German Guideline Program
in Oncology (GGPO)

# Evidenced-based Guideline
# for Colorectal Cancer

**Guideline** (Long Version)

DKG
KREBSGESELLSCHAFT

Deutsche Krebshilfe
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AWMF

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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 Gastroenterology, Digestive and Metabolic Diseases (DGVS)



## 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): S3-Guideline Colorectal Cancer, long version 2.1, 2019, AWMF registrationnumber: 021-007OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/ [cited: DD/MM/YY]

## 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 printed. 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 OL-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, the German Cancer Society, and the German Cancer Aid 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. Available Documents on the Guideline and Implementation

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

- German Guideline Program in Oncology (https://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/)
- AWMF (http://www.awmf.org/leitlinien/detail/ll/021-007OL.html)
- Involved medical societies (e.g. https://www.dgvs.de/wissen-kompakt/leitlinien/leitlinien-der-dgvs/)
- Guidelines International Network (www.g-i-n.net)

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
- three patient guidelines concerning screening, early stage and advanced stage colorectal cancer (update currently in progress)
- guideline report
- translation (English)
- separate evidence reports and publications (Screening, preoperative diagnostics, therapy for patients with metastases and in the palliative situation: Analysis of the use of angiogenesis inhibitors and anti-EGFR-antibodies for patients with metastasised CRC)

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

## 1.9. Composition of the guideline group

### 1.9.1. Coordination and editorial work

Prof. Dr. Wolff Schmiegel (Bochum) and PD Dr. Christian Pox (Bremen)

Assistance: Jutta Thurn (Bochum)

### 1.9.2. Involved medical societies and authors

Table 1 contains the medical societies and other organisations and the mandated experts that were involved in the the guideline. Table 2 contains the members of the different working groups.

**Table 1: Involved medical societies and organisations**

| Involved medical societies and organisations | Mandated member/involved expert |
|---|---|
| Arbeitsgemeinschaft „Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin" in der DKG (ASORS) | J. Körber*, R. Caspari (Vertr.) *** , H. Link* |
| Arbeitsgemeinschaft Deutscher Tumorzentren (ADT) | H. Barlag*** |
| Arbeitsgemeinschaft für Psychoonkologie in der DKG (PSO) | P. Heußner |
| Arbeitsgemeinschaft Internistische Onkologie in der DKG (AIO) | M. Geissler***, R.-D. Hofheinz***, S. Stintzing***, V. Heinemann*** D. Arnold***, S. Hegewisch-Becker***, C.-H. Köhne*** |
| Arbeitsgemeinschaft Konferenz Onkologische Kranken- und Kinderkrankenpflege in der DKG (KOK) | M. Landenberger* |
| Arbeitsgemeinschaft Onkologische Pathologie in der DKG (AOP) | G. Baretton* |
| Arbeitsgemeinschaft Onkologische Pharmazie in der DKG (OPH) | M. Höckel*** |
| Arbeitsgemeinschaft Prävention und integrative Medizin in der Onkologie in der DKG (PRIO) | J. Hübner** |
| Arbeitsgemeinschaft Radiologische Onkologie in der DKG (ARO) | H. A. Wolff*** |
| Arbeitsgmeinschaft Bildgebung und Radioonkologie in der DKG (ABO) | J. Menke*** |
| Berufsverband Niedergelassener Gastroenterologen Deutschlands (bng) | A. Theilmeier*, B. Bokemeyer** |
| Bundesverband der Niedergelassenen Hämatologen und Onkologen in Deutschland (BNHO) | M. J. Eckart*** |
| Bundesverband Deutscher Pathologen (BDP) | C. Wittekind** |
| Chirurgische Arbeitsgemeinschaft für Colo-Proktologie in der DGAV (CACP) | S. Post** |
| Chirurgische Arbeitsgemeinschaft für Minimal Invasive Chirurgie in der DGAV (CAMIC) | M. Walz** |

| Involved medical societies and organisations | Mandated member/involved expert |
|---|---|
| Chirurgische Arbeitsgemeinschaft für Onkologie in der DGAV (CAO-V ()) | H.-R. Raab***, H. Lang*, J. Weitz**, M. Sailer** |
| Chirurgische Arbeitsgemeinschaft Onkolologie in der DKG (CAO) | C. T. Germer*** |
| Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) | A. Glitsch***, C. T. Germer***, W. Hohenberger**, M. Anthuber**, W. Bechstein**, K-W. Jauch**, K-H. Link**, H-R. Raab** |
| Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM) | J.-F. Chenot***, G. Egidi (Vertr)*** |
| Deutsche Gesellschaft für Chirurgie (DGCH) | W. Hohenberger***, H.-R. Raab*** |
| Deutsche Gesellschaft für Ernährungsmedizin (DGEM) | S. C. Bischoff**, J. Ockenga**, W. Scheppach** |
| Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO) | M. Geissler***, R.-D. Hofheinz***, S. Stintzing***, V. Heinemann***, D. Arnold***, S. Hegewisch-Becker***, C.-H. Köhne***, M. Heike**, T. Höhler** |
| Deutsche Gesellschaft für Humangenetik (GfH) | N. Rahner**, J. Epplen** |
| Deutsche Gesellschaft für Innere Medizin (DGIM) | T. Seufferlein***, J.F. Riemann** |
| Deutsche Gesellschaft für interventionelle Radiologie und minimal-invasive Therapie (DeGIR) | P. L. Pereira*** |
| Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DGKL) | S. Holdenrieder***, M. Neumaier*** C. Wagener** |
| Deutsche Gesellschaft für Koloproktologie (DGK) | W. Hohenberger*** |
| Deutsche Gesellschaft für Nuklearmedizin (DGN) | H. Amthauer***, K. Scheidhauer**, H. Ahmadzadehfar*** |
| Deutsche Gesellschaft für Pathologie (DGP) | A. Tannapfel*, A. Jung***, T. Kirchner*, P. Schirmacher***, G. Baretton*, C. Wittekind** |
| Deutsche Gesellschaft für Radioonkologie (DEGRO) | C. Rödel*, W. Budach***, H. Schmidberger***, R. Sauer** |

| Involved medical societies and organisations | Mandated member/involved expert |
|---|---|
| Deutsche Gesellschaft für Rehabilitationswissenschaften (DGRW) | J. Körber*** |
| Deutsche Gesellschaft Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) | R. Kiesslich***, W. Schmitt***, F. Kolligs*, H. Neuhaus***, C. Pox*, T. Rösch***, J. Trojan***, R. Porschen*, G. Folprecht***, U. Graeven*, M. Ebert***, W. Schmiegel*, T. Seufferlein***, J.F. Riemann**, S. C. Bischoff**, J. Ockenga**, W. Scheppach**, A. Sieg**, K. Schulmann**, B. Bokemeyer**, U. Melle**, A. Reinacher-Schick**, A. Holstege** |
| Deutsche Morbus Crohn/Colitis Ulcerosa Vereinigung (DCCV ) | C. Witte** |
| Deutsche Röntgengesellschaft (DRG) | A. Schreyer***, T. J. Vogl*, C. Stroszczynski (Vertr)***, H-J. Brambs**, P. L. Pereira** |
| Deutscher Hausärzteverband (HÄV) | P. Engeser** |
| Eingeladene Fachexperten (ohne Stimmrecht) | H.Brenner**, P. Lux** |
| Felix-Burda-Stiftung | C. Maar** |
| Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen (AQUA) | S. Ludt** |
| Stiftung Lebensblicke | J.F. Riemann** |
| Vereinigung für Stomaträger und für Menschen mit Darmkrebs (Deutsche ILCO) | M. Hass* |
| Zentralinstitut der Kassenärztlichen Versorgung in der BRD (ZI) | L. Altenhofen** |
| period of involvement<br><br>*   = 2011-2017 (Version 1 and 2);<br>**  = 2011-2012 (Version 1)<br>*** = 2013-2017 (Version 2) | |

Furthermore the guideline update 2017 was performed in cooperation with the DGP (Deutsche Gesellschaft für Palliativmedizin).

**Table 2: Members of the working groups**

| Working group | Members of the working group (WG-leaders in bold) |
| --- | --- |
| Chapter 3:<br>Prevention asymptomatic population | **J.F. Riemann,** S. C. Bischoff, F. Kolligs, J. Ockenga, W. Scheppach |
| Chapter 4:<br>Screening asymptomatic population | **C. Pox, A. Sieg,** L. Altenhofen, H-J. Brambs, H. Brenner, P. Engeser, A. Theilmeier |
| Chapter 5:<br>Risk groups | **N. Rahner, K. Schulmann,** G. Baretton, B. Bokemeyer, J. Epplen, U. Melle, R. Porschen, J. Weitz, C. Witte |
| Chapter 6:<br>Endoscopy: Performance and Polyp management | **T. Rösch, W. Schmitt,** G. Baretton, A. Glitsch, R. Kiesslich, F. Kolligs, H. Neuhaus, C. Pox, A. Schreyer, A. Tannapfel, A. Theilmeier, J. Trojan |
| Chapter 7:<br>Pre-operative diagnostics and surgery | **W. Hohenberger, S. Post,** M. Anthuber, W. Bechstein, U. Graeven, M. Hass, M. Heike, K-W. Jauch, T. Kirchner, H. Lang, K-H. Link, P. Pereira, H-R. Raab, A. Reinacher-Schick, C. Rödel, M. Sailer, R. Sauer, K. Scheidhauer, A. Tannapfel, T. Vogl, C. Wagener, M. Walz, C. Wittekind |
| Chapter 8:<br>Adjuvant and neoadjuvant therapy | **C. Rödel, R. Porschen,** W. Budach, G. Folprecht, M. Geissler, R.-D. Hofheinz, W. Hohenberger, S. Holdenrieder, J. Körber, J. Menke, H.-R. Raab, H. Schmidberger, S. Stintzing |
| Chapter 9:<br>Management of patients with metastases and in the palliative situation | **V. Heinemann, U. Graeven,** H. Amthauer, D. Arnold, R. Caspari, J.-F. Chenot, M. Ebert, M. J. Eckart, G. Egidi, C. T. Germer, M. Hass, S. Hegewisch-Becker, M. Höckel, A. Jung, T. Kirchner, C.-H. Köhne, M. Landenberger, H. Lang, H. Link, M. Neumaier, P. L. Pereira, P. Schirmacher, W. Schmiegel, T. Seufferlein, C. Stroszczynski, T. J. Vogl, H. A. Wolff |
| Chapter 10:<br>Follow-up care | **A. Holstege,** P. Heußner, T. Höhler, J. Hübner, J. Körber, M. Landenberger, H. Link |
| Quality indicators | **S. Wesselmann,** T. Langer, H. Ahmadzadehfar, D. Arnold, G. Baretton, H. Barlag, M. Ebert, M. Hass, V. Heinemann, W. Hohenberger, T. Kirchner, C.H. Köhne, F. Kolligs, M. Nothacker |

