognosis as MSI-H [685]. Due to its sensitivity and specificity, it can be used as a simple and inexpensive substitute for molecular MSI testing for MSI-associated prognosis evaluations [686-689]. The immunohistochemistry for hMLH1 and hMSH2 detects sporadic MSI-H-carcinomas and some of the MSI-H-carcinomas in Lynch-syndrome. The connection of CRC with Lynch-syndrome cannot be reliably assessed with this test and requires additional testing.

7.8.2. Number of LN to be Removed

7.61.	Consensus-based Statement	2013
GCP	12 or more lymph nodes shall be removed and examined.	
	Strong consensus	

7.62.	Recommendation	2013
GCP	The ratio of tested and affected lymph nodes should be documented.	
	Strong consensus	

7.63.	Consensus-based Statement	2013
GCP	The greater the number of affected and examined lymph nodes, the better the prognosis of patients with CRC UICC-stage II and III. The number of affected and examined lymph nodes can be used as a surrogate marker for the quality of treatment. The size of a lymph node does not correlate with the probability of metastazation.	
	Strong consensus	

Background

The number of affected and examined lymph nodes depends not only on the tumor biology, but also on the surgeon and pathologist. The 7th edition of the UICC-TNM-classification 2010 specifies that for category „pN0“ a regional lymphadenectomy and histological examination of usually twelve or more lymph nodes should be done.

Although the quality of studies on the number of lymph nodes is poor, it is still true that patients with a larger number of removed and examined lymph nodes have a better prognosis in UICC-stage II and III. The correlation has been repeatedly demonstrated in cohort studies such as in 3411 stage II and III patients of the so-called intergroup-trials [579]. The so-called INTACC-study with 3491 patients also showed that the prognosis correlates with removed/examined lymph nodes [690]. However, not only the number of lymph node metastases is important, but also the number of lymph nodes in general. Both studies showed a prognostic effect even for nodal negative tumors which correlated with the number of removed/examined lymph nodes [691].

This effect was demonstrated in numerous cohorts [692-695].

The number of lymph nodes can be used as a surrogate marker for the treatment and diagnosis quality of the surgeon as well as the pathologist.

The "optimal number" of lymph nodes to be removed/examined for correct staging is controversial in the literature. However, it is definite that twelve lymph nodes are not sufficient. The sole histopathological examination of the largest lymph nodes in the preparation is not sufficient, because the lymph node size does not correlate with the probability of metastazation.

In the literature it is suggested to report the ratio of examined to affected lymph nodes [696-698].

For patients who have had pre-operative radiochemotherapy for locally advanced rectal cancer the number of lymph nodes is smaller. An analysis of 615 patients who were operated for primary rectal adenocarcinoma showed that 33% fewer lymph nodes were found if a neoadjuvant therapy had been performed pre-operatively [699].

7.8.3. Relevance of Distance Between the Tumor Margin and Resection Area of the Mesocolon in Colon Cancer

7.64.	Consensus-based Recommendation	2013
GCP	Analogous to the quality evaluation of the resection in rectal cancer, the quality of the colon cancer resection should also be categorized as follows: Grade 1 (good): intact mesorectum Grade 2 (moderate): mesorectal surface irregularities Grade 3 (poor): defects down to the muscularis propria or the tumor These assessments should be made by a pathologist.	
	Consensus	

Background

There are no data comparable to rectal cancer on the circumferential safety margins of primary tumors in colon cancer. In addition, in colon cancer the chance of reaching a sufficient circumferential safety margin to adjacent structures or organs is much more frequent despite extensive deep-infiltration of the primary tumor. In rare cases this is not possible (e.g. for sigma-carcinoma, which is located on the iliacal vessels).

Therefore, when appropriate, analogous to rectal cancer, the circumferential safety margin should be documented.

However in the meantime, publications analogous to those for rectal cancer on the quality of the evaluation of colon cancer resections have become available. Similar to rectal cancer, it has been confirmed that tears down to the muscularis propria or reaching the tumor lead to a poorer survival rate (a 15% lower 5-year-survival rate with tears muscularis propria vs. mesorectum). In the case of lymph node metastases (UICC stage III) the difference is more pronounced (27% higher survival rate after 5 year follow-up) than if lymph node metastases are absent [700, 701].

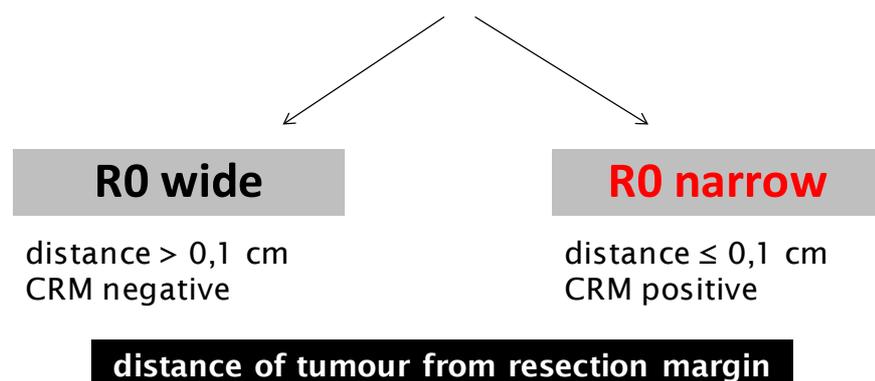
7.8.4. Relevance of Distance From the Circumferential Resection Margin (CRM-Classification) with Colon and Rectal Cancer

7.65.	Consensus-based Recommendation	2013
GCP	The circumferential safety margin is negative if it measures 1mm or more (R0 "wide"). A circumferential safety margin is positive if the circumferential safety margin is less than 1mm (R0 "close") or if tumor tissue reaches it directly (R1). The distance should be documented quantitatively.	
	Strong consensus	

Background

According to the official definition of the AJCC, the residual tumor is defined as R1 if the cancer actually histologically reaches the resection margin (RR).

R0 (curative resection)



Taking into account continuous primary tumour spread, satellites, involvement of lymphvessels, venous infiltration, perineureum infiltration, lymphnode metastases

However, especially publications from The Netherlands and Great Britain have shown that a circumferential safety margin of less than 1mm also significantly increases the local recurrence risk for rectal cancer (3-year local recurrence rate: 6% for CRM- and 17% for CRM+ ; 3-year tumor-free survival rate 79% for CRM- and 50% for CRM+ [560, 702]).

Whether a safety margin of less than 2mm leads to a poorer prognosis is controversial [703, 704].

7.8.5. Relevance of Documenting the Quality of the TME-Preparation

7.66.	Consensus-based Recommendation	2013
GCP	<p>Since the quality of the surgical resection specimens according to the abovementioned categories allows conclusions on the prognosis of local recurrence, it must be described in the pathohistological report as follows:</p> <p>The quality of the resection specimens is graded by the integrity of the mesorectal fascia in 3 categories:</p> <ul style="list-style-type: none"> * Grade 1 (good): mesorectal fascia is intact * Grade 2 (moderate): intramesorectal surface tearing * Grade 3 (poor): tearing down to the muscularis propria or the tumor <p>In case of rectal extirpation, preparation irregularities and tumor positive circumferential safety margins are not as frequent with a complete resection of the levator musculature. [705]</p> <p>Therefore, the pathohistological report must describe the radicality in the levator musculature region. The following categories should be used:</p> <ul style="list-style-type: none"> * Grade 1 (good): levator musculature included in resection, no opening of the intestine or tumor * Grade 2 (moderate): muscularis propria intact, no opening of the intestine or tumor * Grade 3 (poor): parts of the muscularis propria are missing or opening of the intestine or tumor <p>The analysis has to be performed by a pathologist.</p>	
	Consensus	

Background

The quality of the rectal resection specimen significantly influences the local recurrence rate. If the mesorectum remained intact, the 5-year tumor-free survival was 65% compared to 47% with a defective mesorectum ($P < 0.05$) [706]. After a 3 year follow-up, the local recurrence rate with intact mesorectal fascia was 4% (3–6%), 7% (5–11%) with intramesorectal tearing, and 13% (8–21%) if tearing had reached the muscularis propria-layer [702].

For the evaluation of preparations after rectal extirpation a distinction is made between cylindrical and standard excisions. Following a cylindrical excision, the circumferential resection margin is not as frequently affected and perforations are also significantly less frequent [700, 705]. To date, data on the effect on the local recurrence and survival rate do not exist.

The quality evaluation of the surgical specimen should be performed according to the abovementioned criteria by a pathologist and not the surgeon.

7.9. Psychooncological Aspects

7.67.	Recommendation/ GCP ⁶	2013
Grade of Recommendation B	Psychooncological care should be included in the overall therapy concept.	
Level of Evidence 1b	[708-735]	

7.68.	Recommendation/ GCP ⁷	2013
GCP	All patients should be informed early by a physician about the possibilities of psychooncological support.	

Background

Throughout the course of cancer, psychological burden and disorders requiring treatment occur with a frequency of 20 – 35% (cancer patients with any tumor location and stage). Most common are adaptive (F 43.12), next acute stress (F 43.0), followed by depressive disorders (major depression 8-20%, dysthymia 5-15%) [710-713]. For the CRC patient group the numbers are similar [714, 715]. Advanced disease stage, marked functional impairment, and high somatic discomfort are associated with a high risk of psychological disorders [716]. The additional creation of colostomies is usually an invasive change for affected patients. Its acceptance is harder the more impairing the functional limitations are and the more massive the physical disfigurement is perceived. The patient's self-esteem can be greatly reduced as a result of a stoma, so that physical, sports, and social activities as well as going back to work are experienced as difficult and burdening. This can lead to psychological impairments. Especially the external physical change that can be seen as a result of the stoma makes adjustment difficult and leads to self-esteem and adaptive disorders up to depression [715, 717]. For many affected patients the feelings of shame and disgust as well as the fear of filth and smell become a great psychological burden so that the need for intimacy is of secondary importance. Thus, stoma carriers often feel that their sex life is negatively affected [718].

A large proportion of psychological disorders in tumor patients is not correctly diagnosed and is insufficiently treated [712, 719, 720]. This results in negative affects on patients' physical wellbeing, functional status, symptoms (pain, nausea, fatigue), and quality of life. Therefore, the patient's psychological health should be assessed

⁶ Taken from the interdisciplinary S3-guideline for the diagnostics, therapy and follow-up of breast cancer. 707. Kreienberg, R., et al. *Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms*. Informationszentrum für Standards in der Onkologie (ISTO), Deutsche Krebsgesellschaft e.V., 2008. **1. Aktualisierung**

⁷ Taken from the interdisciplinary S3-guideline for the diagnostics, therapy and follow-up of breast cancer. 707. Ibid.

regularly during the course of the illness i.e. in all crisis phases and at times of expected high burden. Recent studies argue for the efficacy of prevention/follow-up-based psychosocial interventions for tumor patients [711, 721, 722]. Prevention/follow-up measures include the answering of some simple targeted questions by the patient either in personal contact or with the help of questionnaires. Different screening procedures are available for the identification of patients with high psychological burden or comorbidities that require treatment. An overview of different screening methods can be found in [723], which can be obtained online under www.pso-ag.de .

Professional psychological support/co-therapy should be available to all patients and their families. It can be performed by psychosomatic or psychiatric counseling/liaison services, by psycho-oncologic staff in organ and oncologic expert centers, or by including practicing physicians or psychological psychotherapists with psycho-oncologic qualification [724-726]. It should be done in close cooperation and with feedback to the treating physicians and nurses.

All CRC patients should be informed by their medical therapist (doctors and nurses) about the professional psychological support that is available.

The efficacy of different psycho-educative and psychotherapeutic interventions in tumor patients for symptom reduction (depression, anxiety, pain, fatigue), disease processing, and improvement of the quality of life has been confirmed [709, 720, 727-735].

In addition, look at the S3-Guideline Psychooncology, completion expected in 2013.

8. Adjuvant and Neoadjuvant Therapy

8.1. Adjuvant Therapy of Colon Cancer

8.1.1. Indications for Adjuvant Therapy of Colon Cancer

A requirement for adjuvant therapy in colon cancer is a R0-resection of the primary tumor. Basis for the indication for adjuvant therapy after tumor resection is a histopathological stage determination, especially the determination of the pN status. To determine a pN0 status, at least 12 regional lymph nodes should be examined (UICC 2002). Immunocytological detection of isolated tumor cells in bone marrow biopsies or lymph nodes as well as cytological tumor cell findings in peritoneal lavages do not serve as indications for adjuvant therapy outside of clinical trials.

Adjuvant therapy is not indicated for patients with curatively resected stage I colon cancer. Patients with UICC stage II and III should, if possible, be enrolled in controlled clinical trials in order to obtain data concerning indications and optimal adjuvant therapy. By means of quality control, the clinical course of patients being treated outside of clinical trials should be documented with regard to disease recurrence, survival rate, and side effects. Applying adjuvant chemotherapy requires considerable experience, and especially knowledge of relevant dose reduction schemes which must be followed when toxicity occurs.

Contra-Indications for Adjuvant Chemotherapy of Colon Cancer

- Performance status worse than 2 (WHO)
- Uncontrolled infection
- Liver cirrhosis Child B and C
- Severe coronary heart disease, cardiac insufficiency (NYHA III and IV)
- Preterminal and terminal kidney insufficiency
- Limited bone marrow function
- Other comorbidities affecting life expectancy
- Inability to attend regular control examinations

8.1.2. Age Limitations for Conducting Adjuvant Chemotherapy

8.1.	Evidence -based Recommendation	2008
Grade of Recommendation A	There is no age limitation for performing adjuvant chemotherapy; general contraindications (see above) should be considered.	
Level of Evidence 1	Strong consensus	

Background

Randomized studies concerning the effect of adjuvant chemotherapy on colon cancer outcome had an under representation of older patients. Among other reasons, this was due to an age limitation as part of the inclusion criteria in most of these studies. A

prospective cohort study including patients with colon cancer who were at least 67 years old showed that also at older age patients have a significant survival benefit from adjuvant chemotherapy in comparison to surgery alone [736]. Additionally, a retrospective study consisting of a smaller number of patients revealed that no significant differences in survival time were found depending upon age [737]*. This result was confirmed by a pooled analysis of seven studies with a total of 500 patients age 70 years or older [738]. In this study occurrence of gastrointestinal side effects did not depend upon age. However, leucopenia was found more often among older patients. In another study, stomatitis was the only side effect seen more often in the group with age over 70 years [739]. Hence, in most cases adjuvant chemotherapy seems to be tolerated well by older patients. Furthermore, a subgroup analysis of the MOSAIC study revealed that the benefit of additional adjuvant therapy with oxaliplatin was not dependent on age [740]. The age of a patient, therefore, has no sole predictive relevance [741].

8.1.3. UICC Stage III

8.2.	Evidence -based Recommendation	2008
Grade of Recommendation A	For patients with R0 resected stage III colon cancer, adjuvant therapy is indicated.	
Level of Evidence 1a	Strong consensus	

Background

Various randomized studies have demonstrated a significant survival benefit for patients with stage III colon cancer due to adjuvant chemotherapy [742, 743]. Meta-analyses and pooled analyses (e.g. Gill et al) including 3,303 patients with stage II and III colon cancer unequivocally showed that, compared to surgery alone, adjuvant chemotherapy is associated with a significant improvement of prognosis for patients with lymph node positive disease (stage III) [738, 744-746].

8.1.4. UICC Stage II

8.3.	Recommendation	2008
Grade of Recommendation 0	For patients with curatively resected stage II colon cancer, adjuvant therapy can be performed.	
Level of Evidence 1b	Strong consensus	

Background

The absolute benefit of adjuvant therapy in UICC stage II without risk factors is between 2 and 5%. Studies and pooled analyses of trials of patients with stage II colon cancer did not show a significant survival benefit from postoperative adjuvant chemotherapy. A pooled analysis of 7 randomized studies which compared adjuvant chemotherapy to sole operation with regard to stage II colon cancer, merely demonstrated a significant improvement of disease-free five-year-survival (DFS) (72 vs. 76%, $p=0.049$) in the univariate analysis. This benefit could not be shown for five-year overall survival (80 vs. 81%; $p=0.1127$). Furthermore, the individual studies differed concerning therapy modalities and included low patient numbers [745]. The British QUASAR study is the largest individual randomized trial published concerning this issue [751]. In this study after a median observation period of 5.5 years, the relative risk for death from whatever cause was significantly lower in the adjuvant therapy group than in the observation group (HR 0.82; 95% CI: 0.70-0.95, $p=0.008$), resulting in an absolute survival benefit of about 3.0% (95% CI: 1.0-6.0). However, this study also showed methodological weaknesses due to its heterogeneous study group (71% colon cancer, 91% Dukes' stage B) and the heterogeneous therapy protocols containing 5-FU (with or without Levamisol, different dosing of folinic acid). Considering the isolated subgroup of stage II colon cancer, the relative risk was not significantly reduced; the effect, however, was the same throughout all subgroups leading to the assumption of a survival benefit for all prognosis groups. Considering the significance of this study with regards to the so-defined "high-risk-situation" (see below), no recommendations can be derived, since data on T-category and/or vascular invasion are merely available for about 20% of all patients. Out of the collective of these 20%, only very few patients actually showed T4- or V1-status. At this time, there is no convincing data available concerning usage of Oxaliplatin in stage II: At the ASCO 2007 [752]* the effect of adjuvant postoperative chemotherapy (FOLFOX4 versus LV5FU2) in stage II was reported in a subgroup analysis. Regarding stage II colon cancers, there was neither a significant improvement of disease-free survival (HR 0.84; 95% CI: 0.62-1.14; $p=0.258$) nor an overall survival benefit (HR 1.0; 95% CI: 0.71-1.42) for those patients being treated with Oxaliplatin combination therapy and having a stage II tumor. Taking all currently available randomized and controlled studies into account, a recommendation for an obligatory use of adjuvant chemotherapy in stage II cannot be given [753-755]. However, due to the positive results of the currently largest trial, the QUASAR study, a benefit of adjuvant therapy in stage II without risk factors cannot completely be excluded – regardless of methodological problems of this study. For this reason, therapy should at least be taken into consideration at this stage [751], potential benefits and risks of such a therapy should always be discussed with the patient.

8.1.5. UICC Stage II with Risk Factors

8.4.	Recommendation	2008
Grade of Recommendation B	In stage II, adjuvant chemotherapy should be taken into consideration in selected risk situations (T4, tumor perforation/tears, surgery under emergency conditions, number of examined lymph nodes too small).	
Level of Evidence 3	Strong consensus	

Background

The factors listed above have been identified as prognostically unfavorable. Thus, it appears to be possible that patients with these risk factors may benefit from adjuvant chemotherapy in stage II cancers. Nonetheless, there are no prospective data available concerning the association of these risk characteristics and the benefit of adjuvant chemotherapy. Therefore, a thorough discussion with the patient about advantages and disadvantages of adjuvant chemotherapy in this indication should be carried out in this subgroup.

Several studies found that poor prognosis was associated with certain risk situations such as T4 tumor, tumor perforation, operation under emergency conditions, and/or too few examined lymph nodes [756, 757]. A recent retrospective trial including 1,306 patients with a stage II tumor revealed in multivariate analysis that T4-category was associated with poor disease-free survival (HR 1.75) [758]. In the study by Moertel (n=318), T4-category in stage II had no additional prognostic relevance [753]. However, in a study by Burdy (n=108) [759], in the Erlanger analysis (n=305) [547], and in the published meta-analysis by Gill [756] such a prognostic relevance was demonstrated.

After emergency surgery a significantly lower five-year survival rate was observed, absolute numbers being 29.8% versus 52.4% ($p < 0.001$). This difference was seen in stage I/II as well as in stage III [760]. Cancer-specific survival after five years was reduced from 74.6% to 60.9% with evidence of anemia, to 51.6% with evidence of stenosis, and to 46.5% with evidence of perforation ($p < 0.001$) [761]. In several studies, the number of examined lymph nodes was also found to be an independent prognostic factor [579, 762]. In 222 patients with CRC stage II a five-year survival rate of 49% was found for patients who had 6 or fewer lymph nodes examined compared to 68% for patients with 7 or more examined lymph nodes [762]. Le Voyer (INT-0089, n=3,411) examined patients in Dukes' stage B2 or C receiving adjuvant therapy with 5-FU, folinic acid (FA), and/or Levamisol. A prognostic relevance depending on the number of lymph nodes removed was found not only for N0-, but also for N1- and N2-status. Patients with tumors of N0-status showed the best overall survival if more than 20 lymph nodes were analyzed [579]. In a study of 3,592 cases of colorectal cancer an English group [763] found a significant survival benefit for each subgroup of patients depending on the number of lymph nodes identified (0-4 lymph nodes, 5-10 lymph nodes, > 10 lymph nodes). This effect was demonstrated for every tumor stage. In the multivariate analysis, the number of examined lymph nodes was shown to be an independent prognostic factor. An analysis of the SEER database [764] correlated the number of examined and/or removed lymph nodes with long-term survival.

In the multivariate analysis a reduction of cancer mortality by 20.6% was found if more than 15 lymph nodes were examined compared to patients for whom only 1-7 lymph nodes were examined. This result was independent of tumor stage and other patient or tumor characteristics. Even if study results are heterogeneous regarding the exact number of lymph nodes to be examined, it is the opinion of experts that at least 12 lymph nodes should be analyzed, regardless of the fact that this number cannot be achieved at all times. In this context, please also take note of the scheduled revision of the topic "Surgical treatment of colorectal cancer".