### 1.9.3.     Patientinvolvement

The guideline was produced under direct particpation of patient representatives. Maria Hass (Deutsche ILCO) and C. Witte (DCCV) participated in the guideline update with voting rights during the consensus conferences.

### 1.9.4.     Methodological Support

By the guidelines programm oncology

- Prof. Dr. Ina Kopp (AWMF), Marburg (2011/2012)
- Dr. Monika Nothacker, MPH (AWMF), Berlin (2013-2017)
- Dr. Markus Follmann, MPH MSc (DKG), Berlin (2011-2017)
- Dipl. Soz.Wiss. Thomas Langer (DKG), Berlin (2013-2017)

By external contractors:

- Dr. Barbara Buchberger, MPH, Laura Krabbe, M.A., Dr. Beate Lux, MPH (Essener Forschungsinstitut für Medizinmanagement GmbH): Evidence report for Version 2, see Chapter 1.8
- Dr. med. Simone Wesselmann, MBA (Update of quality indicators)
- Dr. Barbara Buchberger, Dr. Romy Heymann (Alfried Krupp von Bohlen und Halbach-Stiftungslehrstuhl für Medizinmanagement): Evidence report for Version 1, see Chapter 1.8)
- Dr. Michaela Eikermann, Christoph Mosch, Thomas Jaschinski, Monika Becker (Institut für Forschung in der Operativen Medizin [IFOM]): Evidence report for Version 1, see Chapter 1.8

## 1.10.        Abbreviations used

| Abbreviation | Explanation |
|---|---|
| AFAP | Attenuated FAP |
| ADR | Adenoma detection rate |
| AHB | Follow-up treatment |
| ASS | Acetylsalicylic adid |
| AWMF | Task Force of Scientific Medical Prefessional Societies |
| BMI | Body Mass Index |
| BSC | Best supportive Care |
| CEA | Carcio-embryonic Antigen |
| CT | CT scan |
| CTC | CT-Colonography |
| CU | Colitis Ulcerosa |
| DGE | German Society for Nutrition |
| EC | Expert Consensus |
| EMR | Endoscopic mucosal resection |
| ESD | Endoscopic submucosal dissection |
| FAP | Familial adenomatous polyposis |
| FICE | Fujinon intelligent colour enhancement |

| Abbreviation | Explanation |
|---|---|
| FOBT | Fecal occult blood test |
| FS | Folic acid |
| HNPCC | Hereditary colorectal cancer without polyposis |
| IEN | Intra-epithelial neoplasia |
| iFOBT/ FIT | Immunologic FOBT |
| IHC | Immunohistochemical test |
| CRC | Colorectal cancer |
| LITT | Laserinduced interstitial thermotherapy |
| LL | Guideline |
| MAP | MUTYH-associated polyposis |
| MMR | Mismatch-repair gene |
| MSA | Microsatellite analysis |
| MSCT | Multi-slice-CT |
| MSI | Microstellite instability |
| MSI-H | Microsatellite instability high |
| MSI-L | Microsatellite instability low |
| MSS | Microsatellite stability |
| NBI | Narrow Band Imaging |
| EGD | Esophagogastroduodenoscopy |
| OL | Oncology headquarters of the DKG |
| OR | Odds Ratio |
| ORR | Overall response rate |
| PCI | Peritoneal cancer index |
| PET | Positron emission tomography |
| PJS | Peutz-Jeghers-syndrome |
| PSC | Primary sclerosing cholangitis |
| RCT | Randomized controlled study |

| Abbreviation | Explanation |
|---|---|
| RFA | Radiofrequency ablation |
| RR | Relative risk |
| RT | Radiotherapy |
| SIRT | Selective internal radiation therapy |
| SR | Systematic review |
| SSA | Sessile serrated adenoma |
| TME | Total mesorectal excision |
| TSA | Traditional serratted adenoma |
| WHO | World Health Organization |

# 2.    Introduction

## 2.1.    Important new features of the updated guideline (Version 2, 2017)

The following chapters were updated:

- Chapter 6: Endoscopy: Performance and Polyp management

- Chapter 8:  Adjuvant and neoadjuvant therapy and

- Chapter 9: Management of patients with metastases and in the palliative situation

A detailed list of changes performed in the update can be found in chapter 12.4.

In chapter 6 especially the recommendation on the time interval of surveillance colonoscopy after endoscopic removal of sessile serrated adenomas was changed (see recommendation 6.25) as well as the recommendation on the time interval of surveillance colonoscopy after removal of 1 or 2 adenomas < 1 cm without high grade intraepithelial neoplasia was updated (see recommendation 6.18 and 6.19). A recommendation concerning the importance of tumor budding was also added (see recommendation 6.10 and 6.12).

In chapter 8 the update included the time interval of adjuvant chemotherapy after colon cancer surgery (see recommendation 8.2. and 8.3.), neoadjuvant therapy of rectal cancer (see recommendation 8.2.1) and the role of adjuvant chemotherapy after neoadjuvant therapy of rectal cancer (see recommendation 8.33.).

Chapter 9 was completely updated and newly structured.

## 2.2.    Scope and Purpose

### 2.2.1.    Goal and Issues

Colorectal cancer (CRC) is one of the most common malignant tumors in Germany with over 64.000 newly-diagnosed cases and about 26,000 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,  2008 the TC IV, VI, and VII and 2011/2012 the topic complexes I, II, III, V und VIII as well as parts of IV, VI and VII).  The current update concerns the topic complexes IV, VI and VII.

During the update process in 2017, the guideline group decided that recommendations would be made on the following issues:

- When should a surveillance colonoscopy be performed after removal of a sessile serrated adenoma?

- When should a surveillance colonoscopy be performed after removal of 1 or 2 adenomas < 1 cm without high grade intraepithelial neoplasia?

- Up to which time interval after surgery of a colon cancer should an adjuvant chemotherapy be performed?

- Which rectal cancer patient should receive neoadjuvant treatment?

- Is there an indication for adjuvant chemotherapy after neoadjuvant treatment of rectal cacer?

- What is the benefit of adjuvant treatment after R0-resection of liver metastases?

- What is the benefit of a combination therapy with an EGFR-antibody or VEGF-pathway Inhibitor in the firstline-therapy?

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

### 2.2.2.      Audience

This guideline is mainly directed at physicans who work on prevention and treatment of CRC in the ambulatory and inpatient sector. Furthermore it is intended to provide information on good clinical practice for cooperation partners of the medical profession (departments in the health care sector), professional associations, patient- and support groups, national and federal quality assurance networks and projects (eg. KoQK, ADT, IQWiG, GEKID, IQTIG), public health institutions and decision-makers on the national and federal level, certification institutions (eg. OnkoZert), paying authorities als well as the (professional) public.

### 2.2.3.      Period of Validity and Update Processes

The S3-Leitlinie is valid until the next update. The validity is approximately 5 years. Intended are regular updates of the whole guideline, in case of urgent need of change individual recommendations/topics can be revised.

In the recommendation boxes the date of the last update are listed (2008, 2013 or 2017).

Comments and suggestions for the update are explicitly welcome and can be addressed to the guideline secretariat.

Guideline coordination: PD Dr. Christian P. Pox

Guideline secretariat

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## 2.3. 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.

### 2.3.1. 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 1economic studies |
| 1b | Individual RCT (with narrow confidence interval) | Individual inception cohort study with > 80% follow-up; CDR validated in | Validating cohort study with good reference standards; or CDR tested within one | 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 |

| Level | Therapy/ Prevention, Etiology / Harm | Prognosis | Diagnosis | Differential diagnosis / symptom prevalence study | Economic and decision analyses |
|---|---|---|---|---|---|
| | | a single population | clinical center | | |
| 1c | All or none§ | All or none case-series | Absolute SpPins and SnNouts" " | All or none case-series | Absolute better-value or worse-value 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 |
| 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 | Non-consecutive cohort study; | Analysis based on limited alternatives or costs, poor quality |

| Level | Therapy/ Prevention, Etiology / Harm | Prognosis | Diagnosis | Differential diagnosis / symptom prevalence study | Economic and decision analyses |
|---|---|---|---|---|---|
| | | | without consistently applied reference standards | or very limited population | 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" | 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" | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" |

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

" Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)

"¡ See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.

§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

" " An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.

"¡"¡ Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.

| Level | Therapy/ Prevention, Etiology / Harm | Prognosis | Diagnosis | Differential diagnosis / symptom prevalence study | Economic and decision analyses |
|---|---|---|---|---|---|

" " " Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

" " " " Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.

** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

*** By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.

 **** Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 – 5 years chronic

## 2.3.2.          Scheme of the Grades of Recommendation

The methodology of the guideline programme oncology asks - according to the AWMF-rules – for the allocation of a grade of recommendation by the guideline authors in the context of a formal consensus process. Accordingly moderated nominal group processes as well as structured consensus conferences took place [1]. As part of this process a formal vote was taken on the recommendations by all mandate holders. The result of each vote (degree of consensus) is categorized according to Table 4 for each recommendation.

For all evidence-based statements (see Chapter 2.3.3) and recommendations, the evidence level (see Chapter 2.3.1) of the underlying studies as well as for recommendations the degree of recommendation (Grades of Recommendation) 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**

| Grades of Recommendation | Description | Syntax |
|---|---|---|
| A | Strong recommendation | shall/shall not |
| B | Recommendation | should/should not |
| 0 | Recommendation open | may/can |

**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 |

## 2.3.3.    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.

## 2.3.4.    Expert consensus

Recommendations are classified as expert consensus (EC) if no literature research was performed. Usually these recommendations address fields of good clinical practice for which no scientific studies are necessary or to be expected. For the grading of expert consensus there are no symbols, the strength of recommendation is a result of the wording (shall/should/can) according to Table 4**Fehler! Verweisquelle konnte nicht gefunden werden.**.

## 2.3.5.    Independence and Declaration of Possible Conflict of Interest

The drafting and update of the guideline was performed independently of the funding organization, the German cancer aid (Deutsche Krebshilfe). The mandate holders and experts are to be thanked for their voluntary work without which the formulation of the S3-guideline would not have been possible.

All members of the guideline group gave a written statement concerning possible conflicts of interest. These can be found in the guideline report (http://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/).

The relevance of the conflicts of interest for the guideline was discussed in several meetings (kick-off meeting and consensus conference) and by email. In the update 2010-2013 (Version 1) the conflicts of interest were reviewed and evaluated by the coordinators. For the update 2015-2017 (Version 2) Prof. Kolligs the authorized conflict of interest representative performed the review and evaluation of the disclosed conflicts of interest.

As proposed by Prof. Kolligs the guideline group decided that there would be no restrictions for any delegate in the voting process as inappropriate distortion of guideline recommendations was considered highly unlikely. The reason for this was the methodological approach as well as the multidisciplinary composition of the guideline group.

During the update 2010-2013 Prof. Schmiegel abstained from voting on FOBT/iFOBT, genetic stool tests and M2-PK because of a possible conflict of interest.

The risk of interference by conflicts of interest was also reduced by engaging independent external institutes for literature search, selection and assessment for politically sensitive topics. The formal consensus process and interdisciplinary drafting of the guideline are additional instruments to minimize interference by industry.

## 2.4. Editorial information

### Gender neutral formulations

Solely for better legibility no gender neutral formulations are used. All personalized terms should therefore be considered to be gender neutral.

**Participatory decision making**

All recommendations in the guideline should be seen as recommendations, which are made using a participatory decision making process between physicians and patients and their family.

# 3.        Prevention Asymptomatic Population

## 3.1.        Lifestyle Habits

| 3.1. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | To reduce the risk of colorectal cancer regular physical activity is recommended. | |
| Level of Evidence<br><br>**2a** | Evidence from update literature search[1]:  [2-13] | |
| | Strong consensus | |

| 3.2. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | To reduce the risk of colorectal cancer weight reduction is recommended for overweight persons. | |
| Level of Evidence<br><br>**2a** | Evidence from update literature search:  [2, 9, 14-19] | |
| | Strong consensus | |

| 3.3. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | It is recommended to refrain from smoking. | |
| Level of Evidence<br><br>**2a** | Evidence from update literature search: [2, 11, 20-26] | |
| | Strong consensus | |

**Background**

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

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 30 % lower risk of cancer. Already 30 to 60 minutes of moderate physical activity per day is associated with a lower cancer risk [2-13].

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 [19] It is not clear whether the risk increase is due to obesity, altered hormone levels, increased calorie uptake, or absence of physical activity [2, 9, 14-19].

Smoking is associated with a risk for colon adenomas that is twice as high and an increased risk of cancer [2, 11, 20-26].

## 3.2.        Diet Recommendations

| 3.4. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2b** | A specific diet recommendation to reduce the CRC risk can currently not be given. | |
| | Evidence from update literature search: [27-33] | |
| | Consensus | |

| 3.5. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [27]. 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 [28-31]. However, there have also been studies that found no correlation between diet factors and CRC [32, 33]. 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. | Evidence-based Recommendation | 2013 |
|------|-------------------------------|------|
| Grade of Recommendation<br><br>**B** | To reduce the risk of CRC fiber uptake should be at least 30 g per day. | |
| evel of Evidence<br><br>**2a** | Evidence from update literature search: [34-38] | |
| | Consensus | |

**Background**

Despite controversial data, the evidence is sufficient to recommend a fiber rich diet of 30 g/day [34-38]. 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 % [34]. 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 [37]. 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 Grade of Recommendation B was determined.

| 3.7. | Evidence-based Recommendation | 2013 |
|------|-------------------------------|------|
| Grade of Recommendation<br><br>**B** | To reduce the risk of CRC alcohol consumption should be restricted. | |
| Level of Evidence<br><br>**2a** | Evidence from update literature search: [39-42] | |
| | Consensus | |

**Background**

There is a positive correlation between high alcohol consumption and the development of CRC [39-42 especially in persons with low folic acid and/or methionine uptake [40].Abstinent persons and persons who drink little alcohol have a significantly lower cancer risk [39-42]. 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 [42]. The risk correlates with the amount of alcohol consumed not with the type of alcoholic beverage [40].

| 3.8. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Red or processed meat should only be consumed in small amounts (not daily). | |
| Level of Evidence<br><br>**2a** | Evidence from update literature search:  [38, 43-47] | |
| | Consensus | |

**Background**

A high consumption of red meat (beef, veal, pork, and lamb) and processed meat is associated with a higher CRC risk [38, 43-47]. There is no positive correlation between poultry and/or poultry products [46]. 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 [47].

| 3.9. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2a** | No recommendation can be given about an increased fish consumption. | |
| | Evidence from update literature search : [43, 45, 46, 48-50] | |
| | 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 [48]. However, the data are contradictory. This is probably due to the different amounts of fish that were consumed in the different studies [43, 45, 46, 48-50]. 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 |
|---|---|---|
| **EC** | 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 [51-53].

| 3.11. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [54, 55]. 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 [56]. 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 |
|---|---|---|
| **EC** | 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 [57]. 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 [31, 32, 38, 48, 58-60] .

| 3.13. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2b** | There is no connection between acrylamide uptake and CRC risk. | |
| | de Novo: [61-64] | |
| | 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) [61]. This study confirmed previous trials that showed no connection between acrylamide and CRC manifestation in men and women [62-64].

## 3.3.  Micronutrients

| 3.14. | Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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: [65] |
| 3b | ... including -carotene | de Novo: [65] |
| 3b | ... vitamin A | de Novo: [65] |
| 4 | ... vitamin C, vitamin D, vitamin E | de Novo: [65-67] |
| 1a | ... and folic acid | de Novo: [68-72] |
| 1b | These recommendations are also valid for calcium | Update literature research: [66, 67, 73-75] |
| 2b | ... magnesium | de Novo: [76] |
| 2b | ... and selenium. | de Novo: [77, 78] |
| | 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 [73-75] . However, data on a CRC risk reducing effect of calcium or vitamin D, alone or in combination, were not convincing [66, 67].

There is no evidence that the intake of beta-carotene, vitamin A, or vitamin E can reduce the CRC risk. A meta-analysis [65] 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 [68]. Studies on the recurrence of colon adenomas led to divergent results [69-72].

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 [77, 78].

## 3.4.        Drugs

| 3.15. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | COX-2 inhibitors shall not be taken prophylactically against CRC by the asymptomatic population. | |
| Level of Evidence<br><br>**3b** | de Novo: [79-82] | |
| | Consensus | |

| 3.16. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Statines should not be taken as a primary prophylaxis against CRC. | |
| Level of Evidence<br><br>**2b** | de Novo: [83] | |
| | Strong consensus | |

| 3.17. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Acetylsalicylic acid shall not be taken prophylactically against CRC by the asymptomatic population. | |
| Level of Evidence<br><br>**2a** | Guideline adaptation: [84-87] | |
| | Consensus | |

| 3.18. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Hormone therapy[2] should not be given for CRC risk reduction in women. | |
| Level of Evidence<br><br>**1a** | Guideline adaptation: [88, 89] | |
| | 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 [79]. 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 [80-82]. 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 [83]. 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 [90]. 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 [85]. Another meta-analysis of 8

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

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 [86]. 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 randomized studies [85]. Due to the frequent incidence of gastrointestinal bleeding under ASS [87] 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 [84].

Hormone therapy can reduce the risk of CRC [89]. 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 [88] and the guideline Hormone Therapy in Peri- and Postmenopause of the German Society for Gynecology and Obstetrics [91].

# 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 |
|------|--------------------------------|------|
| **EC** | 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 [92, 93]. A prospective colonoscopy study showed that there was a lower rate of advanced adenomas among 40 to 49 year old subjects (3.5%) [94]. 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 [95]. However, it may be considered for individual cases. The incidence of advancing neoplasias increases with age [96]. Performing endoscopic procedures also seems to be safe in older patients [97]. However, in a cohort study the complication rate increased with age [98]. 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 [99]. 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) [100, 101]. In addition, as was recently demonstrated, the CRC-associated mortality is reduced [102].