A study in which patients with stage II tumors and high-risk characteristics were represented in a small subgroup showed no benefit of adjuvant chemotherapy compared to sole operation [743]. In contrast, the MOSAIC study included a high-risk population consisting of patients with stage II tumors with T4-status, tumor perforation, ileus, blood vessel invasion, and/or less than 10 lymph nodes examined;

for this high-risk population postoperative adjuvant FOLFOX4 chemotherapy tended to result in an improvement of disease-free survival by 7.2% (HR 0.74; 95% CI: 0.52-1.06) in comparison to 5-FU/FA chemotherapy. However, possibly due to the small number of patients, a significant improvement of overall survival could not be shown [752]*.

8.5.	Recommendation	2008
Grade of Recommendation A	At this time, additional parameters (e.g. level of CEA-protein, level of differentiation of the tumor, 18q loss, isolated tumor cells in lymph nodes or in bone marrow, microsatellite status, DNA ploidy and TS/p53 expression, lymph and blood vessel invasion) should not be used as an indication for adjuvant chemotherapy.	
Level of Evidence 4	Strong consensus	

Background

It has been demonstrated in some, but not in all studies that certain parameters have a prognostic relevance for colorectal cancer. Yet, there are no prospective studies available on the benefit of adjuvant chemotherapy with the presence of one or more of these factors. In some studies level of differentiation was shown to be an independent prognostic factor in stage III [670, 765] as well as in stage II and III [745]. In contrast, an analysis by Hermanek demonstrated that the level of differentiation only has prognostic significance in a certain subgroup of stage III (any T N2 M0) [766].

In several studies, loss of 18q-allele was shown to have an independent prognostic role in stage II cancers [767-771].

Regardless of this, a study of patients with stage II colorectal cancer (n=70) came to the conclusion that 18q loss did not have any prognostic significance [772]. Moreover, it is unclear whether tumors showing 18q loss might respond poorer to chemotherapy.

In 10-15% of all sporadic colorectal cancer microsatellite instability (MSI) can be detected. Microsatellite instability is caused by defects of the DNA-mismatch-repair-(MMR)-system (MMR-system) caused by an inactivation of the MLH 1, MSH 2, MSH 6, and PMS 2 genes. The results of a study of 718 patients in Italy indicate that patients with MMR protein-negative tumors have a better long-term prognosis than patients with MMR protein-positive cancer. This positive prognostic effect was seen in stage II as well as stage III. Adjuvant chemotherapy led to an improvement of prognosis for patients who had MMR protein-positive tumors [773]. A study by Sinicrope demonstrated that microsatellite instability and DNA diploidy were also associated with a better prognosis [774].

A recently published meta-analysis clearly proved a negative prognostic significance of DNA aneuploidy. Patients with aneuploidic colorectal cancer had a significantly higher mortality rate five years after their operation than patients with diploid tumors. This applied to all subgroups analyzed and in particular for stage II [775].

Among 570 patients in stage II (55%) and stage III (45%) analyzed together in the IMPACT study, adjuvant chemotherapy led to an improvement in survival; with existence of higher-grade microsatellite instability, however, it resulted in a decreased

survival [776]. A study of 876 patients with stage III tumors revealed that microsatellite status had no prognostic relevance for the group that had not received adjuvant chemotherapy (5-year survival rate: 43 vs. 36%). However, for the group treated with chemotherapy a significantly better survival rate was demonstrated for patients with MSI-positive tumors [777]. None of these studies were designed in a prospective manner to investigate prognostic and predictive parameters.

8.1.6. Chemotherapy Protocols

8.1.6.1. Stage III

Oxaliplatin in Combination with 5-FU/Folinic Acid (FA)

8.6.	Recommendation	2008
Grade of Recommendation A	For adjuvant chemotherapy of colon cancer in stage III, a therapy containing Oxaliplatin should be given.	
Level of Evidence 1	Strong consensus	

FOLFOX (LV5FU2 + Oxaliplatin):

e.g. FOLFOX4: Folinic acid (FA) (200 mg/m² as a 2-hour infusion, day 1 and 2) plus 5-FU (400 mg/m² as a bolus, then 600 mg/m² as a 22-hour infusion; day 1 and 2) in combination with Oxaliplatin (85 mg/m² as a 2-hour infusion; day 1), repeated on day 15. 1 cycle lasts 2 weeks, 12 cycles total.

Background

Several randomized studies demonstrated a significant reduction of disease recurrence rate as well as total survival rate when a combination of 5-FU and folinic acid was administered [742, 743, 746].

The MOSAIC study (2,246 patients) compared adjuvant chemotherapy consisting of 5-FU/FA (LV5FU2) with a FOLFOX4 scheme (LV5FU2 + Oxaliplatin 85 mg/m²) every 2 weeks for 12 cycles. With regard to the total study population, the FOLFOX4 chemotherapy demonstrated a significant improvement in disease-free survival compared to LV5FU2 chemotherapy (73.3 vs. 67.4%, p=0.003) [752, 778]*. When focusing on stage III only, FOLFOX4 chemotherapy demonstrated a difference in disease-free survival of 7.5% (HR 0.78; 95% CI: 0.65-0.93; p=0.005). Overall survival was also significantly improved by FOLFOX4 chemotherapy in stage III reflected by an increase of 4.4% (p=0.029). Four years after therapy, occurrence of peripheral-sensory neuropathy was found at a rate of 12% (grade I), 2.8% (grade II), and 0.7% (grade III) [752, 778].

The NSABP study C-07 included 2,407 patients with stage II (28.6%) or stage III tumors who received either the Roswell-Park-scheme with a weekly administration of 5-FU/FA as a bolus (3 cycles, 8 weeks each) or the same 5-FU/FA scheme with Oxaliplatin 85

mg/m² in weeks 1, 3, and 5 in an eight-week schedule (FLOX scheme). Patients in the FLOX group showed 20% fewer recurrences (p<0.04).

Disease-free survival after four years was 73.2% for the FLOX group and 67.0% for the group of patients treated with 5-FU/FA [779]. When choosing between 5-FU and an Oxaliplatin-containing regimen, the side effects of the individual protocols should be considered. Due to the higher cumulative dose of Oxaliplatin in the MOSAIC study, a slightly lower rate of level 3-4 neuropathies was observed in the NSABP study (12.4 vs. 8.4%). However, level 3 and 4 diarrhea was observed more often in the bolus FLOX than in the infusional FOLFOX4 protocol (38 vs. 10.8%). In the NSABP study, five patients (0.4%) died within the first 60 days after beginning chemotherapy due to a chemotherapeutically-induced enteropathy [779]. While showing comparable effectiveness, the toxicity of the FLOX protocol is not acceptable in comparison to that of the FOLFOX4 protocol. Hence, the FLOX protocol should not be used in adjuvant situations. Internationally, at this time the modified FOLFOX6 scheme, which consists of a 46-hour continuous infusion of 5-FU after an initial 5-FU bolus on day 1, is preferred; this scheme represents the control arm of international studies. This way, the patient avoids the 5-FU bolus and changing of the pump on day 2 of therapy (dose: Oxaliplatin 85 mg/m² IV, folinic acid 400mg/m² + 5-FU 400 mg/m² bolus, then 2400 mg/m² continuously IV for 46 hours every 2 weeks). So far, for the combination of Capecitabine and Oxaliplatin in comparison to different bolus regimes of 5-FU/FA only toxicity data exist [780].

Adjuvant therapy with protocols including Irinotecan cannot be recommended on the basis of the available phase III study data [781-783].

Monotherapy with Fluoropyrimidines

8.7.	Recommendation	2008
Grade of Recommendation A	In case of contraindications against Oxaliplatin-containing regimes, a monotherapy with fluoropyrimidines should be given. Here oral fluoropyrimidines should be preferred over infusional schemes. Bolus regimes should no longer be used due to higher toxicity.	
Level of Evidence 1	Strong consensus	

Oral 5-FU Prodrugs:

e.g. Capecitabine 2x 1250 mg/m² body surface p.o. day 1-14, every 3 weeks for 8 cycles.

Background

1,987 patients with stage III colon cancer were randomized to either the Mayo Clinic scheme (983 patients) or were given Capecitabine as monotherapy (1004 patients) over a period of 24 weeks each (X-ACT study). The primary aim of the study was achieved by proving that Capecitabine was at least equivalent to the Mayo scheme with regard to disease-free survival. The analysis showed a trend towards an improved disease-free survival with Capecitabine (HR 0.87; 95% CI: 0,75-1,00; p=0.05).

Furthermore, overall survival also did not show a significant difference. However, again a trend towards superiority of Capecitabine was found (81.3 vs. 75.6%; $p=0.05$) [784].

Even though a randomized study with UFT + folinic acid versus 5-FU/FA [576] did not detect a difference in overall and disease-free survival and a Japanese meta-analysis of 3 studies even found a significant improvement of overall and disease-free survival [786], UFT is currently not recommended, because it has not been approved for adjuvant chemotherapy of colon cancer in Germany.

Infusional 5-FU/Folinic Acid:

- **LV5FU2**
e.g. folinic acid (FA) (200 mg/m² as 2-hour infusion, day 1 and 2) plus 5-FU (400 mg/m² as bolus, then 600 mg/m² as 22-hour infusion; day 1 and 2) 1 cycle lasts 2 weeks, 12 cycles total
- **5-FU/folinic acid scheme**
e.g. folinic acid (FA) (500 mg/m² as 1-2-hour infusion) plus 5-FU (2600 mg/m² as 24-hour infusion) 1x per week over a period of 6 weeks (day 1, 8, 15, 22, 29, 36). Repetition of therapy in week 9 (day 50). 2 cycles total.
- **Protracted venous 5-FU infusion (PVI)**
e.g. 5-FU as long-term infusion over 12 weeks total (300 mg/m²/day)

Background

Compared to bolus schemes, several therapeutic studies with different types of infusional application show no difference to giving 5-FU/FA as a bolus in relation to disease-free and overall survival. However, the noticeably better toxicity profile obviously speaks in favor of infusional application [787, 788]* [789, 790]. A comparison of a 12 week therapy with the "protracted venous infusion" (PVI) of 5-FU (300 mg/m²/day) versus a 6-months Mayo scheme showed no significant difference in recurrence-free survival (RFS) and in overall survival while demonstrating lower toxicity for PVI 5-FU [791]. Beginning of adjuvant chemotherapy within a period of 8 weeks after surgery showed a significant survival benefit [792]. Optimal duration of chemotherapy was 6 months [789, 793, 794].

8.1.6.2. Stage II

8.8.	Recommendation	2008
Grade of Recommendation 0	If patients with stage II tumors have adjuvant chemotherapy, fluoropyrimidines can be administered as monotherapy.	
Level of Evidence 1	Strong consensus	

Background

see Chapter 8.1.4 UICC-Stage II.

8.2. Perioperative Therapy of Rectal Cancer

8.2.1. Indications for Perioperative Radiotherapy or Radiochemotherapy

8.2.1.1. Stage I

8.9.	Recommendation	2008
Grade of Recommendation A	Perioperative therapy is not indicated for stage I tumors.	
Level of Evidence 5	Strong consensus	

Background

Cancer of the rectum in UICC stage I (T1/2 N0) show a low rate of local recurrence and distant metastasis when the treatment consists of a sole radical operation with en-bloc dissection of lymph nodes and total mesorectal excision (TME) for tumors in the lower (up to 6 cm from the anocutaneous line) and middle third of the rectum (> 6-12 cm from the anocutaneous line) or a partial mesorectal excision (PME) for tumors in the upper third of the rectum (> 12-16 cm from the anocutaneous line) [795]. For this reason, this tumor stage has been excluded from early American studies as well as from modern trials looking at the role of neoadjuvant radiochemotherapy [796].

Nevertheless, Swedish and Dutch studies on pre-operative short-term pre-radiation with 5x5 Gy versus an operation alone included tumor stage I. A subgroup analysis performed in a more recent Dutch study showed no significant difference in local recurrence rate between sole TME and additional radiotherapy for tumors in UICC stage I [795, 797]. The older Swedish study demonstrated a significant benefit of additional radiation for stage I, but here the concept of TME had not yet been implemented [798].

The relevance of radio(chemo)therapy before or after local excision of a T1 high-risk cancer (G3/4, L1, V1, diameter larger than 3 cm, R1 resection) is not verified [799]. A radical tumor excision including lymph node removal should be performed within 4 weeks for patients showing incomplete resection (R1) or risk-constellations (see above). For patients with T1 high-risk cancers localized in the lower part of the rectum or T2-N0-tumours in UICC stage I who refuse an extirpation, pre-operative radio(chemo)therapy followed by local excision can be an option [800]. This, however, is a procedure that has not been validated.

8.2.1.2. Stage II/III

8.10.	Recommendation	2008
Grade of Recommendation A	For UICC stages II and III neoadjuvant radiotherapy or radiochemotherapy is indicated. cT1/2 cancers with questionable lymph node involvement are an exception; here, primary surgery (if necessary followed by adjuvant radiochemotherapy in the presence of pN+) is a possible therapeutic option.	
Level of Evidence 1b	Strong consensus	

Background

Meta-analyses show an improved effectiveness of pre-operative radiation in comparison to postoperative radiation [801, 802]. An early randomized study on pre-versus postoperative sole radiation showed a significantly lower rate of local recurrences in the pre-operative arm [803]. A German study on adjuvant and neoadjuvant radiochemotherapy (RCT) of rectal cancer in UICC stages II and III (CAO/ARO/AIO-94) also demonstrated a significant reduction of the rate of local recurrences in the neoadjuvant arm [804]. The rate of postoperative complications was not increased for preoperative RCT in comparison to immediate operation; acute and chronic toxicity overall were significantly lower in the preoperative RCT-arm. For deep-seated tumors for which the surgeon had assessed an obligatory indication for extirpation prior to randomization, the rate of sphincter-retaining operation procedures was doubled by pretreatment in comparison to immediate surgery. A problem of every neoadjuvant therapy is the potential “overstaging” and, thus, the resulting “overtreatment” of patients for whom, falsely, a wall-penetrating (T3) or lymph node positive tumor (N+) has been diagnosed. Since sensitivity and specificity are limited especially for the evaluation of lymph node involvement, for T1/2 tumors showing questionable N+ status in imaging techniques the primary operation is considered an advisable option.

Several centers and study groups have stated – taking into account the chronic side effects associated with radiotherapy [805, 806] – further selection criteria for primary operations. These are T3 tumors infiltrating the mesorectal fatty tissue by not more than 5 mm as well as tumors showing a distance of more than 1 mm to the mesorectal line of resection (MRI diagnosis is obligatory) [807, 808]. These selection criteria have to be evaluated further in clinical trials.

8.11.	Recommendation	2008
Grade of Recommendation 0	The relevance of radiation therapy for cancers in the upper third of the rectum is considered controversial. Adjuvant therapy as for colon cancer or perioperative radio(chemo)therapy as for rectal cancer can be performed.	
Level of Evidence 3a	Strong consensus	

Background

The following arguments speak in favor of treating the upper third of the rectum (> 12-16 cm from the anocutaneous line, measured with a rigid rectoscope) in the same way as colon cancer:

- Data from American studies on adjuvant therapy which established radiochemotherapy for treatment of rectal cancer, were based exclusively on rectal tumors showing a margin of up to 12 cm in between the distal edge of the tumor and the anocutaneous line.
- The Dutch TME study showed no significant improvement of the local disease-recurrence rate by additional radiotherapy for tumors of the upper third of the rectum (here defined as: 10-15 cm from the anocutaneous line) [797].

The following arguments speak in favor of treating the upper third of the rectum in the same way as rectal cancer:

- The analysis of the Dutch TME study represents the results of an explorative subgroup analysis. Thus, the authors of the trial did not conclude that patients with tumors in the upper third of the rectum do not require radiotherapy.
- The British MRC-CR07 study, which so far has only been published in abstract form, has shown a significant advantage of general pre-operative short-term radiotherapy versus selective postoperative radiochemotherapy for all rectal thirds only if the circumferential resection margin was affected [809]*.
- A current subgroup analysis of the German CAO/ARO/AIO study 94 found no significant difference in the local disease-recurrence rate for tumors in the middle and upper third of the rectum.
- In contrast to the Dutch TME study, in Germany tumors in the upper third of the rectum are treated with a partial mesorectal excision (PME). This procedure is possibly associated with an increased rate of local disease-recurrence. The GAST-05 study led by Prof. Becker and Dr. Liersch will examine the question of whether tumors in the upper third of the rectum require a TME.

8.12.	Recommendation	2008
Grade of Recommendation A	In situations in which a downsizing of the tumor is attempted (T4 tumors, insufficient safety margin to the mesorectal fascia in thin-layer MRI - margin of 1 mm or less - or desired sphincter retention for tumors in the lower third), pre-operative radiochemotherapy should be preferred over short-term radiotherapy. For cT3 tumors or cN+ tumors for which downsizing is not attempted, pre-operative therapy can be conducted in form of either radiochemotherapy or short-term radiation.	
Level of Evidence 3b	Strong consensus	

Background

For pre-operative radiotherapy, two radiation schemes are principally available: Short-term radiation with 25 Gy in single doses of 5 Gy over five consecutive days directly followed by the operation and conventionally fractionated radiation up to a total

reference dose of 45 to 50.4 Gy in 25-28 fractions followed by the operation after 4-6 weeks. A randomized Polish study found that in comparison to short-term radiation conventionally fractionated neoadjuvant radiochemotherapy was associated with a significantly superior result in relation to downsizing and downstaging as well as with a significantly lower rate of R1 resections [810]. Nevertheless, the rate of sphincter-preserving surgical procedures (primary endpoint) as well as local control (secondary endpoint) showed no significant difference in both arms [811]. To maximize tumor shrinkage prior to operation, conventionally fractionated radiochemotherapy should be preferred over short-term radiation for those indications listed above. With the latter no relevant tumor shrinkage is achieved due to the short duration of therapy and the directly following surgery [812].

8.13.	Recommendation	2008
Grade of Recommendation A	Neoadjuvant radiochemotherapy should include 5-Fluorouracil monochemotherapy with or without folinic acid.	
Level of Evidence 1b	Strong consensus	

Background

The value of combining conventionally fractionated pre-operative RT with a 5-FU/folinic acid chemotherapy conducted simultaneously was analyzed in the EORTC-22921- as well as in the FFCD-9203-study (the EORTC-study additionally analyzed the relevance of adjuvant chemotherapy [813, 814]). The essential result of both studies was the significant reduction of local disease-recurrence rate by pre-operative radiochemotherapy in comparison to solitary radiotherapy. In the German CAO/ARO/AIO-94 study, 5-FU was administered in the first and fifth week of radiation with a dose of 1000 mg/m²/day as a 120-hour infusion. In the EORTC-22921 and the FFCD-9203 study, patients received 5-FU at a dose of 350 mg/m²/day and folinic acid at a dose of 20 mg/m²/day in the first and fifth week of radiation over a period of 5 days each.

Neoadjuvant radiochemotherapy including new substances and combinations (Capecitabine, Oxaliplatin, and Irinotecan) showed complete remission rates of up to 30% in several phase II studies [815]. The value of these combination therapies is currently being tested in phase III studies.

8.2.2. Adjuvant Therapy

8.2.2.1. Adjuvant Therapy After Primary Surgery (without neoadjuvant therapy)

8.14.	Recommendation	2008
Grade of Recommendation A	In stage I, adjuvant therapy is not indicated after a R0-resection.	
Level of Evidence 1b	Strong consensus	

Background

In all randomized studies of adjuvant therapy, patients with UICC stage I were excluded due to an altogether low rate of local disease-recurrence and distant metastases.

8.15.	Recommendation	2008
Grade of Recommendation A	Patients with UICC stage II and III, who have not undergone neoadjuvant radiochemotherapy or short-term radiotherapy, should receive adjuvant radiochemotherapy.	
Level of Evidence 1b	Strong consensus	

Background

The addition of chemotherapy to postoperative radiation reduced not only the rate of local disease-recurrence, but also improved overall survival in comparison to (conventional) operations only [816, 817]. Data on the use of adjuvant radiochemotherapy after pathologically confirmed adequate excision of the mesorectum and a distance of more than 1 mm between the tumor and the circumferential resection margin are not yet available. The rates of local disease-recurrence, even without an additional adjuvant therapy, are specified here with a total less than 10%. However, for subgroups such as tumors in the lower third of the rectum, they might be higher. Patients with tumors in UICC stage II and III should be included in randomized studies. This would clarify whether after quality-assured surgery certain subgroups of patients exist (e. g. pT3N0-tumours with little infiltration of the perirectal fatty tissue or pT1/2-N+-tumours), whose disease-recurrence risk is comparable to that of patients in UICC stage I and who, therefore, do not benefit from adjuvant radio- and chemotherapy [818, 819]. Concerning the question of tumor therapy in the upper third of the rectum see Chapter 8.2.1.2.

The British MRC-CR07 study, which until now has only been published as an abstract, has shown that a risk-adapted algorithm (postoperative radiochemotherapy only for

patients with positive circumferential resection margins after TME) is significantly inferior to a general pre-operative radiotherapy with 5x5 Gy for all cancers of the rectum with regard to local control and disease-free survival [809].

8.16.	Recommendation	2008
Grade of Recommendation B	After a R1-resection or intraoperative tumor tears, a postoperative radiochemotherapy should be conducted unless neoadjuvant radio(chemo)therapy has been performed previously.	
Level of Evidence 4	Strong consensus	

Background

R1-resections and intraoperative tumor tears are associated with a high risk of local disease-recurrence and justify a postoperative RCT. An unplanned subgroup analysis of the Dutch TME study showed no significant improvement in the rates of local disease-recurrence if a solitary postoperative radiotherapy with up to 50.4 Gy was conducted [820].