Although the participation rate was low compared to FOBT, individual randomized studies showed that in an intention to screen analysis both sigmoidoscopies [103] and colonoscopies [104] detect more advanced neoplasias. This was particularly due to the clearly higher sensitivity for advanced adenomas.

### 4.2.1.1.   Colonoscopy

| 4.2. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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 [3] 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<br><br>**3b** | De Novo: [98, 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 prognostis 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 [98]. In Germany, about 1/3 of the detected cancer in screening colonoscopies are located proximal to the colon descendens [98]. In further studies, 46 to 52% of patients with proximal neoplasias

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[3] https://www.g-ba.de/informationen/richtlinien/17/

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 [98]. 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 [121].

## 4.2.1.2. Sigmoidoscopy

| 4.3. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Quality assured sigmoidoscopies should be offered as a screening measure to those who refuse a colonoscopy. | |
| Level of Evidence<br><br>**2b** | De Novo: [122] | |
| | Strong consensus | |

| 4.4. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | For the possible detection of proximal cancer, an annual FOBT test should be performed in addition to a sigmoidoscopy. | |
| Level of Evidence<br><br>**3b** | De Novo: [109, 112, 123-130] | |
| | 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 % [122]. 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, 123], and in one study even as long as 16 years [124]. 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 [125]. Another study in 2,146 participants with negative sigmoidoscopies compared screening/follow-up intervals of 3 and 5 years [126]. 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 [127]. In several studies, however, a combination of sigmoidoscopy and one-time FOBT was not significantly better than sigmoidoscopy alone [128, 129]. In the most recent study from Japan, a combination of sigmoidoscopy and FIT detected 10% (absolute) more advanced neoplasias [130].

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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Capsule colonoscopy should not be used for colon cancer screening in the asymptomatic population. | |
| Level of Evidence<br><br>**4** | De Novo: [131-137] | |
| | 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 [131-135]. For the second capsule generation (PCC2) with improved technical characteristics, a sensitivity of 84-89% was reported for polyps larger than 6 mm [136, 137]. 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 Tests[4]

### 4.2.2.1.  Fecal Occult Blood Test (FOBT)

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

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

| 4.8. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence **1b** | Annual FOBTs are better to reduce CRC-associated mortality than testing once every two years. | |
| | De Novo: [138] | |
| | Strong consensus | |

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[4] 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.

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

| 4.10. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | Immunologic FOBTs (iFOBT) with a proven high specificity of >90% and sensitivity may be used alternatively to the Guaiac test. | |
| Level of Evidence<br><br>**3a** | De Novo: [103, 139-148] | |
| | 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 [149], repeated testing is required in order to improve detection of CRC [150, 151]. 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) [152].

The results of four large randomized studies exist on the effectiveness of FOBT as a screening method for colorectal cancer [138, 153, 154]. 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) [155]. 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 [138].

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% [138, 156]) 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 [157-159]. 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 [160]. However, the necessity of dietary restrictions for FOBT was questioned in a meta-analysis [161].

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 [162]. In one study it was even only 64% [163].

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 [164].

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) [139]. In two studies which compared the gFOBT HemoFEC® or Hemoccult Sensa® with an iFOBT (Inform® or FlexSure®), however, no significant difference was found [139]. In particular, in the two largest randomized studies from The Netherlands [103, 140] a significant difference was found suggesting a superiorbity 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 [141]. 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 [142, 148]. 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 [144-146]. However, a trial from The Netherlands shows that reducing the cut-off has a similar effect [147] ADDIN EN.CITE [**Fehler! Textmarke nicht definiert.**.

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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Stool tests that measure DNA changes cannot be recommended for CRC screening in the asymptomatic population. | |
| Level of Evidence<br><br>**3b** | De Novo: [165-170] | |
| | 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 [165-168]. 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 [169]. 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 [170]. 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 Hemoccult®-test was 11%, for the Hemoccult-Sensa® 21%. The specificity for the DNA-panel II was not determined. Overall panel I was better than one of the gFOBTs (Hemoccult®) and equal to the other gFOBT (HemoccultSensa®). 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | The M2-PK stool test should not be used for colon cancer screening in the asymptomatic population. | |
| Level of Evidence<br><br>**4** | De Novo: [171, 172] | |
| | 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 [171, 172]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Neither CT-colonography nor MR-colonography should be used for colon cancer screening in the asymptomatic population.<br><br>In case of an incomplete colonoscopy (e.g. adhesions) und if the patient still insists on complete colon analysis a CT- or MR-colonography should be done. | |
| Level of Evidence<br><br>**3b** | De Novo: [173-175] | |
| | 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 [173, 174]. 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 [175].

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. | Consensus-based Statement | 2013 |
|---|---|---|
| **EC** | 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 [140, 176-186].

## 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 [95] and the Asian Pacific consensus recommendation from 2007 [187]. 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. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2a** | First degree relatives of patients with CRC have an increased risk of developing colorectal cancer. | |
| | Evidence from update literature search: [188-202] | |
| | Consensus | |

| 5.2. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2b** | Second degree relatives have a slightly increased risk of developing colorectal cancer. | |
| | Evidence from update literature search: [188, 189, 192, 193, 203, 204] | |
| | 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 [188]. 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 [189-201]. 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 [190, 202].

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 [189, 192, 193, 203, 204]. 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. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2b** | First degree relatives of patients with a colorectal adenoma before age 50 have an increased colorectal cancer risk. | |
| | Evidence from update literature search: [190, 193, 205-208] | |
| | Consensus | |

**Background**

The risk for these relatives to develop colorectal cancer is on average about two-fold higher compared to the general population [190, 193, 205-208]; there is an 80% higher risk for parents and siblings of adenoma patients in comparison to their spouses [205]. 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 [206]. 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. | Evidence-based Statement | 2008 |
|---|---|---|
| Level of Evidence<br><br>**2b** | Every histologically verified adenoma poses an increased risk for a colorectal cancer. This is especially true for:<br><br>• multiple ( ≥3 ) adenomas<br><br>• large ( >1 cm ) adenomas | |
| | [100, 101, 209, 210] | |
| | Consensus | |

**Background**

In general, the removal of small singular adenomas results in a reduced risk of up to 90% to develop metachronous colorectal cancer [100, 101, 209, 210]. 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 [193, 210-217]. In addition, multiple adenomas are also associated with an increased risk (4-6fold) of developing a metachronous cancer [193, 210, 212, 213, 215, 216]. 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, 218].

| 5.5. | Consensus-based Recommendation | 2013 |
|------|-------------------------------|------|
| **EC** | 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 accessable 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/frageboegen/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 [219]. There are currently no data on the other questionnaires.

## 5.1.2.        Primary Prevention

| 5.6. | Evidence-based Statement | 2013 |
|---|---|---|
| **Level of Evidence**<br><br>**1 b** | Special recommendations compared to those of the general population cannot be given for primary prevention (dietetary measures, chemoprevention) due to contradictory data available for the mentioned risk groups. | |
| | Evidence from update literature search: [220-223] | |
| | 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 [220-223].

## 5.1.3.        Screening Tests

### 5.1.3.1.        First-degree Relatives of Patients with Colorectal Cancer

| 5.7. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [193, 195, 202, 204, 224-229].

The recommendation follows the American guideline recommendation [230]. 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 |
|---|---|---|
| **EC** | 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:<br><br>If at least two independent cancer from a family show MSS, colonoscopies should be performed in 3-5 year intervals from age 25.<br><br>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. | |
| | Strong consensus | |

| 5.9. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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:<br><br>If no tumor tissue is available to test for HNPCC-typical characteristics, the interval should not exceed 3 years. | |
| | Consensus | |

| 5.10. | Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [231, 232]. 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 |
|---|---|---|
| **EC** | 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 [93, 195, 204, 206].

## 5.2.  Hereditary Colorectal Cancer

| 5.12. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| **EC** | 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 [233-235]. 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. | **Consensus-based Statement** | 2013 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| **EC** | 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 [236]. 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) [237].

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 [238].

The cumulative lifetime risk for small bowel cancer in the context of an HNPCC is 4-8% [238, 239]. For 35-50% of the cases, HNPCC-associated small bowel cancer are localized in the duodenum [240]. 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 [241] 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%) [242, 243].

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 [244-246]. 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 [247].

| 5.16. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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) [248]. 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 % [249]. 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 |
|---|---|---|
| **EC** | 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 [250-253]. 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) [254]. 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 [254].

### 5.2.1.2. Adenomatous Polyposis-Syndrome

#### 5.2.1.2.1. Patients with Classic Familial Adenomatous Polyposis (FAP)

| 5.18. | **Evidence-based Statement** | 2008 |
|---|---|---|
| Level of Evidence **2a** | All patients with untreated FAP will - with rare exceptions - develop colorectal cancer. | |
| | [255] | |

**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  [255].

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

| 5.19. | Consensus-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**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: [255-263] | |

**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 [255-260]. 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) [261]. In individual cases the clinical differentiation from HNPCC can be difficult [262]. Therefore, a molecular genetic diagnosis can be very helpful (microsatellite analysis, APC, MUTYH) in the clinical differential diagnosis of some cases of attenuated FAP [263]. 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 [263].

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

| 5.20. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**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: [264-271] | |

**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 [264]. It is diagnosed in 15-20 % of the APC-mutation negative colorectal adenomatoses [265, 266].

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) [267]. If untreated, the CRC lifetime risk is about 70-80 % [268]. 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 [269]. In addition, it has been reported that up to 50 % of the MAP patients have hyperplastic polyps [[270].

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 [271].