8.17.	Recommendation	2008
Grade of Recommendation B	Adjuvant therapy should begin 4-6 weeks after the operation.	
Level of Evidence 3a	Strong consensus	

8.18.	Recommendation	2008
Grade of Recommendation 0	Radiation therapy can take place at the same time as the first and second chemotherapy cycle or as the third and fourth cycle.	
Level of Evidence 2a	Strong consensus	

8.19.	Recommendation	2008
Grade of Recommendation A	Radiation therapy should be combined with 5-FU monochemotherapy.	
Level of Evidence 1b	Strong consensus	

Background for the last 3 recommendations:

According to the “NCI scheme”, adjuvant therapy begins 4-8 weeks after surgery by administration of two chemotherapy courses of 5-FU at a dose of 500 mg/m² body surface per day as a bolus application for five consecutive days (day 1 to 5 and 36 to 40). Radiotherapy begins on day 63. The pelvic area of lymphatic drainage should receive a total dose of 45 Gy by applying a single dose of 1.8 Gy five days a week over five weeks followed by a low-volume dose saturation of up to 50.4 Gy in the area showing the biggest risk of local disease-recurrence. During the first and fifth week of radiation, patients receive simultaneous 5-FU chemotherapy in the same dose and application form as for the two initial courses, however, only over a period of three days. After completion of the radiotherapy, two additional courses of chemotherapy should follow (day 134-138 and 169-173), however, only in a reduced dose of 450 mg 5-FU/m² body surface per day over a period of five days [514].

According to study results published by O’Connell et al., during the entire period of radiation a low-dose 5-FU long-term infusion can be given with a dose of 225 mg/m² body surface per day instead of applying 5-FU in bolus form [821]. The Intergroup-0144 study, however, has not confirmed superiority of 5-FU long-term infusional programs in comparison to biochemically (folinic acid/levamisole) modulated 5-FU bolus applications [822]. In a four-arm American intergroup-study (0114), modulation of 5-FU bolus applications with leukovorin and/or levamisole was not superior to the sole administration of a 5-FU bolus [823].

A further possible modification of the NCI scheme involves the time period between the operation and radiotherapy. Tumor and radiation biological reasons speak for a short time interval until the operation is performed. First analyses of a Korean study gave evidence that an early beginning of radiotherapy simultaneously to conducting the first 2 postoperative chemotherapy courses results in a significantly better disease-free survival rate [824]. This, however, was not confirmed by a long-term follow-up [825]*. The postoperative arm of the German CAO/ARO/AIO-94 study can be recommended as an alternative to the NCI scheme (start of RCT 4 weeks after surgery, 1000 mg/m²/day of 5-FU as a 120-hour long-term infusion in the first and fifth week of radiation, 4 courses of adjuvant chemotherapy, 5-FU bolus at a dose of 500 mg/m²/day over 5 days, 3 week break).

8.20.	Recommendation	2008
Grade of Recommendation A	The standard for adjuvant therapy of rectal cancer is a combined radiochemotherapy. There is no indication for sole (adjuvant) chemotherapy or radiotherapy for rectal cancer. An exception is only in case of contraindication against one or the other forms of therapy.	
Level of Evidence 1a	Strong consensus	

Background

Sole postoperative radiotherapy reduces the rate of local disease recurrence, but has – in contrast to the combination of radio- and chemotherapy – no influence on overall survival [826]. Contraindications for radiotherapy are prior radiations in the pelvis as, for instance, in prostate or cervical cancer treatment. Sole chemotherapy reduces the rate of disease recurrence. However, a combination with radiotherapy was shown to be superior to chemotherapy alone [514]. A recently published Japanese phase III study showed a survival benefit for patients in UICC stage III by applying a sole postoperative chemotherapy with Uracil-Tegafur after TME and selective lateral lymph node dissection [827].

8.2.2.2. Adjuvant Therapy After Neoadjuvant Radiotherapy or Radiochemotherapy

8.21.	Recommendation	2008
Grade of Recommendation A	In patients with rectal cancer who have undergone neoadjuvant radiochemotherapy adjuvant chemotherapy is indicated after surgery regardless of the postoperative tumor stage (thus, being indicated also with complete remission or for UICC stages I and II).	
Level of Evidence 1b	Strong consensus	

Background

The reason for this recommendation is that adjuvant chemotherapy was an obligatory component of the CAO/ARO/AIO-94 study as well as of the FFCD-9203 study after preoperative radiochemotherapy. The EORTC study (22921) randomized patients in a four-arm study and a “two-by-two factorial design” between the groups of postoperative chemotherapy and no postoperative chemotherapy after preoperative radiotherapy or radiochemotherapy. Postoperative chemotherapy did not lead to a statistically significant improvement of survival. Nonetheless, the survival benefit was 6% in absolute terms for progression-free survival and 4% for overall survival. This was attained by conducting a therapy with comparatively low toxicity [804].

Subgroup analyses revealed that adjuvant chemotherapy showed a significant survival benefit especially for those patient groups whose histopathological status was ypT0/1/2 after preoperative therapy [804]. In studies on preoperative short-term radiotherapy with 5x5 Gy, generally no adjuvant chemotherapy was applied. In a current Dutch phase III study patients with rectal cancers treated by 5x5 Gy radiation and surgery are being randomized to adjuvant chemotherapy with Capecitabine and observation [813, 828].

8.22.	Recommendation	2008
Grade of Recommendation B	Adjuvant chemotherapy should either be conducted as a 5-FU monotherapy or as a combination with 5-FU/folinic acid.	
Level of Evidence 1b	Strong consensus	

Background

In the CAO/ARO/AIO-94 study, 4 cycles of adjuvant chemotherapy with 5-FU at a dose of 500 mg/m² were administered as an IV bolus over 5 days every 4 weeks. In the EORTC-22921 and FFCD-9203 studies, patients received 4 cycles of adjuvant chemotherapy with 5-FU at a dose of 350 mg/m²/day and folinic acid at a dose of 20 mg/m²/day over 5 days each every 4 weeks.

9. Management of Patients with Metastases and in the Palliative Situation

The following part of the S3-guideline contains updated recommendations from 2007/2008 on tumor therapy of metastatic CRC, which particularly reflect study findings from 2003-2007. Primary resectable metastases will be discussed as well as the special situation of a secondary resectability in a therapy concept that is primarily palliative. Taking into account the availability of new biological substances, a detailed listing will be presented with comments on possible combinations depending on the goal of therapy and the individual situation of the patient. Dividing patients into subgroups should simplify decision-making.

Definition of Subgroups According to Clinical Situations/Therapy Goals:

1. Patients with primarily resectable liver- and/or pulmonary metastases
2. Patients with indication for intensified systemic therapy
 - 2.1. Patients with liver- and/or pulmonary metastases, potentially resectable after response to neoadjuvant therapy and clinically operable patients
 - 2.2. Patients with tumor-related symptoms, organ complications, or rapid progression
3. Patients with possibility for a less-intensive therapy
 - 3.1. Patients with multiple metastases without an option of surgical resection after downsizing of metastases, patients without tumor-related symptoms or organ complications and/or severe comorbidities

For synchronous as well as metachronous metastases of liver and/or lungs, complete surgical resection offers a chance of permanent cure for some patients. The evaluation of resectability is the first step in the decision-making process for the therapeutic management in patients with pulmonary and/or hepatic metastases (citation: NCCN 2007). In patients with R0-resectable metastases surgical resection should be the primary choice (see 9.1). Patients without a possibility for a primary surgical intervention should receive systemic chemotherapy. The choice of the chemotherapy regimen (crucially) depends upon the therapeutic goal. The therapeutic strategy for metastases in palliative situations should e.g. be determined in the context of interdisciplinary tumor boards. Patients have to be thoroughly informed about therapeutic options according to their individual needs and involved in decision-making. Aside from tumor therapy which will be illustrated in the following, securing adequate analgesic therapy and nutrition, need-based psycho-social and psycho-oncological care, as well as supportive therapy schemes are integral parts of a palliative therapy concept (see topic-specific guideline at www.awmf-leitlinien.de (available sources, as of 8/07: Guidelines of the German Society for Nutritional Medicine/ESPEN Guidelines on Enteral Nutrition (www.awmf-leitlinien.de, register no. 073/006e and 073/005e); guideline "tumour pain" registered by DIVS and DKG, currently under development, planned to be published in 2008)). Concerning therapy goals in palliative situations, the disease- and therapy-related quality of life as an easily measurable parameter is now more frequently used as a secondary endpoint in studies. The wish of patients to be informed about all relevant and available measures (tumor-specific, supportive, psycho-social, psycho-oncological therapy options) and

support offers (e. g. cancer counseling offices, self-help groups) has to be met. In addition, complementary/unconventional treatment methods should be discussed with the patient, also to avoid unfavorable interactions with other therapeutics.

9.1. Primarily Resectable Liver and/or Pulmonary Metastases

9.1.1. Primarily Resectable Pulmonary Metastases

9.1.	Recommendation	2008
Grade of Recommendation A	Resectable pulmonary metastases should be resected.	
Level of Evidence 3a	Strong consensus	

Background

The indication for primary resection of pulmonary metastases depends on their number and localization, the level of potential pulmonary pre-damage, and the expected residual volume after resection. The premise for this is that a R0 resection seems generally possible. Resections should be performed parenchyma-preserving, whereby a sufficient degree of radicality should be guaranteed. Patients should be treated in specialized centers by surgeons who have considerable experience in this matter [829]. In a currently published systematic review by Pfannschmidt et al., a majority of the studies consulted agreed only on preoperative CEA tests as an independent prognostic factor, while data on the prognostic relevance of the preoperative number of metastases are inconsistent. However, they show a trend towards a survival benefit for patients with single metastasis (Table 9). Further possible influencing factors, such as the disease-free interval or the initial tumor stage have not been confirmed with regard to their prognostic significance [830-833].

Table 9: Five-Year Overall Survival After R0 Resection of Pulmonary Metastases (according to Pfannschmidt et al. [833]).

Reference	N	5-year survival rate	Mean follow-up (mo)	Level of evidence
Lee 2007	59	50.3%	34.7	III
Pfannschmidt 2003	167	32.4%	58.6	III
Saito 2002	165	39.6%	56.5	III

9.1.2. Primarily Resectable Liver Metastases

Definition [834]: Resectable liver metastases are present if

- a non-resectable extra-hepatic tumor manifestation has been ruled out
- less than 70% of the parenchyma are affected
- less than 3 liver veins and less than 7 segments are involved
- no liver insufficiency or Child B or C cirrhosis is present
- no serious comorbidities are present

9.2.	Recommendation	2008
Grade of Recommendation A	R0-resectable metastases limited to the liver should be resected.	
Level of Evidence 3b	Strong consensus	

Background

The five-year survival rate after resection of colorectal liver metastases ranges from 25 to 40% [835-838].

Table 10: Survival Rate After Resection of Colorectal Metastases

Reference	N	Surgical mortality	5-year-survival rate surgery	5-year-survival rate no surgery	p=	Level of evidence
Nordlinger 1996 [†]	1568	2.3%	28%	---	---	III
Fong 1997 ^{††}	456	2.8%	38%	---	---	III
Scheele 2001 ^{†††}	516	83%	38%	---	---	III
Kato 2003 ^{††††}	763 (585 OP vs 178 w/o surgery)	n.a.	39.2%	3.4%	<0.001	III

[†] adjuvant therapy in 35 % of cases

^{††} adjuvant therapy in 128 patients

^{†††} 43 patients with different regimens of chemotherapy prior to resection of metastases, 26 patients received adjuvant treatment

^{††††} adjuvant therapies among 54.5% of all cases without significant difference in the survival rate

9.3.	Consensus-based Recommendation	2008
GCP	The resectability of metastases should be evaluated by a surgeon with considerable experience in the surgery of liver metastases.	
	Strong consensus	

Background

The prognosis can be estimated preoperatively based on easily obtainable clinical criteria according to the so-called FONG score (Table 11). This preoperative prognosis score from the Memorial Sloan Kettering Cancer Center in New York was calculated based on a large number of patients and is internationally recognized.

Prognostically unfavorable criteria [839]:

- • nodal positive primary tumor
- • disease-free interval <12 months
- • size of metastases > 5 cm
- • number of metastases > 1
- • preoperative CEA > 200 ng/dl

Patients with a score not greater than a maximum of 2 points have a good chance of long-term survival after primary liver resection:

Table 11: Survival After Resection of Colorectal Liver Metastases (according to Fong et al. Annals of Surgery, 1999) [839]

Score	5-year survival
0	57%
1	57%
2	47%
3	16%
4	8%
5	0%

9.1.2.1. Preoperative Imaging

9.4.	Recommendation	2013
Grade of Recommendation 0	A PET-CT can be performed in patients with resectable CRC liver metastases.	
Level of Evidence 2b	Consensus	

9.5.	Recommendation	2013
Grade of Recommendation B	A PET-CT shall not be performed within 4 weeks after systemic chemotherapy or antibody therapy, because this significantly reduces its sensitivity.	
Level of Evidence 2b	Strong consensus	

Background

A preliminary report on the benefit of PET/PET-CT for relapse diagnostics and relapse staging in CRC patients was presented by the IQWiG (Institute for Quality and Economics in Health Care) in August 2011 [552]. Aside from the evaluation of the patient relevant benefit, a systematic evaluation of the prognostic and diagnostic quality of the PET/PET-CT was done. The literature search included a period up to August 2009. More recent publications were mentioned in the text. The guideline recommendations given here are based on the evidence evaluation of the IQWiG report. The Grade of Recommendation was developed under additional inclusion of the clinical evaluation of the procedure. Furthermore, in a more recent literature search from August 2009 – December 2011, a RCT in abstract form [548], 2 systematic reviews [553];[526], a prospective case control study [549], and a retrospective case series [551] were identified. They were also included in the evaluation (for details see evidence report). The previous recommendation of Grade B from the last guideline update in 2008 (9.1.2.1) for PET/PET-CT examinations before resection of colorectal liver metastases with a FONG score > 2 was changed, because the study that led to this recommendation has still not been published as a full article [554].

So far, a RCT as a full publication and 1 RCT in abstract form have been published on the issue of patient-relevant benefit of PET/PET-CT. For patients before resection of CRC liver metastases, a supporting PET/PET-CT has no effect on disease-free or total survival of the patient. Whether supplemental PET-CT examinations help to avoid futile laparotomies as clinical endpoints is not completely resolved. The consensus recommendation here is especially supported by the full published study by Ruers [547] which has, however, methodological weaknesses. In this study 150 patients with colorectal liver metastases who were planned to undergo resections were randomized to 2 study arms (CT or CT plus 18F-FDG PET). The primary study objective was

reported in the publication as rate of futile laparotomies that were avoided as a result of the PET examination. This endpoint is relevant for the patient. The study reported no significant difference in survival in the PET-arm. However, a significantly reduced number of "futile laparotomies" was seen in this study arm. The rate of futile laparotomies was 45% in the control arm and 28% in the PET-arm. This corresponded to a risk reduction of 38% with a very large confidence interval (95% CI, 4-60%, $p=0.042$). The authors concluded that in one in six patients a laparotomy can be avoided with an additional PET before liver metastasis resection. The secondary endpoint DFS and OS were as follows: DFS: 35.5% versus 29.8 % (p -value = 0.194); OS: 61.3% versus 65.8 % (p -value = 0.378). The study's evidence level was downgraded by the consensus conference (see also IQWiG-report, degrading from Ib to II), because the primary study endpoints mentioned in the study plan were different from the ones in the publication (original endpoint: rate of patients who were disease-free after 9 months).

Another multicenter randomized study that has so far been published as an abstract at the ASCO annual meeting 2011 also investigated this issue [548]. Endpoint of this study was the change in patient management after PET-diagnostics (no operation because of additional results or expansion of surgery compared to the intention without/before PET-diagnostics) in a 2:1 randomization design in CRC patients who seemed suitable for liver resection for liver metastases. 404 patients were randomized (270 patients in the PET/CT-arm, 134 patients without PET). There was no difference in management change between both study arms. Thus, the endpoint was not reached. However, as far as could be deduced from the presentation, about 70% of patients had chemotherapy before PET diagnostics. This significantly reduces the sensitivity of the examination method (see below). It should also be critically noted that the endpoint "change in patient management" in contrast to "reduction of futile operations" was not considered patient relevant.

Several studies point out that the sensitivity of PETs is significantly reduced if they are done within 4 weeks after chemotherapy (evidence level IIa-III). Therefore, a PET is not recommended during this time, because too many false negative cases occur. The issue was not evaluated by the IQWiG report. A larger case control study without randomization was published in 2010 which investigated the sensitivity of PET after chemotherapy [549]. The study found a negative predictive value of only 13.3% and a positive predictive value of 94% with a specificity of 22.2% at an accuracy of 85% if the PET was done within 4 weeks after the end of chemotherapy. The authors concluded that diagnostic PET examinations shortly after chemotherapy administration are not useful. A retrospective study from Australia evaluated PET-results of patients with liver metastases before liver resection [555]. This study was small and heterogeneous. 21 patients were systematically treated before surgery, 53 were not. Correct results were determined using PET for 29% of patients after chemotherapy and 53% without chemotherapy. Underestimated results were observed in 52% in the chemotherapy group and only 34% in the group without chemotherapy. This study underscores that PET examinations shortly after chemotherapy are not useful. Another prospective trial [550] and a retrospective study [551] reached similar results.

9.1.2.2. Perioperative Therapy of Primarily Resectable Liver Metastases

9.1.2.2.1. Neoadjuvant Therapy of Resectable Liver Metastases

9.6.	Recommendation	2008
Grade of Recommendation 0	Neoadjuvant systemic therapy of resectable liver metastases can be considered in founded exceptional cases.	
Level of Evidence 3	Strong consensus	

Background

Neoadjuvant therapy is intended to improve the results of a curatively intended surgical intervention and is, therefore, linked to the realistic option of subsequent R0 resection. To compare neoadjuvant (preoperative) or combined (perioperative) versus adjuvant (postoperative) strategy with regard to the target dimension of R0 resectability and long-term survival with primarily resectable liver metastases, there are no prospective, randomized studies available. In a currently published prospective randomized phase III study of the EORTC, the role of perioperative therapy with liver metastases primarily classified as R0 resectable was investigated. In relation to progression-free survival, the intention-to-treat analysis revealed no significant benefit for perioperative therapy with FOLFOX4 in comparison to a sole operation. The difference in progression-free 3-year-survival was 7.3% (28.1 to 35.4%) and just missed the level of significance (HR: 0.79; [0.62-1.02]; p=0.058) (see Table 12). Per protocol analysis, which only considered patients who were actually resected, showed that a significant prolongation of progression-free survival can be achieved with perioperative therapy (33.2 vs. 42.4%; HR: 0.73; 0.55-0.97; p=0.025). The possible benefit of perioperative therapy is in contrast to the significantly increased perioperative morbidity in the chemotherapy arm (25% vs. 16% with sole operation, p=0.04), whereas overall mortality showed no difference [841]. The decision for neoadjuvant therapy of liver metastasis should take into account that - aside from increased perioperative morbidity - perioperative chemotherapy might reduce therapeutic options for recurrent disease. In addition, there is a certain risk that the optimal time window for a resection might be missed, and that all combination protocols cause a significant amount of damage to healthy liver tissue (see section 9.2.1.2.2). A potential advantage is the possibility of an early treatment of micrometastases and the evaluation of response to chemotherapy, which can be helpful in postoperative planning and estimating prognosis [842]. The guideline of the US-American National Comprehensive Cancer Network (NCCN), therefore, recommends that for patients with synchronous, resectable metastases, aside from the sole adjuvant strategy, neoadjuvant therapy (plus adjuvant therapy postoperatively) should be considered as an option. For metachronous metastases, surgery is the primary recommendation if the patient has received chemotherapy within the past 12 months (National Comprehensive Cancer Network. Clinical Guidelines in Oncology: Colon Cancer V2.2007. Available at: "http://www.nccn.org" access on June 4, 2007).

Taking into consideration the potential risks of neoadjuvant therapy, the restrictive recommendation and the striving for a timely resection appears to be justified.

The concept of perioperative chemotherapy for primarily resectable liver metastases is currently being evaluated in on-going studies with chemotherapy regimens of different intensities.

Table 12: Prospective Studies on Neoadjuvant Therapy of Patients with Resectable Liver Metastases.

Reference	N	Therapy regimen	Overall response rate (ORR)	Resection rate (R0)	Long-term survival	Level of evidence
Lorenz 2003 [843] †	42	FOLFOX	47.7%	80.9%	---	IIb - III
Wein 2003 [844] ††	20	5FU /FS /OX	100%	80%	2-y. tumor-related survival 80%	IV
Gruenberger 2008 [845]	56	XELOX + Bevacizumab	73%	93%	---	IIb
Nordlinger 2008 [841] †††	364	FOLFOX 4 pre- und postop. vs OP alone	43%	83.0% vs 84%	3-y. PFS 35.4% vs 28.1% HR:0.79(0.62-1.02) p=0.058	IIb

†Phase I/II-study, target by definition not proof of effectiveness. Nearly exclusively patients with synchronous metastases. Comparison with standard questionable, retrospective case number legitimization. Pilot phase not randomized (n=6 vs. 6), afterwards randomized (n=16 vs. 14).