## 5.2.2. Screening

### 5.2.2.1. HNPCC / Lynch-Syndrome

| 5.21. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**1c** | Evidence from update literature search: [272, 273] | |
| | Strong consensus | |

| 5.22. | **Evidence-based Statement** | 2008 |
|---|---|---|
| Level of Evidence<br><br>**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 [272], 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 [273]. 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 |
|---|---|---|
| **EC** | 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 [245]. 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 [274]. 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 [274-276] (Table 6). A prospective study of the German HNPCC-consortium with 1 year intervals showed a significantly better stage distribution for detected asymptomatic CRC [231].

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 [277]. The colonoscopy may be done as a chromoendoscopy. Prospective studies demonstrated a significant

increase in adenoma detection rate with the use of chromoendoscopy [278-280]. However, currently it is not clear whether this improves the interval cancer rate or the mortality.

| 5.24. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**4** | [244, 281-284] | |
| | Strong consensus | |

| 5.25. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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% [244, 281]. 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 [282-284]. 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 [285], the recommendation of Overview of Guideline-Based Specific Procedural Quality Indicators of Colonoscopy 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 |
|---|---|---|
| **EC** | 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 [238]. A familial cumulation (at least 2 affected members with gastric cancer) was only observed in 26% of the MLH1- and MSH2-mutation carriers [286]. 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% [238, 239]. 35-50% of the small intestine cancer are located in the duodenum [240]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Chemoprevention in HNPCC patients should not be performed. | |
| Level of Evidence<br><br>**2b** | Evidence from update literature search: [287, 288] | |
| | 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 [287]. 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 [288]. 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 |
|---|---|---|
| **EC** | Prophylactic colectomy or proctocolectomy in HNPCC mutation carriers shall not be performed.<br><br>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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**2a** | Evidence from update literature search: [274, 275, 289-292] | |
| | Strong consensus | |

**Background**

Because regular surveillance can detect pre-malignant adenomas and nearly all surveillance detected cancer are UICC stage I or II [274, 275] 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 [289-292].

| 5.30. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | For female patients who are known Lynch-syndrome mutation carriers a prophylactic hysterectomy and, if necessary, an ovarectomy 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 [293]. Following prophylactic ovarectomy, 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. | Evidence-based 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, 294] | |
| | Strong consensus | |

| 5.32. | Evidence-based 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**4** | [120, 193, 294, 295] | |
| | 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 [294]. 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. It always has to be combined with human genetic counseling [GenDG] [120]. 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 [193, 294, 295]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**1c** | Evidence from update literature search: [263, 296-301] | |
| | Strong consensus | |

| 5.35. | **Consensus-based Recommendation** | 2013 |
|---|---|---|
| **EC** | After proctocolectomy a pouchoscopy should be performed regularly. Patients with a remaining rectal stump should untergo 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 [296-300]. 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 [263]. 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) [299-301]. In the natural course of FAP, cancer appear at a median age of 36 [302]. 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 [303]. The long-term prognosis for IPAA (ileo-pouch anal anastamosis) concerning the CRC-rate is better [304-307]. 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 |
|---|---|---|
| **EC** | 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).<br><br>If duodenal-/papillary adenomas are identified, an indication for endoscopic polypectomy should be considered.<br><br>If the duodenal polyposis is severe (Spigelman IV) or an invasive cancer without distant metastases is present, there is an indication for surgical resection. | |
| | Consensus | |

**Background**

The lifetime risk of developing duodenal polyps is between 80 and 90% for FAP patients [233, 234]. 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 [308]. With regard to the extent of duodenal polyposis, the Spigelman classification (see Table 7) should be used [309]. The average age of patients with serious adenomatosis of the duodenum is about 43 (range 24-65) [235]. Altogether, it appears that the growth behavior of duodenal adenomas is slower than that of colorectal adenomas [310, 311] and depends more on increasing age (increases at age >40) than on the initial stage [312]. 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 [313, 314]. The lifetime risk for a duodenal cancer for patients with FAP is between 3 and 4% [315, 316] and is, therefore, up to 300 times more common than in the general population [317]. 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 [318].

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 tubolovillous 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 [310]. 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 [319, 320]. An operative duodenotomy with polypectomy cannot be recommended due to a high rate of recurrence [321, 322]. In principal, even after extensive surgical treatment the appearance of new adenomas cannot be prevented [321]. Currently, it is not clear whether regular duodenal screening prolongs life [315]. 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 [323, 324], 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) [310, 311]. 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 |
|-------|--------------------------------|------|
| **EC** | 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) [325-327], 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 [328]. For raloxifen there are also comparable data from a small case series [329]. Progressive tumors under sulindac or antihormonal therapy should be treated with chemotherapy (doxorubicin and dacarbazine or methotrexat and vinblastin) or radiotherapy [330-332]. Results on surgical resections are controversial [333]. Especially for intra-abdominal desmoids, incomplete resections and high relapse rates are often reported [334-337].

For abdominal wall desmoids surgical procedures often lead to R0-resection and no recurrence [335].

| 5.38. | **Consensus-based Recommendation** | 2013 |
|-------|-----------------------------------|------|
| **EC** | 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 [338]. Cancer often appear multifocal and sometimes bilaterally. Histologically a cribiform variant of a papillary thyroid cancer is usually present.

Two prospective [339, 340] and one retrospective study [341] 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 [339]. 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 [338, 342, 343]. 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 [344]. 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 [345]. Due to the rarity and the unclear data on whether the prognosis for hepatoblastoma patients can be improved, screening is not generally recommended [346, 347].

| 5.39. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Drug treatment of adenomas in the lower and upper gastrointestinal tract should not be generally recommended. | |
| Level of Evidence<br><br>**2b** | Evidence from update literature search: [348-356] | |
| | Strong consensus | |

**Background**

Sulindac reduces the number of colorectal adenomas by more than 50% [348-352]. However, it does not prevent the formation of new polyps [353]. 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 [354], 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% [354] and also affects duodenal polyposis [355]. 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 [356]. 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. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**4** | [256, 257, 259, 260, 357-360] | |
| | Strong consensus | |

| 5.41. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**4** | [358-360] | |
| | 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 [357]. The polyps are often found on the right side of the colon. Hence, a complete colonoscopy must be performed for surveillance [256, 257, 259, 260]. 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 anastamosis with a remaining rectal stump is reasonable. Because extra colonic manifestations can appear as in classic FAP [358-360], 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 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| EC | 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 |
|---|---|---|
| EC | 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 |
|---|---|---|
| EC | 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) [269, 361, 362]. 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%) [264]. 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 |
|-------|-------------------------------------|------|
| **EC** | 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. 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. 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. Specific surveillance examinations for extra-intestinal manifestations are not justified in MAP-patients. A recommendation for drug treatment of adenomas in the upper and lower gastrointestinal tract cannot be given, because of missing data. | |
| | 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 [363]. 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 [265].Therefore, as a screening method a complete colonoscopy must be performed [256, 257, 259, 260]. 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 [364].

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 [271]. In MAP duodenal cancer sometimes also occur without pre-existing duodenal adenomas [365]. 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 [271]. 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. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2a** | These include especially hamartomatous polyposis-syndromes (Peutz-Jeghers-syndrome, familial juvenile polyposis, Cowden-syndrome), hyperplastic polyposis-syndrome, 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: [263, 366-396] | |

**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 [263, 366]. 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-syndrome (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 [367]. 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 [368]. PJS is associated with a significantly higher risk for several intestinal and extra-intestinal tumors [369-375]. Aside from CRC, especially the risk for cancer of the breast, small intestine, pancreas, testicles, ovaries, and uterus is increased [377, 378]. 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 [376-378]. The lifetime risk for gynecologic tumors is reported at 13-18% [377, 378]. 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 [377].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 extracolic 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 displastic portions: a considerable percentage of genetically confirmed cases of juvenile polyposis are initially misdiagnosed as ulcerative colitis or hyperplastic polyposis [379, 380]. 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 noticable 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) [380, 381]. In addition, the risk of pancreas cancer may be increased [382-386]. In case of very severe early manifesting courses **juvenile polyposis of toddlers** should be considered [387].

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 [388] 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% [389]. 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) [390, 391].

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 [392-396]. 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 |
|---|---|---|
| **EC** | 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 methological deficits and gives only little evidence for most of the recommendations [397]. 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 [263]). 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 |
|---|---|---|
| EC | 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 [398])

| 5.50. | Evidence-based 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[5] 3a | [399, 400] | |
| | Consensus | |

| 5.51. | Evidence-based 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 | [401] | |
| | Consensus | |

---

[5] In the guideline ulcerative colitis a different level of evidence is used Evidenzgrad (398. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**4** | [401, 402] | |
| | Consensus | |

| 5.53. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**3a** | [403, 404] | |
| | Consensus | |

| 5.54. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | After subtotal colectomy, in analogy the same endoscopic monitoring strategy as for UC without resection should be followed. | |
| Level of Evidence<br><br>**4** | [405] | |
| | 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 [399]. 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 [400]. 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 pancolotis 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 [406]. 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 [401, 402]. 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 [404] and because cancer arise more frequently on the right side [403].

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 [405]. 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 ileocolonscopies 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 [407].