††Date of analysis 12 months after closing of recruitment, 2 primary endpoints; 2-year tumor-related survival and response rate. The first endpoint was only reached by 10 patients, of whom 6 are alive; phase II study, generalizability is questionable (monocentric, very high response rate), median follow-up to date of evaluation 23 months (12-38).

†††No data on R-status after resection, 151 vs. 152 patients potentially curatively resected.

9.1.2.2.2. Adjuvant Therapy of Resectable Liver Metastases

9.7.	Recommendation	2008
Grade of Recommendation 0	After R0 resection of synchronous or metachronous liver metastases, adjuvant chemotherapy can be considered.	
Level of Evidence 2	Strong consensus	

Background

Despite R0 resection of liver metastases in the long term only approximately 30% of patients remain free of disease-recurrence. The rationale for systemic adjuvant therapy after resection of metastases is based on indirect evidence derived from studies which have demonstrated the effectiveness of adjuvant chemotherapy in stage III CRC. The

available data for systemic adjuvant therapy after resection of metastases are, however, limited; there are no placebo-controlled/blinded studies available (also not for neoadjuvant settings).

In two randomized studies and the following pooled analysis of the collected data the effectiveness of a 5-FU monotherapy was examined [846, 847]* [848] (see Table 13). Neither study accomplished sufficient recruitment to demonstrate a significant effect of chemotherapy on survival, and both studies were terminated early. An interim analysis of the study results showed a trend towards improvement of progression-free interval in one study and a borderline significant improvement of progression-free survival in the second study. The overall survival was not influenced by adjuvant therapy. It should be noted that both studies contained a chemotherapy regimen of low effectiveness (5-FU bolus application). A current study which compared a more effective protocol with sole operation was terminated early due to inadequate recruitment (ADHOC study). In the meantime, the widespread use of adjuvant therapy after metastasis resection, particularly in the US, means that the question whether a systemic chemotherapy offers a benefit for patients compared to surgery only can likely no longer be definitely answered. Evidence that supports the decision for systemic adjuvant therapy is given in the EORTC study which was cited in the previous chapter and from a retrospective analysis of the registry data of two reference centers (Memorial Sloan-Kettering Cancer Centre and the Royal Infirmary of Edinburgh). Over a period of 8 years (1991-1998) all patients who received a liver resection due to colorectal cancer metastases were registered there (n=792). A benefit for 5-FU-based adjuvant chemotherapy was found in comparison to surgery only with regard to overall survival (n=274 vs. 518; median survival 47 versus 36 months, 5-year survival rate 37% vs. 31%; p=0.007, respectively) [849]. The guidelines of the US-American National Comprehensive Cancer Network and the national guidelines of Australia recommend adjuvant chemotherapy after resection of metastases while pointing out the limited evidence resulting from the limited data available [National Comprehensive Cancer Network. Clinical Guidelines in Oncology: Colon Cancer V2.2007. Available at: www.nccn.org Accessed on June 4, 2007; Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. The Cancer Council Australia and Australian Cancer Network, Sydney 2005. Available at www.cancer.org.au Accessed on June 4, 2007].

Table 13: Prospective Studies on Adjuvant Therapy After R0 Resection of Colorectal Liver Metastases.

Reference	N	Therapy regimen	Survival	Median follow-up	Level of evidence
Portier 2006	173	5-FU/FS vs observation	DFS: 33.5 vs 26.7%(p=0.028) OS: 51 vs 41%(p=0.13)	87 mo	Ila
Langer 2002 *	129	5-FU/FS vs observation	DFS: 39 vs 20 mo(p=0.35)OS: 53 vs 43 mo(p=0.39)	n.a.	---
Mitry 2006 *†	302	5-FU/FS vs observation	PFS 2.2 vs 1.55 years(p=0.059)OS 5.09 vs 3.91 years(p=0.125)	n.a.	---
Figueras 2001 [850]	235	especially 5-FU/FS	DFS: 34 mo 5 y. OS 36%	20 mo	III
Parks 2007††	792	5-FU based vs observation	Improved survival with adjuvant CTX(p=0.007, log rank)	1991 - 1998	IIIb

* Only available in abstract form; hence limited ability to judge the evidence.

† The summary in Mitry et al. is a pooled analysis of the studies by Langer and Portier.

†† Limited validity of registry data.

Clinical Groups II and III – Indications for Systemic Chemotherapy – General Recommendations

9.8.	Recommendation	2008
Grade of Recommendation A	Active systemic tumor therapy is generally indicated, because a survival benefit has been proven.	
Level of Evidence 1a	Strong consensus	

Background

At the beginning of the 1990's, two prospective randomized studies with a total of 223 patients demonstrated a survival benefit of systemic chemotherapy compared to best supportive care (BSC). A prospective randomized comparison between best supportive care and chemotherapy with Cisplatin and bolus application of 5-FU/FA including 40 patients found a median overall survival of 5 months versus 11 months with the administration of chemotherapy (p=0.006) [851]. In the studies of the NGTACG the median survival rate was 14 versus 9 months in the control group (log rank p=0.13) [852].

9.9.	Recommendation	2008
Grade of Recommendation A	If an indication for tumor therapy with drugs is given, treatment should be initiated at the time of diagnosis of metastases independent of metastases-related symptoms. When determining indications, potential contraindications should be considered. Age per se is not a contraindication.	
Level of Evidence 1a	Strong consensus	

Background

Even in situations not having a primarily curative intent it should be generally checked whether after medicinal pre-treatment a curative resection may be achieved. Therefore, chemotherapy is indicated independent of the presence of metastases-related symptoms. The choice of chemotherapy depends on the therapeutic aim, i.e. whether a secondary resectability seems achievable or a merely palliative/symptom-oriented therapy is intended. For patients with marginally resectable metastases, therapy should induce a high rate of remissions (the most effective available combination therapy). For patients with tumor-related symptoms, organ complications, or rapid progression should also be offered a highly effective therapy (see group 2). Patients without tumor-related symptoms or organ complications and/or with severe comorbidities (see group 3) can also be treated with a less intensive therapy. Monotherapy, e.g. with fluoropyrimidines, represents a possible option in this treatment situation. The primary aim of therapy is the prolongation of progression-free and overall survival with the best-possible quality of life.

Most patients are older than 65 years when initially diagnosed. In spite of this fact, until a few years ago only few patients over the age of 70 years were recruited into randomized studies. Several studies of the past few years have dealt with the question of tumor therapy for older patients with CRC.

It was shown for the FOLFOX regimen that older study patients benefited from an intensified therapy in the same way as younger patients with regard to remission rate and progression-free as well as overall survival. However, especially hemotoxicity was slightly increased (grade 3 neutropenia 43 vs. 49% $p=0.04$, thrombopenia 2 vs. 5%, $p=0.04$) [740]. Mattioli et al. showed a high efficacy for a bifractionated FOLFOX protocol with a patient group average age 75 years [853]. A phase II study by Feliu et al. analyzed the feasibility of CAPOX or Capecitabine mono as first-line therapy for patients who were older than 70 years [854]. A Spanish group treated a selection of patients older than 72 years with FOLFIRI [855]. An exploratory subgroup analysis of the BICC-C study on patients who were older than 65 years showed no difference in effectiveness and toxicity of an Irinotecan-containing protocol in comparison with younger patients [856]*. An analysis of randomized studies published in 2008 showed an improvement of response-rates with an Irinotecan-based chemotherapy for younger as well as for older patients (>70 years) (46.6 vs. 29.0%, $p<.0001$; and 50.5 vs. 30.3%, $p<.0001$). The same applied for PFS (HR, 0.77; 95% CI, 0.70-0.85; $p<0.0001$ for younger patients respectively HR 0.75; 95% CI, 0.61-0.90; $p=.0026$ for patients >70 years) and, with limitations, for overall survival, where a trend towards an improvement was observed for the older patients (HR, 0.83; 95% CI, 0.75-0.92; $p=0.0003$ und HR 0.87; 95% CI, 0.72-1.05; $p=0.15$ for patients > 70 years) [857]. For patients older than

80 years, the amount of data available is still scarce. Thus, older patients as well should receive chemotherapy when presenting with relevant indications. When choosing the appropriate therapy the change of organ functions with age, any possible comorbidities, as well as age-related limitations of functional status should be considered.

For tumor-specific palliative treatment with inoperable metastases surgical, interventional (endoscopic, radiologic), and radiotherapeutic methods are available in addition to chemotherapy. Their fields of application are discussed in greater detail in the corresponding chapters.

9.10.	Recommendation	2008
Grade of Recommendation 0	If systemic therapy (e. g. inoperable liver/pulmonary filiae) is indicated, the primary tumor does not have to be resected. Exceptions can be symptomatic tumor stenoses and/or Hb-relevant bleeding.	
Level of Evidence 4	Strong consensus	

9.11.	Recommendation	2008
Grade of Recommendation A	In general, patients should have access to all available drugs during the course of their therapy.	
Level of Evidence 5		

9.2. Patients with an Indication for Intensified Systemic Therapy

9.2.1. Patients with Potentially Resectable Metastases

Definition: Defined by clinical criteria, patients in this group have liver and/or pulmonary metastases which are initially classified as irresectable or marginally resectable, and become resectable after response to neoadjuvant therapy.

9.2.1.1. Management of Isolated Primarily Irresectable Pulmonary Metastases

9.12.	Recommendation	2008
Grade of Recommendation A	For primarily irresectable pulmonary metastases, systemic chemotherapy should be conducted.	
Level of Evidence 4	Strong consensus	

9.2.1.2. Management of Isolated Primarily Irresectable Liver Metastases

9.2.1.2.1. Systemic Neoadjuvant Therapy

9.13.	Recommendation	2008
Grade of Recommendation A	For primarily irresectable liver metastases, systemic therapy should be initiated. It is important to perform regular evaluations of a possible secondary resectability after the induction of remission. If the goal of therapy is the induction of remission with secondary resection of metastases, then the most effective available systemic combination therapy should primarily be used (intensified therapy).	
Level of Evidence 4	Strong consensus	

Background

About 35% of all patients with colorectal cancer present with metastases at diagnosis. 15-20% of the synchronous and metachronous metastases can be resected with curative intent. In most cases, however, the metastases are classified as primarily irresectable for various reasons. The possibility to achieve a downsizing of primarily irresectable liver metastases and, thus, a secondary resectability and potential cure with systemic chemotherapy was evaluated in several studies as primary/secondary endpoint and in the context of exploratory subgroup analyses of studies with primarily palliative intention (Table 14).

A retrospective analysis by Giacchetti and Bismuth showed a five-year overall-survival of about 50% after neoadjuvant chemotherapy and subsequent resection. This is comparable to the long-term results after primary resection of liver metastases of

patients with a FONG score of less than 3 [858]. For some chemotherapy regimens particularly good response and resection rates have been described. Falcone achieved a significant improvement of response rates (34 vs. 60%, $p < 0.001$) and a R0 resection rate (6 vs. 15%, $p = 0.033$) with FOLFOXIRI compared to FOLFIRI. This benefit was even more pronounced in patients with isolated liver metastases (12 vs. 36%, $p = 0.017$) [859].

The combination of FOLFIRI and the EGFR antibody Cetuximab achieved an ORR of 46.9% (vs. 38.7% for FOLFIRI alone) in a phase III design. The proportion of R0 resections as a secondary endpoint was increased in the experimental arm (4.3% vs. 1.5%) [860]*. The greatest benefit was achieved for patients who had a wild type k-ras expressing tumor. In this retrospective analysis, a statistically significant difference was seen for PFS in patients with k-ras wild type-expressing tumors who were treated with Cetuximab ($p = 0.0167$; HR: 0.68 [95% CI: 0.051-0.934]), but response rates also were clearly improved (59.3% [Cetuximab + FOLFIRI] vs. 43.2% [FOLFIRI], $p = 0.0025$) [861]*.

A significant correlation between the remission rate and resection rate was found for patients with isolated liver metastases ($r = 0.96$, $p = 0.002$). Furthermore, in large studies with primarily palliative intent and an unselected collective of patients, the response rate also correlated with the resection rate ($r = 0.74$, $p < 0.001$). When interpreting study data one should take into consideration the patient selection and that between individual studies the definition of resectability was often not uniform [862].

Table 14: Response Rates and Survival of Patients After Achieving Secondary Resectability (modified according to [862])

Reference	N	Therapy regimen	Response-rate (%)	R0-Resection-rate (%)	Long-term survival of pat. w/ resec.	Level of evidence
Falcone 2007 †	244	FOLFIRI vs. FOLFOXIRI	34 vs 60 ($p < 0.0001$)	6 vs 15 ($p = 0.033$)	----	Ib
Van Cutsem 2007 (CRYSTAL) ††	1198	FOLFIRI vs. FOLFIRI + Cetuximab	38.7 vs 46.9 ($p = 0.0038$)	1.5 vs 4.3 ($p = 0.0034$)	----	Ib
Adam 2001 †††	701	Oxa +FU/FS (chron)	pCR: 6.3	13.5	5 -J surv: 35%	IIb
Giacchetti 2006 ††††	564	FOLFOX2 vs. LOHP 5FU FS chron.	44 vs 42	R0: 12.4 vs 13.1 pCR: 1.1 vs 2.8	----	IV
Tournigand 2006 ††††	620	FOLFOX 4 vs. FOLFOX 7 + maintenance	58.5 vs 59.2 n.s.	11.3 vs 9.4	38.9 vs 43 mo ($p = 0.93$)	IV
Souglakos	283	FOLFOXIRI vs	43 vs 33.6	8.8 vs 3.4	----	IV

Reference	N	Therapy regimen	Response-rate (%)	R0-Resection-rate (%)	Long-term survival of pat. w/ resec.	Level of evidence
2006 †††† [863]		FOLFIRI	(p=0.168)			
Saltz 2008 †††† [864]	1401	XELOX/FOLF OX 4+ Beva vs. XELOX/FOLF OX 4 + Placebo	38 vs 38 (p=0.99)	n.a.	21.3 vs 19.9 mo (p=0.077)	IV
†	Resection rate secondary endpoint, FOLFOXIRI as continuous infusion, higher dose chemotherapy in FOLFOXIRI - arm as in Souglakos et al.					
††	Resection rate secondary endpoint, benefit only treatment of patients with k-ras wild type tumors					
†††	Prospective observational study, resection rate primary endpoint, potentially curative operated patients, R0 status not reported					
††††	Resection rate as a result of explorative subgroup analyses					

9.2.1.2.2. Chemotherapy Consequences on the Healthy Liver Tissue and Metastasis Localization

9.14.	Recommendation	2008
Grade of Recommendation B	The hepatotoxicity of the protocols listed above such as "blue liver"/chemotherapy-associated steatohepatitis (CASH) should be considered in differential therapeutic decision-making and planning of surgery.	
Level of Evidence 3	Strong consensus	

Background

In the past few years, several groups have dealt with the question to what extent preoperative chemotherapy influences the risk of complications in partial liver resection. Aloia et al. examined a cohort of 303 patients for whom a partial liver resection was carried out due to colorectal liver metastases. 92 patients were randomly chosen, 75 had received preoperative chemotherapy, 17 patients had not. Those who had received preoperative chemotherapy required intraoperative transfusions significantly more often. The predominant histopathological changes in healthy liver tissue were vascular lesions in terms of sinusoidal obstruction syndrome (SOS) and – when appearing in a severe form – correlated positively with the need of intraoperative transfusions. Postoperative morbidity depended on the duration of the preoperative chemotherapy [865]. In another retrospective study, 61% of the examined patients received preoperative chemotherapy. Therapy with Oxaliplatin was more frequently associated with sinusoidal obstruction in healthy liver tissue without noteworthy mortality (1.6%). In contrast, Irinotecan-containing therapy was associated with steatohepatitis. Patients with steatohepatitis had a higher 90-day mortality than those without steatohepatitis (14.7% vs. 1.6%) [866].

9.15.	Recommendation	2008
Grade of Recommendation B	An intraoperative exploration of the liver should be performed based on the localization of metastases in initial imaging. If possible, a surgical resection of all previously known lesions should be performed.	
Level of Evidence 3b	Strong consensus	

Background

Benoist et al. showed despite complete remission verified radiologically by CT according to RECIST criteria that in 83% of the cases residual tumor tissue was still found either macroscopically or microscopically or a disease-recurrence was seen in-situ within one year. 38 patients with a total of 66 liver metastases were included. Hence, the resection of metastases should be performed as early as possible if there is a possible option of a R0 resection, and should be guided by the primary borders of the lesions prior to therapy [867].

9.2.1.2.3. Local ablative therapies for liver metastases Radio-Frequency-Ablation (RFA)

9.16.	Recommendation	2013
Grade of Recommendation 0	A RFA can be performed if non-resectable liver metastases are present or if the patient's health status does not allow a resection, especially following previous liver resection.	
Level of Evidence 3a	De Novo: [586-588]	
	Strong consensus	

Background

The current level of evidence on the safety and efficacy of radio-frequency-ablation for colorectal liver metastases is sufficient to recommend this method for patients who either have non-resectable liver metastases, whose health status does not allow a resection, or who have previously had a liver resection [586].

A RFA can also be performed primarily in combination with surgical resection.

Recent studies indicate that results with RFA for solitary liver metastases <3cm are as good as with resections [587, 588]. However, present data on this subject are contradictory and comparative controlled randomized studies still do not exist.

Selective Internal Radiation Therapy (SIRT)

9.17.	Recommendation	2013
Grade of Recommendation B	SIRT for the treatment of disseminated CRC liver metastases should only be performed in patients who have no other treatment option, and then only as part of a clinical study.	
Level of Evidence 2a	De Novo: [589, 590]	
	Consensus	

Background

Patients with absent or limited extrahepatic metastazation, and without options of further systemic chemotherapies show a prolonged median survival and longer interval to progression of liver metastases in individual studies using SIRT (also called radioembolization). There are too few data for a conclusive evaluation especially on survival and quality of life. Therefore, patients who are eligible for SIRT should only be treated as part of clinical studies [589, 590].

Laser-Induced Interstitial Thermotherapy (LITT)

9.18.	Recommendation	2013
Grade of Recommendation B	A LITT for the treatment of CRC liver metastases should only be performed as part of a clinical trial.	
Level of Evidence 4	De Novo: [591, 592]	
	Strong consensus	

Background

The interstitial laser thermo-ablation was a safe and effective method in individual case-series for patients with inoperable CRC liver metastases [591, 592]. Data comparing it to percutaneous radiofrequency ablation do not exist. The data are not sufficient for conclusive evaluation especially of survival and quality of life. Therefore, patients who are eligible for LITT should only be treated as part of clinical trials.

9.2.2. Patients with an Indication for Intensified Palliative Therapy

The management of this patient group matches for the most part the management described in section 9.2.1.

9.19.	Recommendation	2008
Grade of Recommendation B	Patients with tumor-related symptoms, organ complications, or rapid progression should receive the most effective combination therapy while taking the general condition of the patient into account (intensified therapy).	
Level of Evidence 5	Strong consensus	

9.3. Patients with the Option for Less Intensive Therapy

Patients with multiple metastases without option for resection after regression of metastases, without tumor-related symptoms or organ complications and/or severe comorbidities.

The primary goal of therapy in this group of patients is not the induction of remission but rather lengthening progression-free and overall survival with low toxicity and good quality of life.

9.20.	Recommendation	2008
Grade of Recommendation 0	Patients with multiple metastases without option for resection after regression of metastases, without tumor-related symptoms or organ complications, and/or severe comorbidities can receive a monotherapy as first-line therapy.	
Level of Evidence 1	Strong consensus	

Background

Several studies have dealt with the question of optimal sequence of the different chemotherapy protocols in the treatment of colorectal cancer. The CAIRO study investigated whether a sequential monotherapy is equivalent to an initial combination therapy in relation to overall survival.

820 patients were randomized to one of the two therapy arms and were either treated with sequential monotherapy (consisting of Capecitabine Irinotecan CAPOX) or with combination therapy (CAPIRI CAPOX). No significant difference in overall survival was found with comparable toxicities (16.3 vs. 17.4 months, $p=0.3281$) [868]. However, the results of this study should be critically examined with respect to study design and patient selection and are not transferable without limitation [869].

The FOCUS trial, which was the largest single study on colorectal cancer with a total of 2,135 patients, demonstrated that a combination therapy as first- and/or second-line therapy is superior to a sequence of monotherapies (arm A). Starting with a 5-FU

monotherapy followed by 5-FU in combination with either Oxaliplatin or Irinotecan (arm B) resulted in an overall survival of 15.2 and 15.0, respectively, vs. 13.9 months in arm A ($p=0.24$); with combination therapy as first- and second-line therapy (arm C) the benefit in overall survival reached statistical significance (FOLFOX 15.4 months, FOLFIRI 16.7 months vs. 13.9 months, $p=0.02$) [870]. Another reason contradicting the general use of monotherapy as first-line therapy has been shown by a currently published retrospective subgroup analysis of the N9741 study. In this study complete remission was found to be associated with an improved overall survival. The rate of complete remissions after 5-FU monotherapy was only about 1%, whereas after FOLFOX4 complete remission rates of 6.2% have been described [871]. In summary, it can be concluded that, as first-line therapy, a therapy as active as possible should be conducted. However, 5-FU monotherapy followed by combination therapy is an acceptable alternative in specific cases (e.g. group 3) and should, therefore, be discussed with the patient. Sequential monotherapy (e.g. 5-FU monotherapy followed by Irinotecan monotherapy) cannot be recommended based on these data. Therapy sequences of 5-FU bolus followed by 5-FU infusional protocols, without extension to a second or even third substance is obsolete. It appears important that patients have access to all active substances during the course of their therapy [872]. The relevance of biological substances within the respective oncological overall-concept will be discussed in the relevant sections.

9.4. Chemotherapy Protocols

9.4.1. First-Line Therapy

The options for treating metastatic colorectal cancer have been drastically improved through the introduction of new chemotherapeutic drugs such as Irinotecan and Oxaliplatin, oral 5-FU pro-drugs, and later biological substances.

Therapy options in first-line therapy are monotherapies and fluoropyrimidine-based combination therapies with Oxaliplatin and/or Irinotecan. For those patients with a necessity for intensified therapy and who qualify, monotherapy is not indicated at the beginning. The choice of a therapy regimen is driven by the goal of therapy, i.e. achieving good remission and possibly a secondary resectability or lengthening of progression-free survival and overall survival along with good quality of life. When making a decision, it is important to consider the specific side effect profile of the individual chemotherapeutic drugs as well as possible comorbidities (e.g. CHD, chronic diarrhea), but also the personal and occupational life situation of the patient. If toxicity occurs, the administration of the toxic agent should be interrupted in concordance with the usual proceedings in oncology. If an initial drug therapy has been de-escalated, for instance after achieving a "best response" or due to intolerable side effects, the initial therapy should be resumed with the appearance of progression, as long as toxicity is tolerable (e.g. analogous to the Optimox scheme). If this is not the case, an alternative therapy scheme should be employed. This applies for mono- as well as combination therapies. However, with progression under or relatively shortly after primary therapy, one should change to an alternative therapy protocol.

9.4.1.1. Monotherapy (5-FU)

9.21.	Recommendation	2008
Grade of Recommendation B	If a fluoropyrimidine-monotherapy is conducted, oral administration of 5-FU should be preferred over intravenous administration. With the infusional protocols available, the de-Gramont scheme should be preferred over the AIO scheme, because the de-Gramont scheme puts less strain on the patient due to a 14-day application with probably similar efficacy.	
Level of Evidence 4	Consensus	

Background

5-FU was the standard chemotherapeutic agent from the 1950's onwards in treating colorectal cancer and led to remission rates of 10-15% and a median overall survival of about 6-9 months. At the end of the 1980's, the combination of bolus 5-FU with biomodulators such as folinic acid resulted in remission rates of about 20% and a median survival time of about 12 months [873, 874]. Randomized studies which compared 5-FU bolus application with continuous administration until progression, showed higher response rates (7 vs. 30%, $p < 0.001$) without effect on overall survival (10.3 vs. 11.3 months, $p = 0.379$). The continuous administration showed higher incidence of hand-foot syndromes (23 vs. 0%, $p < 0.001$) but less grade 3-4 neutropenia (1 vs. 22%, $p < 0.001$). Four deaths due to neutropenic sepsis were documented in the bolus arm [875]. In 1997, de Gramont demonstrated a statistically significant improvement in response rates (32.6 vs. 14.5%, $p = 0.0004$) and average progression-free survival (27.6 vs. 22 weeks, $p = 0.001$) with a two-week infusional protocol while showing lower toxicity [876]. A meta-analysis from the same year confirmed this benefit in overall survival. Although the numbers were not statistically significant in the individual studies, the analysis of six studies with a total of 1,219 patients showed a significant difference in overall survival of 12.1 months with continuous 5-FU administration versus 11.3 months with bolus protocols ($p = 0.04$) [877]. Oral fluoropyrimidines can increase the quality of life even more, since they allow out-patient therapy without port systems and pumps. These are associated with a complication rate of about 10% (thromboses, infection, dislocation) [878-880]. Furthermore, the costs are lower. The side effects of Capecitabine are mainly hand-foot syndrome, hemotoxicity, and diarrhea. Studies have shown that patients prefer oral administration, as long as effectiveness is not compromised [881, 882]. Twelves examined 97 patients with mCRC. In direct comparison with Capecitabine only the modified out-patient de Gramont scheme resulted in similar patient satisfaction. In fact, the gain in quality of life for the study patients was actually higher for the out-patient infusional scheme ($p < 0.05$) [883]. The effectiveness of Capecitabine in comparison with a 5-FU protocol was studied in two randomized multicenter phase III studies. In both studies, the control arm consisted of a bolus 5-FU protocol (Mayo protocol) which at the time corresponded to the standard of therapy. Van Cutsem demonstrated response rates of 18.9% for Capecitabine and 15% for 5-FU/FA, median overall survival was 13.2 versus 12.1 months ($p = 0.33$). The administration of Capecitabine led to a lower incidence of grade 3 and 4 stomatitis and neutropenia ($p < 0.00001$), but more-frequent appearance of hand-foot syndromes ($p < 0.00001$) [884]. Hoff demonstrated similar results in his study of 605 patients [885]. A pooled

analysis of these two studies, published in 2004, included a total of 1,207 patients and demonstrated highly significant different response rates of 26% for those patients treated with Capecitabine versus 17% in the 5-FU arm ($p < 0.0002$). Overall survival was not prolonged (12.9 versus 12.8 months) [886]. A direct randomized comparison of Capecitabine with an infusional 5-FU protocol is at this time only available in combination with Irinotecan/Oxaliplatin with or without Bevacizumab. Here, Capecitabine represents an effective and well-tolerated alternative to infusional 5-FU protocols (see Table 15).

For patients who received a 5-FU/folinic acid-based therapy, favorable prognostic factors that have been identified are ECOG performance status (0-1), leukocyte count ($< 10 \times 10^9/L$), alkaline phosphatase ($< 300 U/l$), and evidence of only one metastatic site [887].

Table 15: Capecitabine (Cape) in Comparison to Bolus 5-FU/FA in First-Line Therapy

Reference	N	Therapy regimen	Response-rate	TTP (mo)	OS (mo)	Level of evidence
Van Cutsem 2004	1207	Cape/Mayo	26 vs 17 ($p < 0.0002$)	4.6 vs 4.7 ($p = 0.95$)	12.9 vs 12.8 ($p = 0.48$)	Ia
Van Cutsem 2001	602	Cape/Mayo	18.9 vs 15	5.2 vs 4.7 ($p = 0.65$)	13.2 vs 12.1 ($p = 0.33$)	Ib
Hoff 2001	605	Cape/Mayo	24.8 vs 15.5 ($p = 0.005$)	4.3 vs 4.7 ($p = 0.72$)	12.5 vs 13.3 ($p = 0.974$)	Ib

9.4.1.2. Combination Therapy

In recent years, a series of large phase III studies on first-line therapy of mCRC were published. In these studies patients were randomized to a group with a fluoropyrimidine-monotherapy or to a group with combination chemotherapy consisting of fluoropyrimidine and Irinotecan or Oxaliplatin. Combination therapy improved response rates and progression-free survival in all of these studies; in two of the three Irinotecan-based therapy studies a significant survival benefit was shown for combination therapy. However, the influence of second- and third-line therapies on overall survival should be considered when evaluating the importance of first-line therapy.

Oxaliplatin + 5-FU/Folinic Acid

Background

The combination of infusional 5-FU/FA with Oxaliplatin resulted in a significant increase of progression-free survival as compared to the sole administration of an infusional 5-FU therapy (median PFS of 9 months versus 6.2 months for 5-FU/FA alone; $p = 0.0003$) (see Table 16). Additionally, response rates were significantly better with the intensified therapy (50.7 vs. 22.3%, $p = 0.0001$), although more grade 3-4 toxicities were observed. Especially neutropenias and neurological complications occurred significantly more often in the Oxaliplatin arm ($p < 0.001$). Overall survival was not significantly longer (16.2 vs. 14.7 months, $p = 0.12$) [888].

Table 16: Oxaliplatin-Containing Protocols in First-Line Therapy – Phase III Studies

Reference	N	Therapy regimen	Response-rate (%)	PFS (mo)	OS (mo)	Level of evidence
de Gramont 2000	420	FOLFOX4 vs 5FU/FS	50.7 vs 22.3 (p=0.0001)	9.0 vs 6.2 (p=0.0003)	16.2 vs 14.7 n.s.	Ib
Giacchetti 2006 [889]	564	FOLFOX2 vs Oxaliplatin/5FU (chronomod.)	44.3 vs. 42.0	8.4 vs 8.4 n.s	18.7 vs 19.6 n.s	Ib
Giacchetti 2000 [890]	200	Oxaliplatin/5FU vs 5FU (both chronomod.)	53 vs 16 (p<0.001)	8.7 vs 6.1 (p=0.048)	19.4 vs 19.9	Ib

Irinotecan + 5-FU/Folinic Acid (FA)

Background

The combination of Irinotecan and bolus 5-FU/FA (IFL) shows an unfavorable effect/side effect ratio and is, therefore, obsolete.

The comparison of a 5-FU/FA monotherapy to a combination therapy consisting of infusional 5-FU/FA and Irinotecan revealed a significant benefit for the combination therapy; the decision whether the patients were treated according to the AIO scheme (weekly) or the de Gramont scheme (every two weeks) was made by the individual centers. A total of 387 patients were treated (see Table 17). The response rates were 35% for the Irinotecan-containing protocol and 22% for the 5-FU/FA monotherapy (p<0.005). Progression-free survival and overall survival were significantly prolonged (6.7 vs. 4.4 months, p<0.001 and 17.4 vs. 14.1 months, p=0.031, respectively).

The spectrum of side effects included CTC-grade 3 and 4 diarrheas in 44.4% (versus 25.6% in the 5-FU monotherapy arm, p=0.055) and grade 3 and 4 neutropenias in 28.8% of the patients in the Irinotecan group (versus 2.4% in the 5-FU monotherapy arm, p=0.001) [891]. In another study in which 430 patients were treated with Irinotecan and a weekly 5-FU scheme (AIO scheme) at two different dose levels, the comparison with the AIO scheme alone also showed a benefit for combination therapy. The differences in response rates and progression-free survival were highly significant. However, overall survival, was not shown to be significantly longer [892]. Grade 3 and 4 toxicities in this study were especially diarrheas (29% for Irinotecan-containing protocols vs. 21% for 5-FU monotherapy). Saltz showed in his three-armed study that combination therapy consisting of bolus 5-FU and Irinotecan (IFL) also resulted in considerably improved response rates and significant prolongation of progression-free survival and overall survival in comparison to monotherapy consisting of either bolus 5-FU/FA or Irinotecan; the results for Irinotecan monotherapy and bolus 5-FU monotherapy were comparable. However, the bolus 5-FU arm had the highest rate of grade 3-4 neutropenias (66.2 vs. 53.8% with combination therapy, respectively, and 31.4% after Irinotecan monotherapy) and neutropenic complications in 14.6% (vs. 7.1

and 5.8%, respectively). Gastrointestinal toxicity with diarrhea and vomiting was higher in the combination arm [893]. Considering the different combinations of 5-FU/FA and Irinotecan, FUFIRI and FOLFIRI (infusional 5-FU) are of approximately equal effectiveness, although the rate of alopecia is probably lower in the weekly protocol. Irinotecan plus bolus 5-FU (Saltz protocol) shows the most unfavorable ratio of effect and side effects and should, therefore, no longer be used.

Table 17: Irinotecan-Containing Protocols in First-Line Therapy – Phase III Studies

Reference	N	Therapy regimen	Response- rate (%)	PFS (Mo)	OS (Mo)	Level of evidence
Kohne 2005	430	AIO+CPT 11 vs AIO	62.2 vs 34.4(p<0.0001)	8.5 vs 6.4(p<0.0001)	20.1 vs 16.9n.s.	Ib
Douillard 2000	387	FOLFIRI vs 5-FU/FS	35 vs 22(p<0.005)	6.7 vs 4.4(p<0.001)	17.4 vs 14.1 (p=0.031)	Ib
Saltz 2000	683	IFL vs Mayo (vs CPT 11 mono)	39 vs 21(p<0.001)	7.0 vs 4.3(p=0.004)	14.8 vs 12.6 (p=0.04)	Ib

Comparison of Irinotecan- Versus Oxaliplatin-Containing Combination Therapies

Background

If an indication for combination chemotherapy is given, FOLFOX or FOLFIRI can be employed in first-line therapy.

In contrast to the Oxaliplatin-based protocols (see above), a survival benefit was demonstrated for two of the three Irinotecan-containing combination chemotherapies. However, in direct comparison, FOLFOX and FOLFIRI have been observed to be similarly effective [894]. Hence, the spectrum of toxicities should be especially taken into consideration when choosing between a fluoropyrimidine-based Irinotecan- or Oxaliplatin-containing combination. Colucci and colleagues documented the same efficacy of FOLFIRI and FOLFOX in direct comparison (see below) while observing different toxicities. The most frequently observed side effects were alopecia and those affecting the gastrointestinal tract in arm A (Irinotecan) and thrombocytopenia and neuropathies in arm B (Oxaliplatin). Grade 3 and 4 toxicities were observed in both arms (neutropenia (27 and 28%, respectively) and diarrheas (28%) especially for the Irinotecan-containing protocols and neuropathy (12%) for the Oxaliplatin-containing protocols) [895] (see Table 18).

Table 18: Oxaliplatin- Versus Irinotecan-Containing Protocols in First-Line Therapy

Reference	N	Therapy regimen	Response-rate (%)	PFS (mo)	OS (mo)	Level of evidence
Tournigand 2004	220	FOLOFOX6 – FOLFIRI vs rev sequence	54 vs 56 n.s.	8.0 vs 8.5 n.s.	20.6 vs 21.5 n.s.	Ib
Goldberg 2004 [896]	795	FOLFOX vs IFL (vs IROX)	45 vs 31 (p=0.002) (vs 35)	8.7 vs 6.9 (p=0.0014) (vs 6.5)	19.5 vs 15 (p=0.0001) (vs 17.4)	Ib
Goldberg 2006 [897]	305	rIFL vs FOLFOX	32 vs 48 (p=0.006)	5.5 vs 9.7 (p<0.0001)	16.3 vs 19 (p=0.026)	Ib
Colucci 2005	360	FOLFIRI vs FOLFOX	31 vs 34 (p=0.6)	TTP : 7 vs 7	14 vs 15	Ib
Comella 2005 [898]	274	OXAFUFU vs IRIFUFU	44 vs 31 (p=0.029)	7 vs 5.8 (p=0.046)	18.9 vs 15.6 (p=0.032)	Ib

Capecitabine in Combination with Oxaliplatin or Irinotecan

Oxaliplatin and Capecitabine

Background

Two large phase III studies with a total of 822 patients are available in which infusional 5-FU/FA was compared with the oral prodrug Capecitabine each in combination with Oxaliplatin. The Spanish group chose the FUOX regimen as the standard arm, the AIO study group employed a weekly infusional protocol of 5-FU/FA/Oxaliplatin (FUFOX) [899, 900]. The German study documented a progression-free survival of 7.1 months (versus 8 months in the FUFOX arm; HR: 1.17; 95% CI: 0.96-1.43; p=0.117) and an overall survival of 16.8 months (versus 18.8 months in the FUFOX arm; HR: 1.12; 95% CI: 0.92-1.38; p=0.26) for the CAPOX arm. Response rates were 48% for CAPOX (95% CI: 41-54%) and 54% for the FUFOX regimen (95% CI: 47-60%). The most frequent non-hematological side effect was polyneuropathy in 27% versus 25% of the cases, respectively; only the hand-foot syndrome in grades 2 and 3 was significantly more frequent in the CAPOX arm (p=0.028) [900].

Study design and results were comparable in both studies and, therefore, both therapy regimens represent an active first-line therapy.

Another large phase III study clearly showed the non-inferiority of Capecitabine and Oxaliplatin (in the XELOX protocol) in relation to progression-free and overall survival in comparison with FOLFOX4 (HR: 1.04; 97.5% CI: 0.93-1.16 for PFS and HR: 0.99; 97.5% CI: 0.88-1.12 for OS, respectively) [901] (see Table 19).

Table 19: Capecitabine and Oxaliplatin Combinations in First-Line Therapy – Phase III Studies

Reference	N	Therapy regimen	Response-rate (%)	PFS (mo)	OS (mo)	Level of evidence
Cassidy 2008 NO 16966	2034	XELOX vs FOLFOX 4	37 vs 37	8 vs 8.5(HR: 1.04; 97.5% CI: 0.93-1.16)	19.8 vs 19.6(HR: 0.99; 97.5% CI: 0.88-1.12); p=n.s.	lb
Porschen 2007	474	CAPOX vs FUFOX	48 vs 54	7.1 vs 8.0(HR: 1.17; 95% CI: 0.96-1.43; p=0.117)	16.8 vs 18.8 (FUFOX HR: 1.12; 95% CI: 0.92-1.38; p=0.26)	lb
Diaz-Rubio 2007	348	CAPOX vs FUOX	37 vs 46 n.s.	8.9 vs 9.5 (p=0.153)	18.1 vs 20.8 (p=0.145)	lb

Irinotecan and Capecitabine

Background

The data currently available on efficacy and toxicity of Capecitabine and Irinotecan are less uniform than for the combination of Capecitabine/Oxaliplatin. Two studies analyzed the effectiveness of CAPIRI in comparison to an infusional 5-FU protocol. In the BICC-C study, CAPIRI was clearly inferior to FOLFIRI with regard to progression-free survival. The very high toxicity with nearly 50% of grade 3-4 diarrheas probably plays a crucial role here (2 x 1 g/m² Capecitabine/day 1-14, 250 mg Irinotecan/m² on day 1). Response rates and overall survival were not significantly different [902]. A study published in 2007 reported intolerable side effects of the CAPIRI regimen, which also led to early termination of the study (2 x 1 g/m² Capecitabine/day 1-15 and 22-36, 250 mg Irinotecan/m² day 1 + 22). In the CAPIRI group especially hemotoxic side effects in 61% of the cases made a dose reduction necessary, in the FOLFIRI arm only 7% dose reductions were necessary. Six of eight deaths occurred in the group treated with CAPIRI, three patients died of a thromboembolic event and three due to high-grade diarrheas [903]. With a total of 820 patients, the CAIRO study is so far the largest study on the combination of Capecitabine and Irinotecan. In this study, Capecitabine was administered at a dose of 2 x 1g/m²/day 1-14 along with Irinotecan 250 mg/m²/day 1 in a 3-week cycle. The frequency of grade 3-4 toxicities was not significantly different between the two groups, with the exception of the more frequent appearance of grade 3 hand-foot syndromes in the sequential treatment arm [868].

In this study the rate of severe diarrhea was significantly lower than in the BICC and EORTC studies, which may be explained by the fact that the Dutch centers in the CAIRO study were specifically trained to execute the study and to manage possible side effects. Due to its toxicity, the CAPIRI regimen can currently not be considered as a standard therapy. Preliminary data from the AIO, however, indicate that with a dose-reduction (200 mg/m² Irinotecan day 1 + 2 x 800 mg/m² Capecitabine/day 1-14) CAPIRI can be administered with tolerable side effects. The most frequent CTC grade 3-

4 toxicities were diarrhea in 17/15.5%, hand-foot syndrome in 5.9/2.7%, and neurotoxicity in 15.3/0% of all patients, respectively [904]* (Table 20).

Table 20: Capecitabine in Combination with Irinotecan in First-Line Therapy – Phase III Studies

Reference	N	Therapy regimen	Response-rate (%)	PFS (mo)	OS (mo)	Level of evidence
Koopman 2007 (CAIRO)	820	CAPIRI vs Cape mono	41 vs 20 (p<0.0001)	7.8 vs 5.8 (p=0.0002)	17.4 vs 16.3 n.s.	Ib
Fuchs 2007 (BICC-C)	430	FOLFIRI vs mIFL vs CAPIRI	47 vs 43 vs 39 n.s.	7.6 vs 5.9 vs 5.8 (p=0.004 and 0.015 resp.)	23.1 vs 17.6 vs 18.9 n.s.	Ib
Kohne 2007(EORTC 40015)	85	CAPIRI vs FOLFIRI (+/- Celecoxib)	48 vs 46	5.9 vs 9.6	14.8 vs 19.9	IIb

Irinotecan, Oxaliplatin + 5-FU as Combination Therapy – FOLFOXIRI

Background

In a phase III study published in 2006, no statistical superiority of the FOLFOXIRI regimen was demonstrated in comparison with the FOLFIRI regimen. Median overall survival was 21.5 vs. 19.5 months (p=0.337), response rates were 43 vs. 33.6% (p=0.168), respectively. The rate of side effects (alopecia, diarrhea, neurotoxicity) was significantly higher than in the FOLFIRI arm (p=0.0001 for alopecia and diarrhea and p=0.001 for neurotoxicity) [863]. Falcone et al., however, demonstrated a significant improvement of progression-free as well as overall survival with FOLFOXIRI. This survival benefit was accompanied by significantly more frequent grade 2-3 peripheral neurotoxicity and grade 3-4 neutropenias (0 vs. 19% and 28 vs. 50%, p<0.001 and p=0.0006, respectively) [859]. In both studies response rates were better in comparison to FOLFIRI alone; in Falcone's study this benefit reached statistical significance. However, the results of the two studies are only partially comparable due to different protocols and study populations. Response rates and resection rates, which were the primary and secondary endpoints of the Italian study, were convincing, so that the FOLFOXIRI protocol should especially be considered for induction of remission and possible secondary resection of liver metastases (see also 9.2.1.2) (see Table 21).