## 5.4.        Appendix: Figures and Tables of TK III

### 5.4.1.        Algorithmus: Genetic diagnostics and screening

**Algorithm: Genetic diagnostics and screening**
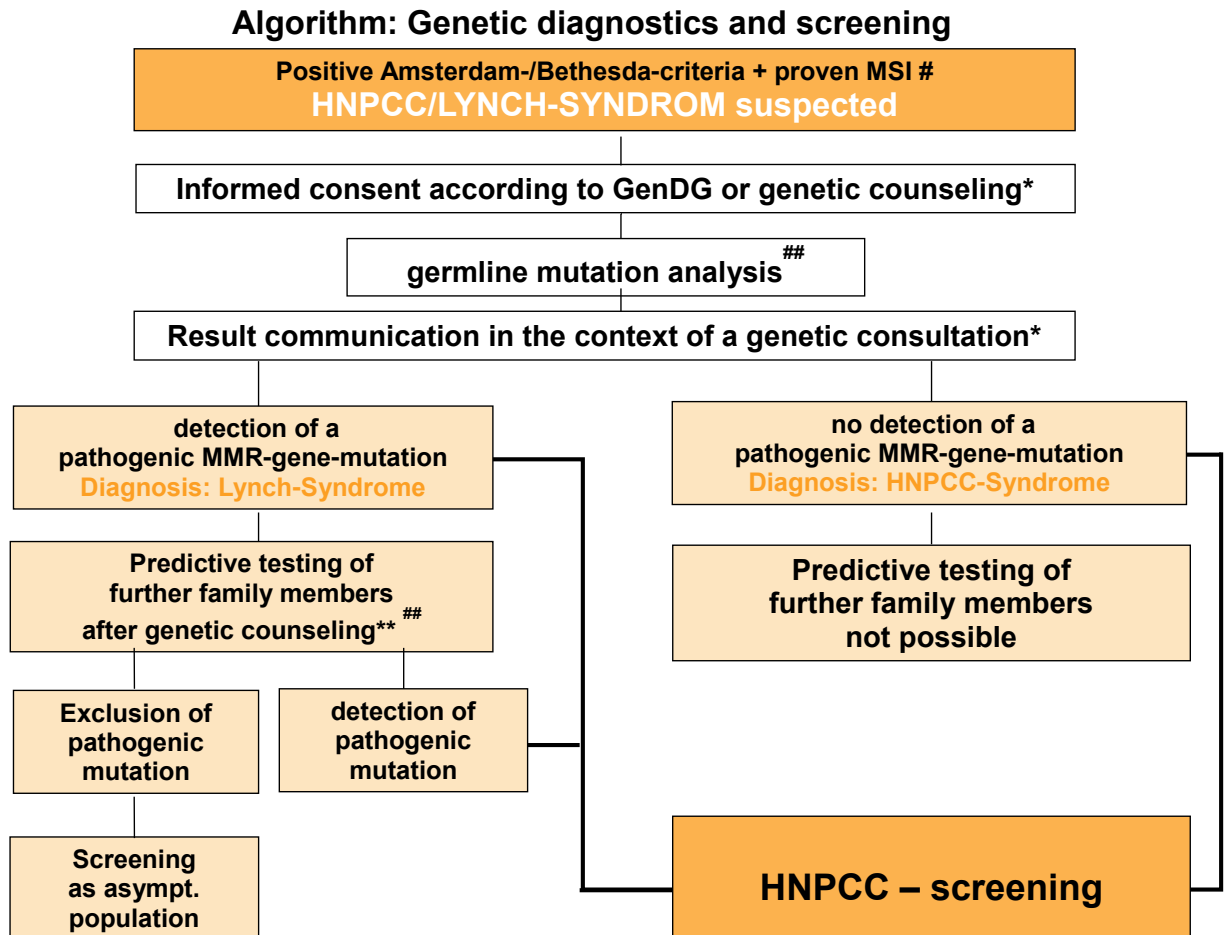


* A diagnostic germline exam requires informed consent and documentation of contents of the consultation by the initiating physician according to the GenDG . Alternatively, a genetic consultation may be performed. The results must be communicated in a genetic consultation according to the GenDG.

** 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 1: 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 2**

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

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

| Positive Amsterdam-/ revised Bethesda Criteria |
|:---:|

| Immunohistochemistry of tumour tissue (biopsy/surgical specimen) |
|:---:|

```
MLH1/PMS2          MSH2   MSH6   PMS2              MLH1
MSH2/MSH6
present*              └──absent**──┘              absent**

MSI - testing                                    BRAF-testing

stable   unstable           │            wildtype   mutated
  │          │              │               │          │
MSS CRC      └──→  HNPCC/LYNCH-SYNDROME ←──┘      sporadic
                        suspected                 MSI CRC
```
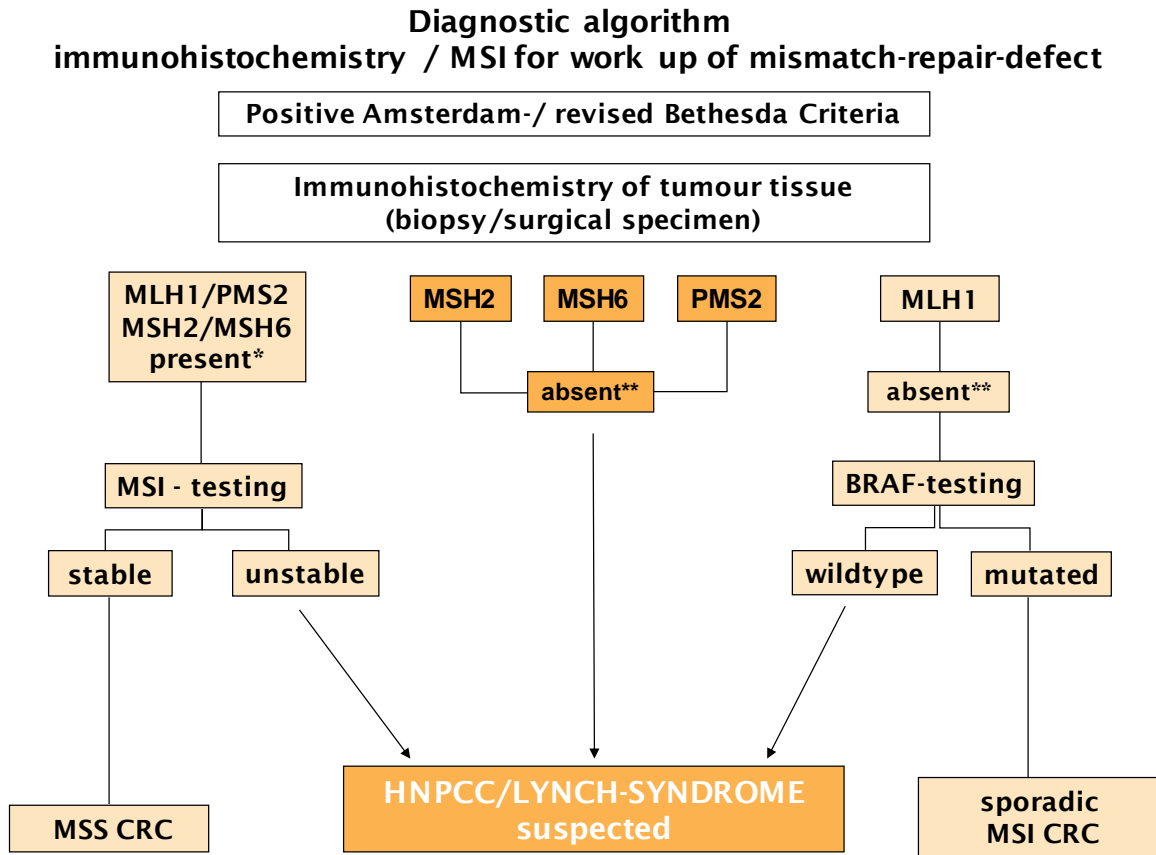
\* >10% of tumor cells are nucleus positive in each; ** in <10% of tumor cells are nucleus positive

**Figure 2: Algorithm on the Molecular Pathologic Differential Diagnosis Procedures of Mismatch-Repair-Defects if HNPCC-/Lynch-syndrome is Suspected. Please see Figure 1 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 [309])**

| | 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: Performance and Polyp management

## 6.1. Role of Endoscopy in the Diagnostics of Polyps and Colorectal Cancer

| 6.1. | Evidence-based Statement | 2017 |
|---|---|---|
| Level of Evidence<br><br>**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. | |
| | Sources: [173] | |
| | Strong consensus | |

| 6.2. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | If a colonoscopy was incomplete due to a stenosing tumour, an additional preoperative CT colonography can be performed. | |
| **A** | A complete colonoscopy shall be performed postoperatively. | |
| Level of Evidence<br><br>**4** | Sources: [408-411] | |
| | Strong consensus | |

| 6.3. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | If a colonoscopy was incomplete due to other causes (e.g. adhesions), a CT colonography should be performed. | |
| Level of Evidence<br><br>**3b** | Sources: [408, 409, 412] | |
| | Strong consensus | |

**Background**

When carried out to high quality standards, colonoscopy is the most reliable method for detecting colorectal carcinomas and polyps. Important quality characteristics include an endoscopic examination all the way to the caecum, optimal preparation of the colon with few or no remaining stool residues and a thorough inspection of the intestinal mucosa when withdrawing the endoscope. The so-called adenoma detection rate (ADR) is the most important surrogate parameter for the outcome of the colonoscopy (screening) [413, 414].

Several quality guidelines from Europe and the US have recently been published, and the quality characteristics of a colonoscopy described therein partly differ from one another [415-419]. The main quality parameters specific to the individual procedures are listed below. They do not affect recommendations that in general apply to all endoscopies (sedation, complications, device disinfection, etc.), even if the practical implementation of individual parameters (recording and auditing of complication, number of procedures) would be interesting topics for discussion.