Table 21: FOLFOXIRI in First-Line Therapy

Reference	N	Therapy regimen	Response rate (%)	PFS (Mm)	OS (Mm)	Level of evidence
Falcone 2007 †	244	FOLFOXIRI vs FOLFIRI	60 vs 34(p=0.0001)	9.8 vs 6.9(p=0.0006)	22.6 vs 16.7(p=0.032)	Ib
Souglakos 2006 ††	283	FOLFOXIRI vs FOLFIRI	43 vs 33.6(p=0.168)	8.4 vs 6.5(p=0.17)	21.5 vs 19.5(p=0.337)	Ib
†	5-FU as continuous infusion					
††	5-FU as bolus, protocol with reduced doses of Irinotecan and Oxaliplatin					

5-FU/Folinic Acid + Bevacizumab

Background

This combination is particularly suitable for patients who do not qualify for an Oxaliplatin-containing/Irinotecan-containing protocol or for patients for whom a prolongation of progression-free and overall survival along with good quality of life is the primary goal of therapy (matching group 3). In a prospective randomized placebo-controlled phase II study Kabinavaar et al. analyzed the effectiveness of a combination of Bevacizumab with a 5-FU/FA monotherapy according to the Roswell Park scheme in comparison with a sole 5-FU/FA monotherapy [905]. The results show a highly significant prolongation of progression-free survival in combination with Bevacizumab (9.2 vs. 5.5 months, respectively, $p=0.0002$) without achieving a significant improvement in response rates (26 vs. 15.2%, $p=0.055$). The difference in overall survival was also not significant (16.6 vs. 12.9 months, respectively, $p=0.16$). The therapy was well tolerated although this study involved a high-risk population (the median age was 72, the performance status was >0 for 72% of the patients).

Oxaliplatin +5-FU/Folinic Acid + Bevacizumab

Background

The recently published randomized multi-center study NO16966 was initially designed as a two-armed study which examined the non-inferiority of Capecitabine and Oxaliplatin (as XELOX protocol) in comparison to FOLFOX4 [901]. After publication of data of the phase III study by Hurwitz (see below), which revealed a significant benefit by adding Bevacizumab, the original study protocol was expanded to a 2x2 factorial design and extended by Bevacizumab. The study showed a significant improvement of progression-free survival for the combination of chemotherapy and Bevacizumab (XELOX / FOLFOX +/- Bevacizumab). PFS as the primary endpoint was increased in median from 8.0 to 9.4 months (HR: 0.83; 97.5% CI: 0.72-0.95; $p=0.0023$) [864]. A possible explanation for this relatively small difference of only 1.4 months in PFS under a triple combination therapy could be that the average therapy duration in both arms was only about six months (190 days). The administration of the combination chemotherapy and Bevacizumab was then stopped, probably due to toxicity. In line with this, only 29% of the patients who were treated with Bevacizumab were treated until progression. A planned subgroup analysis of these patients indicates that continuing therapy up to progression could result in prolongation of the "time of

tumor control." Overall survival as a secondary endpoint was not significantly improved (21.3 vs. 19.9 months, HR: 0.89; 97.5% CI: 0.76-1.03; $p=0.077$), response rates were the same (38 vs. 38%, OR 1.00; 97.5% CI: 0.78-1.28, $p=0.99$). 59 patients (8.4%) in the Bevacizumab arm and 43 patients (6.1%) in the placebo arm were operated with curative intention; the effect on R0 resectability cannot yet be conclusively determined. Resectability was not defined as a secondary endpoint in this trial [864] (see also 9.2.1.2).

Irinotecan + 5-FU/Folinic Acid + Bevacizumab

Background

The direct comparison of IFL plus placebo with IFL plus Bevacizumab showed a significant prolongation of overall survival from 15.6 months to 20.3 months ($p<0.001$), respectively. The median time until progression could also be extended from 6.2 months to 10.6 months by combination with the antibody ($p<0.001$). In the non-placebo group response rates were significantly higher with 44.8% compared to the placebo group (34.8%; $p=0.004$). The spectrum of toxicity included a grade 3 hypertension for 11% of the patients treated in the experimental arm in contrast to 2.3% in the standard arm. Further grade 3 and 4 toxicities were leucopenia in 37% and diarrhea in 32.4%. Since then, Bevacizumab has been approved for use in combination with 5-FU/FA with or without Irinotecan for first-line therapy of colorectal cancer [906]. A direct comparison of FOLFIRI plus Bevacizumab with mIFL plus Bevacizumab in the BICC-C study revealed a clear superiority for the 5-FU protocol in progression-free survival, overall survival (not yet reached vs. 19.2 months with mIFL + Bevacizumab, $p=0.007$). Response rates were not significantly different (57.9 vs. 53.3%, respectively) [902]. Also due to the more favorable toxicity profile, the infusional 5-FU protocol should be preferred over the IFL protocol.

Oxaliplatin + Capecitabine + Bevacizumab

Background

The results of the N016966 study are presented in detail above. Both XELOX in combination with Bevacizumab and XELOX without the antibody are not inferior to the infusional protocol. The response rates which were acquired by an independent review committee were equal being 38% for both the FOLFOX and the XELOX arm. A predefined subgroup analysis indicates a benefit of 1.9 months in median progression-free survival for the combination of Bevacizumab with XELOX compared to XELOX alone (7.4 vs. 9.3 months, respectively, HR: 0.77; 97.5% CI: 0.63-0.94; $p=0.0026$). The availability of Bevacizumab in the FOLFOX arm did not result in prolongation of progression-free survival in this subgroup analysis (8.6 vs. 9.4, respectively, HR: 0.89; 97.5% CI: 0.73-1.08; $p=0.1871$) [864].

5-FU-Folinic Acid + Oxaliplatin + Cetuximab

Background

A randomized multicenter phase II study from Europe analyzed the effectiveness of a combination of FOLFOX +/- Cetuximab (OPUS study). 337 patients were randomized. Response rates were 45.6% in the experimental arm and 35.7% in the standard arm, while showing comparable grade 3-4 toxicity. Survival data were not yet available at the time of the presentation in 2007. The most frequent side effects were neutropenia,

diarrhea in both groups and acne-like skin rash in the group treated with Cetuximab [907]*.

There are no phase III data that support a treatment of mCRC with a combination of FOLFOX and Cetuximab in first-line therapy.

Hence, a general recommendation concerning the use of this combination cannot be given at this time.

However, Cetuximab is permitted for first-line therapy of CRC in combination with Oxaliplatin for those patients who have wild type k-ras tumors.

5-FU-Folinic Acid + Irinotecan + Cetuximab

Background

Until now, there are no phase III data available as fully published manuscripts concerning the use of Cetuximab in first-line therapy. The data of the phase III study (CRYSTAL) presented at ASCO in 2007 are promising and demonstrate a statistically significant increase in response rates and progression-free survival in comparison with FOLFIRI alone. The combination of FOLFIRI and Cetuximab resulted in a response rate of 46.9% (in comparison with 38.7% for FOLFIRI; $p=0.005$). The rate of R0 resections as a secondary endpoint was increased in the experimental arm as well [860]*. The high response rates from phase I/II studies (ORR 67%) which discussed an outstanding role for Cetuximab as a possible therapy for downsizing marginally resectable liver metastases [908], were not achieved.

A retrospective analysis of the CRYSTAL study which was presented at ASCO showed that only patients with wild type k-ras tumors benefit from a therapy with Cetuximab [861]*.

Cetuximab can be used according to its approval for this group of patients in combination with an Irinotecan-containing therapy as a first-line therapy of CRC.

9.4.2. Duration of Therapy / Interruption of Therapy in First-line Therapy / Reinduction

9.22.	Recommendation	2008
Grade of Recommendation B	There is not sufficient evidence to justify stopping an initiated systemic chemotherapy before disease progression has occurred.	
Level of Evidence 1b	Consensus	

Background

Overall survival and duration of tumor control can be considerably extended in each line of therapy with new chemotherapeutic agents and combination chemotherapies. Thus, the question of chemotherapeutic-associated side effects and the resulting quality of life are also becoming more and more important. As a result, studies have

been performed that analyze the importance of a maintenance therapy with less-intensive therapy schemes (OPTIMOX 1) or a complete stopping of therapy after an induction phase in contrast to therapy until progression (OPTIMOX 2). The OPTIMOX 1 study analyzed the administration of FOLFOX4 up to progression in comparison to FOLFOX7 followed by a maintenance therapy with 5-FU/FA and reinduction of FOLFOX7 with the appearance of progression. The differences in progression-free and median survival were not significant, the rate of grade 3 neurotoxicities was more favorable (13 vs. 18%, $p=0.12$, respectively) [909]. Such a de-escalation strategy with reinduction of Oxaliplatin with documented progression should also be used in clinical routine and be discussed with patients as a possible option. The OPTIMOX 2 study examined the possibility of a complete halt of therapy in comparison to maintenance therapy as in OPTIMOX 1. With this study concept, median progression-free survival was significantly longer in the control arm (OPTIMOX 1) than in the experimental arm (8.3 vs. 6.7 months, respectively; $p=0.04$); median overall survival was considerably better as well (24.6 vs. 18.9 months, respectively; $p=0.05$). So far, the data are only available in abstract form and were not fully conclusive in the presentation [910]*. A recommendation for a planned complete interruption of therapy without maintenance therapy cannot be given on the basis of these data. The group around Maughan observed a considerably lower toxicity with an intermittent administration of a 5-FU-containing protocol with no clear survival benefit for the continuous administration (HR 0.87 for intermittent administration, 95% CI: 0.69-1.09; $p=0.23$) [911].

Labianca found no difference in overall survival as the primary endpoint between an intermittent FOLFIRI protocol in comparison with a continuous administration up to progression while observing comparable toxicity (HR=1.11; 95% CI: 0.83-1.48) [912]*.

In contrast to a conceptual interruption of therapy, there are short-term interruptions in chemotherapy due to the patient's personal living situation (e.g. vacation). In this case, short-term interruptions of therapy are tolerable.

Table 22: Studies Concerning the Question of Treatment Interruption/ Maintenance Therapy

Reference	N	Therapy regimen	Response-rate (%)	PFS (mo)	OS (mo)	Level of evidence
Labianca 2006	336	FOLFIRI intermitt vs cont.	29 vs 35	8.8 vs 7.3(HR: 1.00. 95% CI: 0.74-1.36)	16.9 vs 17.6(HR: 1.11 95% CI: 0.83-1.48)	Ib
Tournigand(OPTIMOX 1) 2006	620	Ctx bis PD vs maintenance with 5FU/FS	58.8 vs 59.2 n.s.	9 vs. 8.7n.s.	19.3 vs 21.2n.s.	Ib
Maindrault 2007(OPTIMOX 2)	202	Maintenance vs pause	63 vs 61	8.3 vs 6.7($p=0.04$)	24.6 vs 18.9 ($p=0.05$)	Ib
Maughan 2003	354	5-FU/FS12 w Ctx vs cont.	21 vs 8	3.7 vs 4.9(HR:1.2 95% CI: 0.96-1.49)	10.8 vs 11.3(HR: 0.87; 95% CI: 0.69-1.09)	IIb

9.4.3. Chemotherapy Protocols in Second- and Third-Line Therapy

Overall, studies on first-line therapy of mCRC show a high variability concerning overall survival ranging from 14.1 to more than 22 months. Assuming that there were no great differences in patient selection, the type of chosen second- and third-line therapy and certainly their different availability are possibly responsible for these discrepancies. The choice of second- and third-line therapy depends on previous therapies and the time interval without therapy as well as on the individual situation of the patient and the particular goal of therapy. Although in first-line therapy options are currently being taken into consideration concerning the reduction of the duration of therapy or “stop-and-go” strategies (see above), second- and third-line therapies should still follow the principle that therapy should be administered up to disease-progression.

9.23.	Recommendation	2008
Grade of Recommendation A	Due to the lack of sufficient evidence, none of the therapeutic agents described above should be continued after documented progression under therapy with the exception of fluoropyrimidines or the administration of Irinotecan in combination with Cetuximab after failure of an Irinotecan-containing therapy. This also applies to Cetuximab and Bevacizumab.	
Level of Evidence 2	Strong consensus	

Background

The importance of an effective second-line therapy for overall survival has been analyzed in several phase III studies. Thus, a second-line therapy with Irinotecan after failure of Fluorouracil monotherapy resulted in a significant benefit in overall survival in comparison with BSC [913] or infusional 5-FU/FA [914].

Combination therapy with Oxaliplatin and Fluorouracil after failure of an Irinotecan-containing protocol in first-line therapy was superior to 5-FU/FA and/or Oxaliplatin monotherapy with respect to the resulting response rates as well as in relation to the time until progression [915]. The combination therapy of 5-FU/FA with Oxaliplatin and/or Irinotecan, which shows response rates (CR + PR) of 40-55% in first-line therapy, achieves response rates of 4% (FOLFIRI) up to 15% (FOLFOX) and a progression-free survival of about 2.5-4.2 months in second-line therapy. The median survival of the patients was about 20 months each for both therapy sequences (FOLFOX □ FOLFIRI and/or FOLFIRI □ FOLFOX) [894]. The introduction of monoclonal antibodies such as Cetuximab, Bevacizumab, and Panitumumab has also extended the possibilities for second- and third-line therapy. The so-called BOND-1 study for the first time verified the effectiveness of Cetuximab in combination with Irinotecan as second-line therapy for advanced CRC's after Irinotecan failure (RR 22.9%, overall survival 8.6 months) [916]. The so-called EPIC study showed that a combination of Cetuximab plus Irinotecan was also effective after a previously administered therapy containing Oxaliplatin, and in direct comparison was more effective than an Irinotecan-monotherapy [917].

9.4.3.1. Combination Therapy in Second- and Third-line Therapy Background

In his work published in 2004, Tournigand compared FOLFOX and FOLFIRI as first- and second-line therapy, respectively, and vice versa. Median survival of the respective sequences was not significantly different between the two arms (20.6 months for FOLFOX vs. 21.5 months for FOLFIRI in first line treatment) [894]. For response rate or progression-free survival also no significant benefit was shown for one sequence or the other (see Table 23).

Oxaliplatin + Fluoropyrimidine

Table 23: Oxaliplatin-Containing Protocols in Second-Line Therapy

Reference	N	Therapy regimen	Response-rate (%)	PFS (mo)	Level of evidence
Giantonio 2007 [918]	829	FOLFOX 4 vs FOLFOX + Bevacizumab vs Bevacizumab mono	8.6 vs. 22.7 (p<0.0001) vs 3.3	4.7 vs 7.3 (p<0.0001) vs 2.7	Ib
Rothenberg 2007 [919]	627	XELOX vs FOLFOX	n.a.	TTP:4.8 vs 4.7	Ib
Tournigand 2004	220	FOLFIRI FOLFOX 6 vs. rev. sequence	4 vs. 15	2.5 vs 4.2	Ib
Rothenberg 2003	463	FOLFOX 4 vs FS-5 FU(vs Oxaliplatin mono)	9.9 vs 0 vs 0	TTP: 4.6 vs 2.7 (p<0.0001)	Ib

Capecitabin und Oxaliplatin

Background

627 patients with progression under irinotecan-containing therapy were treated in second line either with XELOX or FOLFOX. The median time to progression was 4.8 months in the XELOX arm compared to 4.7 months in the FOLFOX arm.

Grade 3/4 toxicity occurred in 60.1% of cases in the XELOX arm and in 72.4% of FOLFOX treated patients. These were mainly diarrhea (20 vs 5%), neutropenia in 5 and 35%, respectively, and nausea and vomiting in 5-6 % of patients [919].

Irinotecan + Cetuximab

Background

In the BOND study, 329 patients who showed progression within three months after receiving Irinotecan-containing therapy were treated. The patients were either randomized to chemotherapy with Irinotecan and Cetuximab or to Cetuximab monotherapy. Compared to monotherapy, the combination treatment resulted in significantly higher response rates (22.9 vs. 10.8%, p=0.007, respectively).

Progression-free survival was also significantly prolonged (4.1 vs. 1.5 months, $p < 0.001$, respectively). Overall survival was 8.6 and 6.9 months, respectively ($p = 0.48$) [916].

The EPIC study analyzed the effectiveness of this combination with patients who had shown progression under treatment with an Oxaliplatin-based therapy. In this phase III study, patients were either treated with Cetuximab + Irinotecan ($n = 648$) or with Irinotecan mono ($n = 650$). Response rates were significantly improved with the administration of combination therapy (16.4 vs. 4.2%, $p < 0.0001$). Median PFS was extended from 2.6 months to 4.0 months with the availability of Cetuximab (HR: 0.692, $p < 0.0001$). Median overall survival as a primary endpoint was comparable in both arms, since after progression a “crossover” in the other study arm was permitted (10.7 vs. 10 months, respectively, hazard ratio for overall survival = 0.975, 95% CI: 0.854 - 1.114, $p = 0.71$). An accompanying analysis of the quality of life showed an improvement of the general health status ($p = 0.047$) and for functional and individual symptoms (fatigue, nausea/vomiting [$p < 0.0001$], pain [$p < 0.0001$]) in the combination arm, so that this combination can be considered for symptomatic patients [917, 920]*.

Bevacizumab + 5-FU-Folinic Acid + Oxaliplatin

Background

The value of Bevacizumab in combination with Oxaliplatin and 5-FU/FA in second-line therapy after failure of an Irinotecan-containing therapy with patients who had not previously been treated with Bevacizumab was analyzed in a phase III study. 829 patients were randomized to one of the three therapy arms (FOLFOX-Bevacizumab or FOLFOX or Bevacizumab as monotherapy). The additional consideration of Bevacizumab resulted in a significant survival benefit of 2.1 months in comparison to FOLFOX alone (12.9 vs. 10.8 months, respectively, HR: 0.75; $p = 0.0011$). Progression-free survival as well was significantly longer than in the solitary chemotherapy arm (7.3 vs. 4.7 months, respectively, HR: 0.61, $p < 0.0001$). Bevacizumab alone had no clinical relevance. The combination with the VEGF antibody increased the rate of grade 3 and 4 toxicities by 14%. Bleeding, vomiting, and hypertension occurred significantly more often in the experimental arm. The fact that the risk of neuropathy was increased as well is most likely due to longer therapy duration in the combination arm (10 vs. 7 cycles in the FOLFOX arm). The follow-up period was 28 months [918].

Mitomycin C + Fluoropyrimidine

Background

In a trial by Chong with 36 patients an objective response rate of 15.2% was achieved in third-line therapy. Median overall survival was 9.3 months. Data from phase I/II studies are encouraging; results from phase III studies are not available. Fluoropyrimidine and Mitomycin C can be used as a salvage therapy [921-924].

9.4.3.2. **Monotherapy with Biological Substances in Third-Line Therapy** **Cetuximab**

Background

In 2006, Lenz published a large one-armed phase II study with 346 patients which also demonstrated a benefit of Cetuximab monotherapy for Irinotecan-refractory patients (response rate of 11.6%). More than half of the patients showed progression at the time of the first imaging (median progression-free survival: 1.5 months); overall survival was 6.6 months. The BOND study, which was already mentioned above, showed comparable response rates of about 10% in monotherapy. In the latter studies, again, the grade of skin rash correlated with effectiveness [916, 925]. A very recently published study which compared Cetuximab monotherapy with BSC achieved an overall survival of 6.1 months versus 4.6 months in the group with sole BSC [926]. Considering these data and the results of the BOND-1 study, Cetuximab monotherapy is especially recommended for patients who do not qualify for Irinotecan-containing therapy (Cetuximab can only be administered in monotherapy in this way, because approval is still missing).

Translational data on a heterogeneous patient collective indicate that for Cetuximab the k-ras mutational status is also an independent predictive factor. Thus, a k-ras mutation was found in 27% of the Irinotecan-refractory patients and was associated with a resistance against Cetuximab (0 vs. 40% responders among the 24 patients with k-ras mutation compared to 65 patients with k-ras wild type expressing tumors, $p < 0.001$) as well as with a poorer survival (median PFS: 10.1 vs. 31.4 weeks for patients without mutation, $p = 0.0001$; median OS: 10.1 vs. 14.3 months for patients without mutation; $p = 0.026$) [927].

As of August 2008, the k-ras mutation status is relevant for approval. Only patients with a wild type k-ras expressing tumor should receive Cetuximab.

Panitumumab

Background

Panitumumab is the first fully human monoclonal antibody which binds to the epidermal growth factor receptor (EGFR). A phase II efficacy study including 148 patients with pre-treated metastasized colorectal cancer (dose of Panitumumab 2.5 mg/kg/week) showed a partial response to therapy in 9% of the cases; in 29% of the cases the disease remained stable. The average overall survival time was 9 months; the average time to progression was 14 weeks [928]. A subsequently performed randomized controlled multicenter phase III study included 463 patients with metastasized colorectal cancer after failure of cytostatic standard therapy with 5-FU/FA, Irinotecan, and Oxaliplatin. Patients were randomized to Panitumumab along with best supportive care ($n = 231$) or to best supportive care only ($n = 232$). With Panitumumab a significant improvement in progression-free survival was achieved (HR: 0.54; 95% CI, 0.44-0.66, $p < 0.0001$). Median progression-free survival was 8 weeks for patients who were treated with Panitumumab, in contrast to 7.3 weeks for those who had only received best supportive care. 176 of the patients, who had primarily been assigned to best supportive care received Panitumumab by crossover after progression of their tumor [929]. For 168 patients k-ras mutation status was available, 20 patients (12%) showed response; with 32% the disease remained stable. The effectiveness of Panitumumab was limited to tumors that showed no k-ras mutations. These translational studies were published [930]. In the US, Panitumumab was approved in

September 2006, in Europe in December 2007. The approval is limited to patients who have wild type k-ras gene expressing tumors and for whom chemotherapy regimens containing Fluoropyrimidine, Oxaliplatin, and Irinotecan have failed (third-line therapy).

9.5. Procedure for Local Recurrence or for Non-hepatic and Non-pulmonary Distant Metastazation

9.5.1. Local Recurrence

For local recurrence of rectal cancer, which have not been pretreated (radio(chemo)therapy) in the context of the primary operation, this form of therapy should now be mainly preferred. For pretreated patients with the possibility for a R0 resection, surgery can primarily be performed [931]. For those pretreated patients with questionable R0 resectability of a relapse, multimodal surgical procedures must be considered individually and based on the intensity of pretherapy. For locoregional lymph node relapse in colorectal cancer, if possible, complete curative resection should be attempted [932].

9.5.2. Non-Hepatic or Non-Pulmonal Distant Metastases

9.24.	Recommendation	2013
Grade of Recommendation 0	<p>For patients with isolated or limited peritoneal carcinosis cytoreductive surgery followed by hyperthermal intraperitoneal chemotherapy (HIPEC) can be performed if the following criteria are fulfilled:</p> <ul style="list-style-type: none"> - PCI (peritoneal cancer index) < 20 - no extraabdominal metastases - Possibility of macroscopic complete removal or destruction of all tumor manifestations - therapy in a specialized center <p>These procedures should preferably be performed as part of a trial.</p>	
Level of Evidence 2a	Strong consensus	

Background

So far, there is only one completed randomized study comparing systematic chemotherapy and cytoreductive surgery with HIPEC [660]. This study demonstrated also long-term that surgical therapy of peritoneal carcinosis leads to significantly better disease-specific survival [661]. If macroscopic tumor eradication was achieved, the 5-year-survival was 45%. It must be noted that the control arm only received a 5-FU-based systemic therapy. Thus, despite numerous non-randomized studies [662] with promising results, it has not been conclusively defined which patients benefit from surgical therapy with HIPEC compared to modern systemic polychemotherapy.

For isolated bone metastases with pain symptoms local radiation therapy should be conducted. In this context, a meta-analysis showed that single, high-dose therapy is

equally potent as fractionated therapy [933]. Single, high-dose therapy should, therefore, be preferred considering the overall oncologic concept. Biphosphonate administration can additionally follow. Surgery is indicated in case of an increased fracture risk and imminent paraplegia. With isolated brain metastases, if possible, a surgical resection should be performed [934]. If inoperable, radiation therapy, possibly as stereotactic radiation, are potential options [935].

10. Follow-up Care

After diagnosis and therapy of a colorectal cancer, adequate medical care is appropriate regardless of the tumor stage. After curative therapy of colorectal cancer, there is an increased risk for a local or locoregional recurrence (3-24%), distant metastases (25%), or a metachronous second tumors [936-945]. The risk is increased in case of a genetic predisposition [940] and with advancing tumor stages [946, 947]. This is the basic justification for providing regular follow-up for these patients.: a recurrence should be discovered so early that a second operation is possible with a curative intent. Follow-up should also enable the diagnosis and treatment of tumor and therapy related sequelae. Subjective goals of follow-up care are to improve a patient's quality of life [948].

An additional goal is quality control of the diagnostic and therapeutic measures which were carried out before. However, the effect of follow-up care seems marginal with a mean 1% improved survival for the whole group of treated patients [949]. Data from 267 articles relating to this topic were evaluated in a meta-analysis [950]. For long-term survival of one patient with colorectal cancer, 360 positive follow-up tests and 11 secondary operations were necessary. The remaining 359 follow-up tests and 10 operations resulted in either no therapeutic advantage or had negative consequences [950].

A Cochrane review from 2008 which included 8 studies showed that with intensive follow-up the mortality was lower (OR 0.73 (95% CI 0.59 to 0.91) than if no or minimal follow-up was performed.

10.1. Follow-Up for Patients with UICC stage I

10.1.	Consensus-based Recommendation	2013
GCP	A regular follow-up for patients with colorectal cancer and early tumor stage (UICC I) is not recommended after R0 resection considering the low rate of recurrence and the favorable prognosis. Colonoscopy follow-up should be performed according to Chapter 10.3.9.1 .	

Background

Patients with UICC stage I have a good prognosis after a curative resection. In patients with pT2 tumors recurrence occurs more frequently (UICC Ib)(13%) than in those with pT1 tumors (UICC Ia)(4%) [951]. Altogether, the long-term survival of stage UICC I patients according to a prospective cohort study is very good with 86%, and a programmed follow-up is usually not necessary. Similar results were reported in a retrospective study with 541 patients with CRC stage I. The pT1N0M0 (UICC Ia) tumors demonstrated 2.9% recurrences and pT2 cancer (UICC Ib) 5.6% recurrences [952]. In stage Dukes A, recurrences were only seen in patients with rectal cancer (11%, n=6/55), not in colon cancer [953].

In individual cases, if a higher local recurrence risk is expected based on endoscopic, intraoperative (e.g. after intraoperative tumor opening), or pathological findings, a follow-up with shorter intervals may be necessary (e. g. higher risk for distant metastases with invasion of the pericolic veins [954, 955], angiolymphatic invasion

[956, 957], G3/G4 tumors or pT2 tumors) (see Chapter 8). Here the sole assessment of CEA was sufficient [952].

Since patients in stage I also have a higher risk of developing metachronic secondary tumors, a colonoscopy follow-up according to Chapter 10.3 is reasonable.

10.2. Follow-Up for Patients with UICC stage II and III

10.2.	Recommendation/ Consensus-based Recommendation	2008
Grade of Recommendation A	Following R0 resection of UICC stage II and III colorectal cancers, regular follow-up examinations are indicated (see recommendation 10.1.).	
Level of Evidence 1a	[949, 950, 958-967]	
	Strong consensus	

10.3.	Recommendation	2008
GCP	However, follow-up should only be performed if a recurrence would have therapeutic consequences.	
	Strong consensus	

Background

With advanced colorectal cancer (UICC stage II and III) the risk of recurrence is significantly higher [936-947]. There are 6 randomized controlled studies [962-967] on the relevance of follow-up of CRC-patients of which only 2 showed a positive effect on the five-year survival rate of an intensive follow-up in comparison to a "standard follow-up" [965, 967]. Nearly all studies also included patients with UICC stage I.

Different meta-analyses of five of the randomized and controlled studies (1 positive, 4 negative) [949, 950, 958-961] demonstrated a small survival benefit when more tests were performed compared to fewer tests. Liver imaging was significantly better as part of follow-up. The significance was lost, however, if both results were calculated as risk differences and not as odds ratios [960]. An active follow-up led only to a slight survival benefit of 0.5 to 2% after five years [949].

A recent Cochrane publication [968] included 3 other studies in this meta-analysis [967, 969, 970]. A survival advantage after 5 years was found for patients who had intensive follow-up care (OR 0.73; 95% CI 0.59-0.91). However, the absolute number of detected relapses was the same in both groups [30].

A retrospective study compared the effect of regular follow-ups according to the ASCO-guidelines (>70% of follow-up appointments were visited) with few (<70%) and no follow-ups [971]. Compared to the other groups, regular follow-up led to a significantly better 5 and 10 year survival. This is also true for the prognosis of recurrences in these

patients. In addition, a psychological benefit from the follow-up procedures can be derived for the affected patients [972].

Unfortunately, the guidelines are not always followed. It has been observed that only 73.6 % of patients older than 65 years had the recommended colonoscopy and only 46.7 % CEA testing, whereas procedures such as CT and PET-CT were done in 48 % and 7 %, respectively [973].

Definite recommendations on type and frequency of follow-up tests cannot be given, because good studies are missing [974-976]. Follow-ups adapted to the UICC stage or the effect of a complete waiver of follow-up exams have so far not been tested in prospective studies.

Because of the overall poor data available, the expert conference decided, despite the grade 1a of several existing meta-analyses, merely on a Grade of Recommendation B for programmed follow-ups of CRC UICC stage II and III.

10.3. Role of Diagnostic Methods for Follow-up

The following recommendations are given concerning diagnostic tests for follow-up:

10.3.1. Medical History

10.4.	Consensus-based Recommendation	2008
GCP	A symptom-oriented medical history and physical examination are the principle components of follow-up.	
	Strong consensus	

Background

Medical history and physical examinations play a small role in the early detection of colorectal cancer. However, these basic medical measures should precede any further examinations [975, 977]. All participants of the consensus conference agreed on this.

10.3.2. CEA Testing

10.5.	Recommendation	2008
Grade of Recommendation B	The testing of carcinoembryonic antigen (CEA) is recommended every six months for at least two years. An increased CEA value requires further workup, but does not justify the beginning of a systemic chemotherapy in case of suspicion of a metastasized tumor stage.	
Level of Evidence 4	[965, 978, 979]	
	Strong consensus	

Background

CEA was shown to be superior to colonoscopy, computer tomography, and ultrasound for the early detection of liver metastases [965, 978, 979]. A meta-analysis of 7 non-randomized studies showed a survival benefit of 9% for patients for whom the follow-up program included CEA [958]. Other studies showed no or only minimal benefit [963, 980]. CEA was not recommended for follow-up in a literature review [976]. However, American (ASCO) and European (EGTM, European Group on Tumor Markers) follow-up guidelines include the use of CEA [975, 977, 979]. Here the testing is recommended every 2-3 months in the first 2 years.

Adjuvant therapy with 5-fluoruracil can lead to a false higher value. Thus, a sufficient interval to treatment should be observed [981]. 30% of all colorectal tumors do not release CEA [981, 982], while 44% of the patients with normal preoperative values show an increase postoperatively [983]. The further clarification of increased CEA values requires diagnostic imaging and if necessary, 18-fluorodeoxyglucose positron emission tomography [984, 985]

Due to the general controversial data for the use of CEA for the follow-up of colorectal cancer, the expert conference deviated from the recommendations of ASCO and EGTM and decided upon a biannual rather than three-month testing interval in the first two years and then annually over 3 years.

10.3.3. Other Laboratory Parameters

10.6.	Recommendation	2008
Grade of Recommendation B	The routine testing of laboratory values in the context of follow-up is not advisable.	
Level of Evidence 3b	[974, 977]	
	Strong consensus	

Background

In several studies the testing of liver enzymes was part of the follow-up program. However, a study showed that CEA and other imaging procedures became positive earlier than liver function tests [974]. For these reasons, a routine testing of these serum parameters is not advised. The same applies for complete blood count [977].

10.3.4. FOBT

10.7.	Recommendation	2008
Grade of Recommendation A	The testing for occult blood in the stool is not appropriate for follow-up.	
Level of Evidence 3b	[982, 986]	
	Strong consensus	

Background

The testing of occult blood in the stool is not appropriate for follow-up. Only 12% of the local tumor recurrences led to a surface injury of the mucosal membrane [982]. Serial testing of 1,217 patients with curative resection of colorectal cancer showed a very low sensitivity and specificity of the test for recurrent tumors or polyps [986].

10.3.5. Ultrasound

10.8.	Recommendation	2008
Grade of Recommendation A	Abdominal ultrasound is technically appropriate for the detection of liver metastases. Its routine use for follow-up of CRC is not assured by data. However, the expert committee assessed ultrasound as the simplest and least-expensive procedure and, therefore, recommends its use for the diagnosis of liver metastases.	
Level of Evidence 5	[960, 962, 976]	
	Strong consensus	

Background

The sensitivity of abdominal ultrasound for the detection of liver metastases varies widely between 53% and 82% [976]. In most studies it was not as accurate as computer tomography. In a controlled, randomized study [962] the inclusion of abdominal ultrasound and computer tomography had no influence on survival and resection rates of follow-up patients. In a meta-analysis of several randomized studies the use of an imaging test for the evaluation of the liver resulted in a statistically significant survival benefit [960]. If the calculation of these results was done as a risk difference and not as an odds ratio, this advantage was no longer detectable [960]. Because abdominal ultrasound is faster and less expensive than other imaging tests, the participants of the consensus conference recommended abdominal ultrasound for the detection of liver metastases as part of follow-up.

10.3.6. Endoscopic Ultrasound

10.9.	Recommendation	2008
Grade of Recommendation B	Endoscopic ultrasound (EUS) is appropriate for the detection of local recurrences in rectal cancer, especially in combination with an EUS-guided biopsy. Currently, no recommendation can be given for routine primary use in follow-up.	
Level of Evidence 3b	[987]	
	Strong consensus	

Background

In one study endoscopic ultrasound examinations were shown to be helpful for the detection of locoregional recurrences after sphincter-retaining rectal resection if this procedure was combined with a EUS-guided biopsy [987]. 68 perirectal lesions detected by EUS consisted of 36 actual local recurrences in a group of 312 patients. 12 recurrences were detected with a proctoscope. For 22 of the endosonographically detected lesions, the histology was positive. In 41 lesions histology was negative and in 5 inconclusive. In 18 of the 68 patients the endoscopic ultrasound influenced the further course [987]. EUS is not recommended as a primary diagnostic technique for follow-up due to its invasiveness when combined with a biopsy. It is, however, useful for the workup of suspected locoregional recurrences of rectal cancer that have been detected by other tests.

10.3.7. Chest X-Ray

10.10.	Recommendation	2013
Grade of Recommendation 0	A chest x-ray can be performed annually for patients with stage II and III rectal cancer for five years.	
Level of Evidence 3b	de Novo: [988]	
	Consensus	

Background

In a French cohort study 5.8 % of patients developed lung metastases within 5 years after curative resection of CRC [988]. The rate of lung metastases after 1 year was 0.9% and after 3 years 4.2%. The risk of lung metastases was significantly higher in patients with rectal cancer than colon cancer (OR 2.6 95CI 1.65-4.75). The 3-year survival after detection of metachronous lung metastases was 13.8%. After curative resection of these metastases, the relative 3-year survival was 59%.

A systematic literature search on the role of chest x-rays as follow-up examinations identified 18 studies on this topic. These showed that follow-up using chest x-ray detected 0.8 to 7.0% of lung metastases in all patients and between 3.4 and 29.4% of all recurrences. The rate of curative resection of the detected metastases in these studies was 0-100%. More detail on the effect of tumor localization and stage as well as the ideal interval of the x-ray testing is not possible based on the information given in these studies, their low case number, and their heterogeneity.

Overall, according to data by Mitry, the benefit of lung imaging seems to be higher in patients with rectal cancer. Thus, the follow-up of colon cancer patients is still not recommended due to the unknown benefit.

10.3.8. Computer Tomography

10.11.	Recommendation	2013
Grade of Recommendation B	Computer tomography is technically appropriate for the detection of liver metastases, local recurrences, as well as lung metastases. The current data indicates that computer tomography should not be used routinely as part of follow-up.	
Level of Evidence 1b	Evidence from update literature search: [965, 966, 968, 989-991]	
	Strong consensus	

Background

In a randomized, controlled study, the use of computer tomography (CT) as part of follow-up had no influence on patient survival [966]. Liver lesions were found somewhat earlier (12 of 20 were asymptomatic), but CT did not increase the number of curative liver resections. In some studies CEA elevation detected a tumor recurrence earlier than regular CT examinations [965, 966, 991].

An update of the ASCO guideline from 2005 led to the recommendation of annual abdominal CT examinations over 3 years [989]. The committee justified their decision to recommend the use of abdominal CTs in follow-up exams with the work of Chau et al. [990]. 154 tumor recurrences were retrospectively evaluated in 530 patients. The study was originally designed as a therapy study and not to investigate the role of CT in follow-ups. 65 recurrences were detected based on symptoms, 45 by repeated CEA-testing, and 49 using CTs 12 and 24 months after starting adjuvant chemotherapy. 14 of these patients also had an increased CEA and were present in both groups. Resections were performed more frequently in the CT-group (n=13, 26.5%) and the CEA-group (n=8, 17.8%). Two patients were operated in the symptomatic group (3.1%). These differences were significant. However, the importance of ultrasound in comparison to CT was not studied. More recent meta-analyses also do not allow conclusions on the type of method that should be used [968]. Therefore, currently no recommendation can be given on regular CT-examinations in asymptomatic patients as part of follow-up care.

10.3.9. Endoscopic Procedures

10.3.9.1. Colonoscopy

10.12.	Recommendation	2013
Grade of Recommendation B	<p>Colonoscopy is appropriate to detect local recurrences or secondary tumors. All patients should have a complete colonoscopy preoperatively or within 6 months postoperatively. A colonoscopy should be performed after 1 year and subsequently, if negative, every 5 years to detect metachronic cancer or polyps. If a complete colonoscopy was done postoperatively within 6 months, the next one should be done after 5 years.</p> <p>If neoplasia is detected during colonoscopy after 6 or 12 months, further follow-up should be performed according to Chapter 6.5.</p>	
Level of Evidence 2b	de Novo: [961, 992-995]	
	Strong consensus	

10.3.9.2. Sigmoidoscopy

10.13.	Recommendation	2008
Grade of Recommendation B	<p>Sigmoidoscopy is appropriate to detect local recurrences and secondary tumors in the areas within reach. Additional sigmoidoscopies should only be performed in patients with UICC stages II and III rectal cancer who have not received neoadjuvant or adjuvant radiochemotherapy.</p>	
Level of Evidence 4	Strong consensus	

10.3.9.3. Rectoscopy

10.14.	Recommendation	2008
Grade of Recommendation B	<p>A rigid rectoscopy is appropriate to detect local recurrences and anastomotic changes in patients with rectal cancer. It can be used as an alternative procedure to sigmoidoscopy.</p>	
Level of Evidence 4	Strong consensus	

Background

The aim of endoscopic follow-up care is to detect metachronic neoplasia and anastomotic recurrences in a curative stage. It should be considered that a meta-

analysis of various randomized controlled studies showed that colonoscopic follow-up is less effective than the search for extramural recurrences [961]. Furthermore, colonoscopies are costly and there is a risk of complications (although small).

In the publications identified in the literature search (for details see evidence report) the rate of metachronic cancer varied between 0 and 6.4% and the anastomotic recurrence was between 0 and 12% during follow-up (24 to 94 months). In the studies that provided this information the calculated annual incidence of metachronic cancer was 0-2.3%. If the endoluminal anastomotic recurrences are also considered, the annual cancer incidence was 0 to 2.6%. The rate of advanced adenomas that were detected during follow-up was only reported in few studies and varied between 3.7 and 13%.

The rate of curative resections of metachronic cancer and/or anastomotic recurrences was 27 to 100%.

The necessary frequency of colonoscopies during follow-up was investigated in a study that compared intensive colonoscopic follow-up (in the first year every 3 months, in the second and third year every 6 months, and then annually) to a less intensive protocol (after 6, 30, and 60 months) [992]. Recurrences were found in 8.1% of the intensively followed patients and in 11.4% of the patients who had colonoscopies less often. Although the overall survival was comparable, asymptomatic recurrences were significantly increased and the prognosis was better for patients who had to be reoperated. The frequency of metachronic tumors was not mentioned in this study. The high frequency of colonoscopies did not have an effect on overall survival, and especially since most recurrences develop extraluminally a less burdensome protocol for the patients is sufficient.

A study reported 20 of 1002 patients (3.1 %) with secondary cancer of which 9 were detected within 18 months [993]. Advanced neoplasia (defined as adenoma >1 cm, villous histology, HGD, or cancer) was seen more often (15.5%) in colonoscopies after 36-60 months compared to an earlier examination within 18 months (6.9%). Although an early colonoscopy was not associated with a better survival during follow-up, the authors conclude that a first colonoscopy should be performed 12 months after surgery. This is useful to identify metachronic cancer in time that were possibly overlooked during the index examination. Based on these data, it is now recommended to have the first follow-up colonoscopy 12 months after the operation.

Rex et al. also emphasize that the primary goal of colonoscopies during follow-up is not so much the identification of rare anastomotic recurrences, but the detection of metachronic neoplasia [994]. 2-7% of patients had at least one metachronic tumor. It cannot be concluded whether these were real metachronic lesions or whether they were synchronous cancers that were missed during the first colonoscopy. Nonetheless, the authors of this guideline also recommend that the first colonoscopy be performed 12 months after tumor resection. They justify this recommendation with a publication from 1993 from a tumor registry in Nebraska which reported an annual incidence of metachronic tumors of 0.35% [937]. Since the risk of metachronic tumors persists, a colonoscopic follow-up analogous to the screening of colon cancer is indicated [995].

10.3.10. Colon Contrast Enema, Virtual Colonography, and PET

10.15.	Recommendation	2013
Grade of Recommendation B	Colon contrast enema, virtual colonography, PET, PET-CT, and PET-MRI should not be part of a follow-up program.	
Level of Evidence 4	de Novo: [191, 996, 997]	
	Strong consensus	

Background

Only few data exist on the use of PET in follow-up care. The majority of studies includes only patients with suspected recurrence and investigates the role of PET. This procedure was not the goal of the literature search. Instead it was its use for asymptomatic patients without suspected recurrence.

A randomized study [996] with close follow-up examinations showed that recurrences were detected earlier when PET was used after 9 and 15 months and that these were more often R0-resections.