**Table 8: Overview of Guideline-Based Specific Procedural Quality Indicators of Colonoscopy**

|  | DGVS[415] | ESGE[416] | EU[417] | UK[418] | US[419]*** |
|---|---|---|---|---|---|
| Caecal intubation rate | > 90% | > 90% | > 90% | > 90% | yes |
| Withdrawal time | > 6 min | > 6 min | yes | > 6 min | > 6 min |
| ADR | > 20% | individual | individual | > 15%** | yes |
| Bowel preparation | > 90% good | > 90% good | yes | > 90% | no |
| Polyp retrieval | Complete-ness (endoscop.) | detailed* | vague | detailed* | yes |
| Interval lesions | no | yes | vague | recommen ded | no |
| F-up adherence | no | no | >90% | no | no |

* ESGE/UK: retrieval rate, tattooing, ESGE: referral rate  ** > 20% "aspirational"  *** 2006, in most cases, no rates yet

The adenoma detection rate (ADR) is defined as the main outcome parameter of colonoscopy (screening) and shows a virtually negative linear correlation of the ADR with interval carcinomas. However, the studies have multiple methodological flaws (for a detailed discussion see the DGVS S2K guideline on quality requirements for gastrointestinal endoscopy [415]). Opinions differ on how high the adenoma detection rate, which is evaluated only for colonoscopy screening, should be. In women, an ADR of 20% is required, while in men, an ADR of 30% is required! ([420]).

Withdrawal time is also frequently listed as a quality indicator; in this regard, many but not all studies showed a correlation between the polyp detection rate and the withdrawal time after reaching the caecum, whereby the limit was 6 min [421-424]. However, other studies also showed that the adenoma rate does not continue to increase with a further increase in the withdrawal time > 6 min [425, 426] and that the mentioned cut-off of 6 min does not correlate with the ADR in larger-scale database analyses [427].

In case of pathological findings during colonoscopy, a classification by endoscopic-anatomic structures and by diaphanoscopy is insufficient. Details of the distance in cm device length from the anus should only be used for the rectum and lower sigmoid colon. For findings that are either unclear or worthy of surgery, marking by means of a clip (only at a time close to surgery) or ink (in the proximity of the lesion, *not* in the actual lesion) should be performed to facilitate a later retrieval (possibly also X-ray screening during the colonoscopy).

Colonoscopy does, however, have its limitations. For example, cancers and (relevant) adenomas are missed. These so-called interval cancers are mainly attributable to missed lesions. Additional factors are incomplete polypectomy (and failure of the patient to come for prompt surveillance colonoscopy) as well as rapidly growing de novo tumours ([428], [429], [430]). Older retrospective studies with database matching speak of 4-6% missed cancers [431-433]. In polyp follow-up studies, up to 1% of so-called missed cancers or interval cancers following colonoscopy, especially right-sided cancer, were reported in a Canadian study over a period of 3 years [429]. This difference between the sides was also confirmed in a German study, but to a considerably lesser extent [115]. In the two previously cited large-scale studies conducted in Poland and in the US, the rate of interval cancers following colonoscopy was 0.09% [414] and 0.22% [413] within 52 and 35-39 months, respectively, and thus also considerably lower. In Canada, the stronghold of interval cancers, the rate of interval cancers also appears to have halved between 1996 and 2010 (and, ultimately, was found to be 0.04% per follow-up year) [434].

Alternatives and supplementation to colonoscopy: The use of radiation for screening purposes, i.e. in healthy persons, is permitted in Germany only in exceptional cases (breast cancer screening). This is one of the reasons why CT colonography is not used here. Theoretically, incomplete colonoscopy and patients' refusal of (diagnostic) colonoscopy are possible indications for radiological procedures. The sensitivity and specificity of CT colonography have improved in the past years since the publication of the last guideline. In reviews published in recent years, CT colonography either decreased by 10-20% (depending on size) for all neoplasms in the screening setting [173], achieved good (88%) accuracy for adenomas >5 mm in screening candidates with a positive stool test (however only with a specificity of 75% [435]), and was found to be highly accurate for cancers in a radiological review in all indications [412]. Concerning the patients' preference for CT versus colonoscopy, the results appear to depend mainly on the journal of publication (radiology vs. gastroenterology/internal medicine) and on the extent of bowel preparation for the CT [436]. All in all, however, there are still no available outcome studies for screening, even less so for MR colonography [437], which is why the use of this procedure cannot be recommended at the time being. Double contrast barium enemas of the colon are meanwhile obsolete.

Remaining stool and poor expansion of the colorectal lumen can give rise to diagnostic difficulties during CT colonography. It is more difficult to detect flat, sunken and small polyps than prominent polyps. Owing to a lack of standardisation, the results currently depend strongly on the centre performing the procedure.

Due to the above reasons, a complete colonoscopy is considered the gold standard for a positive faecal occult blood test (FOBT) or to clarify a suspected tumour. It allows for both the simultaneous collection of a biopsy for a histological diagnosis and the performance of a polypectomy during the same therapeutic intervention.

In patients with stenotic tumours or incomplete colonoscopies due to other reasons, proximal tumours or polyps were detected in case series using CT [408-411] or MR

colonography [438, 439]. As a result, the use of CT colonography in these cases was recommended in joint guidelines of the ESGE and ESGAR published in 2014 [440]. Meanwhile, however, there is evidence to support the use of colon capsule endoscopy in patients with an incomplete colonoscopy (but obviously not in the presence of stenoses), since this procedure detected twice as many adenomas ≥6mm as CT colonography (24.5% vs. 12.2%) in a smaller randomised study (n=100) published in 2015 [441]. Colon capsule endoscopy was evaluated as the primary method in several studies that were methodologically partly limited and was found to achieve a similar detection rate as CT colonography depending on the size of the adenomas; however, the number of cancers was insufficient for a valid analysis [442]. As a screening method, capsule colonoscopy also achieved good values for adenomas ≥6 mm (sensitivity 81%, specificity 93%). However, one in four cancers was missed and 21% of the patients that were initially enrolled in the study were excluded from the final analysis [443]. Because of these limitations, colon capsule endoscopy currently cannot be recommended as the primary screening method.

The last review performed in 2016 on colonoscopy complications during colonoscopy screening from 21 large, population-based studies reported a pooled rate of perforations, secondary bleeding and mortality of 0.05%, 0.3% and 0.003%, respectively. Following polypectomy, perforations were reported in 0.08% and secondary bleeding in nearly 1% of the procedures. The complication rate was lower for colonoscopy screening/follow-up than for diagnostic colonoscopy [444].

## 6.1.1.    Sigmoidoscopy versus Colonoscopy

| 6.4. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | In case of a positive FOBT/FIT test, suspicion of a tumour, or sigmoidoscopic evidence of neoplastic polyps, a full colonoscopy has to be performed. | |
| Level of Evidence<br><br>**2b** | Sources: [107, 128, 445-447] | |
| | Strong consensus | |

**Background**

Work-up of a positive FOBT test or suspicion of a tumour requires a complete colonoscopy, since this method is also able to detect adenomas and cancer in the right hemicolon. Relevant neoplastic lesions proximal to the sigmoid colon are detected in 25-55% of cases. Screening studies showed that the rectosigmoid colon is free of adenomas in 30 to 46% of cases with proximal advanced neoplasms in the right hemicolon [107, 128, 445-447].

Sigmoidoscopy should only be performed in exceptional cases when complete bowel preparation is not possible. A complete colonoscopy is possible in a high percentage of cases and can usually be performed with a lower rate of side effects in elderly patients as well [448-452]. However, regarding risks and comorbidities, the stress caused by the bowel preparation and the sedation must also be taken into consideration in this group [453-456]. Sigmoidoscopy has no authority for the primary diagnosis if a tumour is

suspected and plays no significant role as a screening method in Germany or in the majority of other European countries [457].

## 6.1.2.    Chromoendoscopy and Related Procedures

| 6.5. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | Chromoendoscopy can be performed in patients with chronic inflammatory bowel disease and HNPCC for improved detection of neoplastic lesions. | |
| Level of Evidence<br><br>**1b** | Sources: [458-464] | |
| | Strong consensus | |

**Background**

Alongside chromoendoscopy with dyes such as methylene blue or indigo carmine, numerous image processing procedures have been developed in recent years that aim to replace the direct application of dyes (narrow band imaging - NBI, Fujinon intelligent colour enhancement-FICE, iScan, etc.). In patients with ulcerative colitis [458-462] or HNPCC [463, 464], a higher detection rate of neoplastic lesions by chromoendoscopy is likely, however, an effect on the overall outcome has not been demonstrated [462]. It is still unclear whether the detection of an increased rate of predominantly smaller lesions is useful for the patient and justifies the greater amount of time required for direct chromoendoscopy.

The number of meta-analyses regarding virtual chromoendoscopy procedures has increased [465-470]. NBI was not found to have an effect on the ADR in any of the meta-analyses; and while FICE is included in one of the meta-analyses, it was also not found to have an impact on the ADR [466]. The results of another recently published three-arm study with NBI and FICE point in the same direction [471]. For I-Scan, two smaller (n=200 and n=67) randomised studies show a benefit [472, 473] which, however, could not be confirmed by a larger, randomised tandem study (n=389) [474]. Interestingly, the latest and most comprehensive meta-analysis attributed an effect on the ADR to conventional chromoendoscopy only [466], and this on the basis of 9 such studies, the majority of which showed an improved detection of small adenomas only, while others had significant methodological flaws.

The aim of chromoendoscopy procedures, on the other hand, is to enable a better delimitation of flat and sunken lesions from the surrounding healthy mucosal tissue [475-480]. Chromoendoscopy can thus be employed prior to the endoscopic removal of flat adenomas.