A prospective randomized study [191] was aimed at determining the role of PET-CT in the follow-up of CRC. In addition to a follow-up that included abdominal ultrasound, chest x-ray, tumor marker assessment, and abdominal CT, a PET-CT was performed after 9 and 15 months and compared to the control group. The recurrence rate was comparable in both groups. Tumors were detected earlier in the PET-group by an average of 3.2 months. Although resections of the recurring tumors were performed more often in the PET-CT group (15 vs 2), conclusions on a better survival could not be made. This was because the study was discontinued early due to the introduction of a new PET-CT generation. Also of concern is that in three cases false positive findings were generated by PET-CT which resulted in unnecessary diagnostic measures and surgical interventions.

In a prospective case series including 31 patients [997] a PET was performed after 2 years. The patients had previously had regular CT/MRI and were considered recurrence-free. In 6 patients the PET was positive and in 5 patients recurrences were identified. The outcome of these patients remains unknown. Overall, the participants considered the data insufficient to include PET/PET-CT/PET-MRI-examinations in routine follow-up care.

Colon contrast enema and virtual colonoscopies have not been evaluated for follow-up and cannot replace the endoscopic methods in follow-up.

10.4. Time Course of Follow-up

10.16.	Consensus-based Recommendation	2013
GCP	The start of follow-up is calculated from the time of the operation.	
	Strong consensus	

Background

80% of all recurrences are detected within the first two years after CRC operations, whereas practically no new recurrences are detected after 5 years [998]. This also applies to rectal cancer, although with this tumor entity a few locoregional recurrences were observed after this period [943]. This, however, does not justify extending follow-up beyond five years.

In most studies the follow-up interval in the first and second postoperative year was 3-months and shorter than in the following years [962, 963, 965, 966]. A 3-month interval was found to be superior to a 6-month interval in one study with otherwise similar examination methods [965]. However, the patients in the 3-month follow-up group received an additional annual CT, which in another study was not beneficial [966]. Due to the lack of clear data, the consensus conference decided on examination intervals of 6 months in the first 2 years. After 5 years, only colonoscopies should be performed to exclude secondary cancers.

10.5. Age Limit for Follow-up

In controlled studies of follow-up care, patients up to 87 years of age [962-967] were included. One cannot derive an age limit from these studies. It makes sense to adjust type and duration of follow-up according to operability, biological age, accompanying diseases, and the will to undergo surgery again if necessary.

10.6. Special Cases

10.17.	Recommendation	2008
Grade of Recommendation B	After local removal of a pT1 low-risk cancer, local endoscopic examinations should be performed after 6, 24, and 60 months (see also Chapter 6.4).	
Level of Evidence 4	Strong consensus	

10.18.	Consensus-based Recommendation	2008
GCP	After palliative tumor resection (R2 resection), programmed follow-up examinations are not necessary.	
	Strong consensus	

10.19.	Consensus-based Recommendation	2013
GCP	After curative therapy of metastases, stage IV patients should undergo a programmed follow-up.	
	Strong consensus	

10.20.	Recommendation	2008
Grade of Recommendation A	For cancer patients with HNPCC who have had a hemicolectomy, colonoscopic examinations and after subtotal colectomy, rectoscopic examinations should be performed in annual intervals (see also recommendation 5.23.).	
Level of Evidence 2a	Strong consensus	

10.21.	Recommendation	2008
Grade of Recommendation A	For cancer patients with FAP who have undergone proctocolectomy, a pouchoscopy should be performed annually (see also recommendation 5.35.).	
Level of Evidence 2a	Strong consensus	

10.22.	Recommendation	2008
Grade of Recommendation A	After ileorectostomy, a rectoscopy is necessary every 6 months (see also recommendation 5.35.).	
Level of Evidence 2a	Strong consensus	

10.7. Rehabilitation After Resection of Colorectal Cancer

10.23.	Consensus-based Recommendation	2013
GCP	After completing primary therapy, rehabilitation should be offered to all eligible patients. If rehabilitation is done directly after surgery, it must be guaranteed that an indicated adjuvant chemotherapy can be initiated timely. Alternatively, rehabilitation can be done after completing the adjuvant chemotherapy.	
	Strong consensus	

Background

The goal of rehabilitation is the elimination of cancer or therapy-related consequences as well as help of accepting remaining handicaps with the goal of an independent occupational, private, and social life. There is no evaluable literature on the relevance of rehabilitation measures for patients with colorectal cancer. Specific rehabilitation centers or clinics with gastroenterologic and oncologic expertise who implement quality assurance standards of the DRV and the requirements of colon centers should be preferred.

The need for rehabilitation after treatment of colorectal tumors is quite variable and significantly dependent on the type and amount of operative procedures as well as the consequences of therapy (continence problems, sexual function disturbances, stoma, etc.).

Psychosocial counseling and, if necessary, support is desirable in case of problems with psychological coping with the tumor disease, with the consequences of therapy, with social adjustment difficulties, and with professional reintroduction [972, 999, 1000].

Contact with persons who have had similar experiences can be especially helpful for those affected who have to cope psychologically or adjust to the changed life situation. Those who have been affected by the same events can convince others that a high quality of life is possible. They can give own examples as well as experiences in everyday life with the disease and handicaps. Therefore, contacts should be arranged with patient organizations.

In coordination with their familial environment, patients should always wait to start rehabilitation until after completing primary therapy. If rehabilitation measures are started before an indicated adjuvant chemotherapy, it must be guaranteed that therapy will be initiated during the rehabilitation process. Aside from the surgery report including the pathological assessment (tumor formula), the decision of the tumor board is also necessary and, therefore, should be made available to the rehabilitation facility.

10.8. Tertiary Prevention

10.8.1. Care Continuity and Continuation of the Health Promoting Activities after Acute Therapy and Rehabilitation

Even after the acute therapy phases and adjuvant chemotherapy, the patient should be counseled and followed by all professionals who participated in the treatment and follow-up care such as practicing physicians, nurses, or physical therapists.

10.8.1.1. Improvement of Care Continuity

An important goal should be the improvement of care coordination to avoid early termination or delayed start of therapy after leaving the hospital or to avoid regional insufficient care due to gaps in the system. The transition management of patients between primary therapy, rehabilitation, and other support with respect to side effects and symptoms is still poor [1001, 1002]. Especially after being discharged from the hospital the ambulatory care by practicing physicians and other caregivers (such as psycho-oncology, physical therapy, ergotherapy) is poorly coordinated. Patients are often faced with a situation of competing and unconnected health professionals. "Access" and "support" are especially poor in economically underdeveloped rural areas with low health care status [1003, 1004]. Studies confirm the advantage for patients of case management by concomitant professional steering of the treatment and follow-up course [1005]. Current systematic reviews show that health care continuity can be optimized especially by care interventions [1006, 1007]. An improved symptom control, an increased guideline compliance, an improved patient satisfaction, and an increased health associated quality of life can be achieved by multiprofessional treatment and follow-up steering [1005-1008].

Patients should also be supported by multiprofessional case management at the beginning of adjuvant therapy to ensure care continuity. Old age, the presence of comorbidities, low socio-economic status, the quality of the primary care facility, and access or distance to specialists were identified as significant risk factors for irregular care during transition from primary surgical to adjuvant (radio)chemotherapy [1001].

10.8.1.2. Continuation of Health Promoting Activities

Patients should be encouraged to continue lifestyle activities (see Chapter 10.8.1.2) that improve their health and quality of life. Furthermore, studies confirm that patients benefit if they can take the management of their symptoms and side effects (nausea, vomiting, pain, fatigue, depression, stoma care etc.) into their own hands [1009, 1010]. This can be supported by simple measures such as follow-up by phone, written information, keeping a patient diary including outcome control ("patient reported outcomes", PRO) [1005, 1007, 1008, 1011]. Cancer counseling centers and self-help groups play an important role in the realization of these measures.

10.8.2. Tertiary Prevention: Physical Activity, Nutrition, as well as Complementary and Alternative Therapy

10.8.2.1. Physical Activity

10.24.	Recommendation	2013
Grade of Recommendation B	Cohort studies indicate a connection between physical activity and a reduced relapse rate and improved survival. Patients should be encouraged to exercise.	
Level of Evidence 2b	Evidence from update literature search: [1012-1014]	
	Consensus	

Background

Three cohort studies [1012-1014] demonstrated that physical activity after curative CRC therapy reduces the relapse rate as well as the mortality. Exercise does not influence these parameters in untreated cancer. The positive effect of physical activity is also seen in overweight patients. However, merely losing weight has no effect on the prognosis.

A statistically significant risk reduction for disease-specific mortality is seen with a weekly physical exercise of 3 Met hours.

10.8.2.2. Nutrition

There is no study on tertiary prevention from which specific nutrition recommendations for patients following curative treatment of CRC can be derived.

Recommendations of the German Society for Nutrition are valid for a healthy lifestyle. An increased BMI does not correlate with relapse rate or survival [1012]. Weight reduction in overweight patients does not reduce the relapse rate [1012]. However, if a patient is very overweight, weight reduction should be the aim for general prevention.

There are no indications that the use of food supplements (vitamins and trace elements) has a positive effect on the relapse rate [1015]. Vitamins and trace elements should only be substituted if a deficiency has been determined.

10.8.2.3. Complementary and Alternative Medicine

Complementary procedures are based on different methods and substances which stem partially from natural medicine or in other ways from ideas of holistic therapy concepts.

They do not replace active antitumor or supportive therapy, but are complementary methods that allow patients to become independently active.

Complementary therapies can have side effects and interactions. Therefore, it is useful to have complementary medicine counseling by oncologically experienced physicians.

The most frequently used complementary treatment is the mistletoe therapy. A review and the Cochrane-review [75,76] conclude that most of the studies published so far are of poor quality. The few methodologically well done studies show no positive effect on survival for various tumor types. For CRC there are two retrospective studies that show a survival benefit [1016, 1017]. However, both have definite methodological flaws. The Cochrane-review and the systematic review found only weak indications for an improvement of quality of life for mistletoe therapy.

A review on the influence of mistletoe therapy on the quality of life was last published in 2010. It included 10 non-randomized controlled studies [1018]. Improvements were reported especially for coping, fatigue, sleep, exhaustion, nausea, appetite, depression, and anxiety. However, the studies characterized in the review as methodologically good by the authors also have considerable shortcomings.

For several mainly herbal substances preclinical data exist which indicate an antitumor effect [1019, 1020]. Currently, they do not justify clinical use outside of studies. So far, two small studies on green tea extract after colon polyps or colon cancer [1020] have been published. Both studies demonstrated that in the therapy group the rate of adenomas or cancer recurrence was significantly reduced.

There are a number of publications on the use of medicinal mushrooms in curatively treated CRC patients [1021, 1022]. These studies are from China and Japan and have been published in the original language. It is not known whether the consistently positive effects on survival rate are scientifically valid. Due to rare, but dangerous side effects the use of preparations from medicinal mushrooms is not recommended.

In traditional Chinese medicine and Ayurveda herbal preparations from Asia traces of heavy metals, pesticides, and drug substances such as corticosteroids and coumarins were repeatedly found. The use is not recommended, because a benefit has not been proven.

A therapeutic benefit of homeopathy as supportive treatment in CRC has not been confirmed [1007, 1023]. A Cochrane-analysis [1023] included a very heterogeneous group of studies. The two studies that were rated as positive did not include homeopathy as such. Therefore, no study confirms the positive effect of homeopathy for tumor patients [1023].

10.8.2.4. Alternative Healing Methods

A number of "alternatives" to scientifically recommended therapies are offered. There is no rationale for their use. These include: Ukrain, vitamin B 17 (apricot pits, bitter almond), "insulin potentiated therapy", low-carbohydrate diet, "vitamin-rich according to Dr. Rath", "Neue Germanische Medizin®", autologous blood cytokines, Zapper, "redifferentiation therapy". It is important to shield patients by taking a clear position on such offers.

Table 24: Programmed Examination for the Follow-Up of CRC UICC II or III

Examination	Months										
	3	6	9	12	15	18	21	24	36	48	60
Medical history, phys. exam, CEA		X		X		X		X	X	X	X
Colonoscopy		X*		X**							X**
Abdominal ultrasound***		X		X		X		X	X	X	X
Sigmoidoscopy (rectoscopy) ****		X		X		X		X			
Spiral computer tomography x	X										
Chest x-ray *****				X				X	X	X	X
<p>* if a complete colonoscopy was not done pre-operatively</p> <p>** if result is negative (no adenoma, no cancer), next colonoscopy after 5 years</p> <p>*** a meta-analysis showed a benefit for imaging procedures for the detection of liver metastases in follow-up care. Therefore, the expert committee decided to use the simplest and cheapest method.</p> <p>**** only for rectal cancer without neoadjuvant or adjuvant radiochemotherapy</p> <p>***** only for rectal cancer an annual chest x-ray may be done</p> <p>x only for rectal cancer 3 months after tumor-specific therapy has been completed (operation or adjuvant radiotherapy/chemotherapy) as initial finding</p>											

11. Quality Indicators

Quality indicators are measured variables that serve the evaluation of the quality of structures, processes, or results they are based on⁸. Their primary goal is the continuous improvement of care. Quality indicators as quality-associated indices, thus, are an important part of quality management. It must be considered, however, that individual indicators only look at individual aspects of the complex care. Therefore, the choice of suitable indicators is very important.

All strong recommendations (Grade of Recommendation A) as well as statements with high evidence level (LoE 1) were the basis for the quality indicators. Quality indicators were derived from the recommendations of this guideline according to the methodological specifications. These individual methodological steps can be found in the guideline report of this guideline.

A total of 10 indicators were included (see Table 25). These should be understood as preliminary suggestions. A final evaluation cannot be made until a necessary pilot study with surveys has been done.

Table 25: Suggestions for Quality Indicators

Quality indicator	Reference recommendation	Evidence basis/further information
QI 1: Report on distance from the mesorectal fascia		
<p>Z: All patients with documented distance to mesorectal fascia in the report</p> <p>N: All patients with rectal cancer and MRI or thin-layer-CT of the pelvis</p>	<p>Recommendation 7.17.</p> <p>The report should include information on the distance to the mesorectal fascia.</p>	<p>GCP, strong consensus</p> <p>References: [559, 560]</p>
QI 2: Lymph node examination		
<p>Z: Number of patients with \geq 12 pathologically examined lymph nodes</p> <p>N: All patients with CRC who have had a lymphadenectomy</p>	<p>Recommendation 7.61.</p> <p>12 or more lymph nodes should be removed and examined.</p>	<p>GCP, strong consensus</p> <p>References: [579, 690, 691]</p>
QI 3: Quality of TME		
<p>Z: Number of all patients with good or moderate quality (grade 1: mesorectal</p>	<p>Recommendation 7.66.</p> <p>Since the quality of the surgical resection according to the</p>	<p>GCP, strong consensus</p>

⁸ Ärztliches Zentrum für Qualität in der Medizin (ÄZQ), Gramsch E, Hoppe JD, Jonitz G, Köhler A, Ollenschläger G, Thomeczek C, (eds.). Kompendium Q-M-A. Qualitätsmanagement in der ambulanten Versorgung. 3rd ed. Köln: Dt. Ärzte-Verl.; 2008.

<p>fascia intact or grade 2: intramesorectal tears) TME</p> <p>N: All patients with radically operated rectal cancer</p>	<p>abovementioned categories allows conclusions on the prognosis concerning the development of local recurrence, this must be described in the pathohistological report as follows:</p> <p>The quality of the resection specimen is assessed by the integrity of the mesorectal fascia in 3 categories:</p> <p>mesorectal fascia is intact intramesorectal surface tears tears down to the muscularis propria or the tumor</p> <p>In case of rectal extirpation, preparation tears and tumor positive circumferential safety margins are not as frequent with a complete resection of the levator musculature.</p> <p>Therefore, the pathohistological report must describe the radicality in the levator musculature region. The following categories have to be used:</p> <p>levator musculature included in resection, no opening of the intestine or tumor muscularis propria intact, no opening of the intestine or tumor parts of the muscularis propria are missing or opening of the intestine or tumor</p> <p>The analysis must be performed by a pathologist.</p>	<p>References: [584, 702, 705, 706]</p>
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QI 4: Report on resection margin

<p>Z: Number of patients for whom the distance of the aboral tumor margin to the aboral resection margin and the distance of the tumor to the circumferential</p>	<p>Recommendation 7.65.</p> <p>The circumferential safety margin is negative if it measures 1mm or more (R0 "wide"). A circumferential safety margin is</p>	<p>GCP, strong consensus</p> <p>References: [560, 702-704]</p>
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mesorectal resection layer has been documented in mm. N: All patients with rectal cancer whose primary tumor was resected in form of TME or PME.	positive if the circumferential safety margin is less than 1mm (R0 "close") or if tumor tissue touches it directly (R1). The measured distance should be documented.	
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QI 5: Presentation in tumor conference

Z: Number of patients who were presented in an interdisciplinary tumor conference before therapy. N: All patients with rectal cancer and all patients with colon cancer stage IV.	Recommendation 7.1. All CRC patients should be presented in an interdisciplinary tumor conference after they have completed their primary therapy (e.g. operation, chemotherapy). Patients with the following constellations should already be presented before therapy: - every rectal cancer - every stage IV colon cancer - metachronic distant metastases - local recurrence - before every local ablative procedure, e.g. RFA/LITT/SIRT	GCP, consensus References: [517-519]
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QI 6: Adjuvant chemotherapy

Z: Number of patients who have undergone adjuvant chemotherapy. N: All patients with colon cancer UICC-stage III who have had an R0-resection of the primary tumor.	Recommendation 8.2. For patients with R0 resected stage III colon cancer, adjuvant therapy is indicated.	Recommendation LoE 1a, strong consensus References: [738, 742-746]
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QI 7: Neoadjuvant radiotherapy and radiochemotherapy

Z: Number of patients who have undergone neoadjuvant radiotherapy or radiochemotherapy. N: All patients with rectal cancer of the middle or lower third and TNM-categories cT3, 4/cM0, and/or cN1, 2/cM0 who have had surgery (= clinical	Recommendation: 8.10. For UICC stages II and III neoadjuvant radiotherapy or radiochemotherapy is indicated. cT1/2 cancer with questionable lymph node involvement are an exception; here, primary surgery (if necessary followed by adjuvant radiochemotherapy in the presence of pN+) is a possible therapeutic option.	Recommendation LoE 1b, strong consensus References: [801-803]
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UICC-stage II u. III).

(LoE 1b, EG A)

QI 8: Anastomotic leakage in rectal cancer

Z: Number of patients with anastomotic leakage grade B (with administration of antibiotics or interventional drainage or transanal lavage/drainage) or C ((re-)laparotomy) after elective interventions.

N: All patients with rectal cancer with creation of an anastomosis during elective primary tumor resection.

Comment:

The guideline committee has decided that not only quality goals based on structural issues, but also on results should be taken into consideration. Therefore, this QI is included in the guideline without strong consensus recommendation.

References:

[1024]

QI 9: Anastomotic leakage in colon cancer

Z: Number of patients with anastomotic leakage requiring re-intervention after elective interventions.

N: All patients with colon cancer who with creation of an anastomosis during elective tumor resection.

Comment:

The guideline committee has decided that not only quality goals based on structural issues, but also on results should be taken into consideration. Therefore, this QI is included in the guideline without strong consensus recommendation.

QI 10: Marking of stoma position

Z: Number of patients with pre-operatively marked stoma position

N: All patients with rectal cancer who have had surgery with stoma construction

Recommendation: 7.42.

The stoma position has to be marked pre-operatively.

GCP, consensus

References:

[636, 637]

12. Appendix

12.1. UICC-Classification of Colorectal Cancer

The UICC-stage classification was introduced by the "Union Internationale Contre le Cancer" (UICC). It is based on statistical studies and gives information on the spread of cancer. The classification is the basis for prognosis and therapy plan preparation.

Table 26: UICC-Classification of CRC

UICC 2010	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1/ T2	N0	M0
Stage II	T3/ T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
Stage III	every T	N1/ N2	M0
IIIA	T1/ T2	N1	M0
	T1	N2a	M0
IIIB	T3/ T4	N1	M0
	T2/ T3	N2a	M0
	T1/ T2	N2b	M0
IIIC	T4a	N2a	M0
	T3/ T4a	N2b	M0
	T4b	N1/ N2	M0
Stage IV	every T	every N	M1
IVA	every T	every N	M1a
IVB	every T	every N	M1b

12.2. Amsterdam Criteria

Amsterdam Criteria (AC)

AC1=only CRC, AC2=also extracolonic manifestations [234, 1025]

1.	At least three family members with HNPCC-associated cancer (colon/rectum, endometrium, small intestine, urothelial (ureter/renal pelvis))
2.	At least two successive generations affected
3.	one first-degree family member affected
4.	A person with the disease at the time of the diagnosis who is younger than 50
5.	Exclusion of a familial adenomatous polyposis

12.3. Revised Bethesda-Criteria

Tumors from patients who fulfill one of the following criteria should be tested for microsatellite instability:

Revised Bethesda-Criteria [246]

Patients with CRC before age 50

Patients with syn- or metachronic colorectal or other HNPCC-associated tumors (colon, rectum, endometrium, stomach, ovaries, pancreas, ureter, renal pelvis, biliary system, brain (especially glioblastoma), skin (sebaceous gland adenomas and cancer, ceratoacanthomas, small intestine)) independent of age at diagnosis.

Patients with CRC before age 60 with typical histology of MSI-H- tumors (tumor-infiltrating lymphocytes, Crohn's like lesions, mucinous or signet ring cell differentiation, medular cancer).

Patients with CRC who have a 1st degree relative with CRC or HNPCC-associated tumor before age 50.

Patients with CRC (independent of age), who have at least two 1st or 2nd degree relatives who have been diagnosed with CRC or HNPCC-associated tumors (independent of age).

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