All in all, mechanical procedures appear to be superior to chromoendoscopy in achieving better results in the detection of adenomas; however, this does not apply to the simple, transparent distance caps, which have already been analysed in 6 meta-analyses [466, 481-484]. Multiple randomised studies suggest that newer so-called endocuffs increase

the adenoma detection rate [485-488], which also appears to apply to balloons that are attached to the endoscope [489].

A classification of the mucosal pattern (pit pattern) and of the microarchitecture of the mucosal and submucosal vessels (vessel pattern) may be useful along with an assessment according to the Paris classification [490]. The goal of zoom endoscopy is to differentiate between hyperplastic and neoplastic lesions based on the pit pattern classification in order to determine – without a histological analysis – which lesions have to be removed endoscopically. Recently, however, the resolution of HD endoscopes with or without image enhancement has improved in a way that makes magnifying endoscopy appear obsolete [491]. Thus, new classifications were also recommended, for example, the so-called NICE classification [492], which is based on the device technology of a specific company.

Numerous papers on the consideration of the endoscopic differential diagnosis of polyps (endoscopic histology) [491] have been published with the goal of no longer histologically analysing smaller polyps ("Resect and Discard" [493, 494], DISCARD policy for short), mainly due to financial reasons [495, 496]. The follow-up recommendations are then mainly based on the endoscopic differential diagnosis between adenomas and hyperplastic lesions, since histological results are no longer available.

Since this procedure has not been sufficiently validated yet, the histological analysis of removed polyps should still be considered the standard procedure in accordance with the S2K guideline on endoscopy quality [415].

Confocal laser scanning microscopy is still subject to further evaluation in clinical studies [497].

## 6.2.      Polypectomy

### 6.2.1.      Endoscopic Resection

| 6.6. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Polyps shall be removed and retrieved with exact recording of the localisation of the polyp. In case of multiple polyps, the removal of polyps can be performed in more than one session. | |
| Level of Evidence<br><br>**1c** | | |
| | Strong consensus | |

| 6.7. | Consensus-based Recommendation | 2017 |
|------|--------------------------------|------|
| **EC** | To obtain a representative histological specimen and achieve a definitive therapy, polyps >5 mm shall be completely removed using a snare.<br><br>In general, diagnostic colonoscopies shall only be performed if the possibility of performing a polypectomy using a snare is given in the same session. | |
| | Strong consensus | |

## 6.2.2. Endoscopic Assessment Prior To Removal

The goal of any colonoscopy must be to achieve a polyp-free colon (clean colon). 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 sensible (risk situation in an outpatient setting, inadequate expertise with larger polyps), the patient should be referred to a specialist centre. Forceps biopsy of larger polyps (>5 mm) is not useful if removal is technically possible. Forceps biopsy is also unreliable with an underestimation of the histopathological diagnosis in 10% of all polyp biopsies and in 60% of advanced neoplasms [498]. Furthermore, extensive biopsies can cause scarring, which can make it more difficult to perform a complete endoscopic removal of the polyp in a subsequent procedure. However, biopsies are mandatory in the presence of clear malignancy criteria with a primary indication for surgery.

The realistic option of a complete removal of the polyp with a low risk of bleeding and perforation is a requirement and limitation for the endoscopic removal of larger polyps. The experience of the endoscopist and the localisation of the polyp can also be limiting factors. Other factors that should be considered include the increased rate of cancer with increasing size of neoplastic polyps (up to 15% in polyps >3 cm), growth pattern, localisation, patient's overall health, increased risk of bleeding and increased risk of perforation in the proximal colon [499-504]. In case of multiple polyps, polypectomy can be performed in multiple sessions.

For larger flat adenomas (known as laterally spreading tumours or adenomas, LST), the predictive value of the so-called non-granular type for the prediction of malignancy is emphasised, which has a ratio of around 15% to 1-3% for the granular growth pattern [505-511] – see also the detailed discussion in the S2K guideline of the DGVS on quality requirements for gastrointestinal endoscopy [415]. Regarding the so-called non-lifting sign [512, 513], it is disputed whether this is a reliable sign of malignancy [512, 514]. However, it can lead to a technically difficult and incomplete resection in low-grade adenomas as well [510].

Exclusively depressed, flat lesions (IIc) that appear suspicious in the endoscopy should as a rule be treated by primary surgery, especially when they fail to lift after an injection, since most of these lesions no longer present so-called early invasive T1 cancer and complete endoscopic removal (R0) is seldom possible. In isolated cases, endoscopic full-thickness resection (eFTR) can be considered (see below). Apart from that, it has been shown repeatedly that the primary assessment of the endoscopic "removability" of a polyp depends on the experience of the endoscopist and that the majority of "non-removable" polyps can be successfully removed in specialist centres [515-520].

*Hyperplastic polyps*

Small (≤5 mm), often multiple, typical hyperplastic polyps in the rectum do not have to be removed if they are clearly identified as such by endoscopy. When located further proximally, polyps that appear hyperplastic should always be removed, since they are frequently classified as serrated adenomas as they increase in size.

Serrated polyposis syndrome (SPS), previously hyperplastic polyposis syndrome, appears to be one of the most frequent colorectal polyposis syndromes. To date, no gene defect has been identified. The current WHO definition (26) for the diagnosis of serrated polyposis syndrome (SPS) consists of three criteria:

1. At least 5 histologically confirmed serrated polyps proximal to the sigmoid colon, two of which are >1 cm

      or

2. Any number of serrated polyps proximal to the sigmoid colon in patients with a first-degree relative with hyperplastic polyposis

      or

3. More than 20 serrated polyps of any size in the colon.

Serrated polyposis syndrome is associated with an increased risk of cancer and requires regular surveillance colonoscopies.

*Endoscopic resection techniques*

The complete removal and retrieval (in particular when parts are removed by so-called fractionated endoscopic mucosal resection - EMR) of a polyp is always required, since high-grade intraepithelial neoplasia or cancer may still be present in residual polyp tissue. To enable a classification, polyps should be retrieved individually for a histological analysis, specifying their localisation. If several small and non-suspicious polyps are present in a segment, combined retrieval of these polyps is acceptable. In so doing, however, the oncological resection margins must be respected in case of unexpected histological findings. Marking of the colon segment where polypectomy has been performed is useful when subsequent surgical resection is required.

The following *endoscopic procedures* are available:

- Removal of small polyps up to 5 mm by forceps or snare
- Polypectomy by snare for polyps >5 mm
- Endoscopic mucosal resection (EMR)

The individual procedures are discussed in detail in the S2K guideline of the DGVS on quality requirements for gastrointestinal endoscopy [415]. For *small polyps* up to 5 mm it was shown that adenoma tissue is frequently left behind during removal by forceps [521] and that this presumably depends on the degree of diligence and the number of biopsies. The best-studied procedure is *cold snare polypectomy*, which must arguably be given preference for small polyps [522-524]. In two smaller randomised studies (around 60 polyps per arm) with a histological follow-up, the rate of completely removed adenomas in the cold snare group was 93.2% and 96.6% versus 75.9% and 82.6% in the forceps removal group, respectively [525, 526].

*Larger polyps* are removed with the snare, flat polyps usually after prior injection; larger (flat) polyps generally require removal using the piecemeal method (*endoscopic mucosal resection*/EMR). The size of the removed polyp, the histological adenoma classification and the severity of intraepithelial neoplasia determines the degree of risk for local recurrences and metachronous polyps. In principle, and for methodological reasons, a differentiation should be made between residual adenoma tissue (diagnosed in the first control examination usually performed shortly after resection) and recurrent adenomas (i.e. recurrence after one or two negative endoscopic control biopsies, depending on the definition). For polyps >2 cm, recent studies have shown a residual/recurrent adenoma rate of up to 20% and higher [527-532]. However, these recurrences can generally be treated by a repeat endoscopy, so that very high success rates of >95% can be expected on the whole.

To improve the histological assessment of the resected tissue and to lower the recurrence rate, the en-bloc resection of larger, flat polyps by *endoscopic submucosal dissection (ESD)* has been propagated for several years. The advantages of this procedure are, however, offset by a markedly increased complexity, usually considerably longer interventions and higher complication rates compared to EMR. In addition, the removal in one piece of benign lesions such as colon adenomas generally has fewer advantages than in the oncological setting of (early) cancers.

The literature on colon ESD is complicated by a strong dominance of studies from the Far East, from Japan in particular, and the local common practice of histological blending of mucosal cancer (= high-grade dysplasia or Tis tumours) and submucosal cancer [533]. Comparative retrospective, and thus non-randomised, studies of ESD with EMR are also only available from the Far East [534-540]. Western results of colon ESD usually [541] show a markedly lower R0 rate with partly considerable (but generally endoscopically manageable) complications [542-544] [545]. For submucosal cancers, which thankfully are mostly analysed separately in these Western studies (only cases of rectal cancer!), the vast majority of patients did indeed undergo secondary surgery following the endoscopy. The data show a problem relating to the selection or indication: The most recent publication [545] also showed that more than 50% of patients with T1 cancers had to undergo secondary oncological resection, because there was no low-risk situation. It remains unclear which polypous cancer benefits from ESD "ex ante". While the technique is considered the best oncological one-piece treatment method for early colorectal cancer, it is currently reserved for only a few special cases in specialist centres for the above reasons and is not suitable for widespread use in the western colon. ESD is not essential for the removal of benign polyps. EMR remains the standard procedure for the removal of benign colorectal polyps.

Removed flat and sessile polyps should be marked with a pin or dye for identification. Fixing on a cork plate is also useful for the histological examination of flat polyps.

If *surgical treatment* is possible or expected to be necessary, preoperative marking of the polyp area with clips or ink must be performed (exception: caecum and distal rectum); marking must be done slightly proximal and/or distal to the lesion and *not* in the actual lesion. Intraoperative colonoscopy is an alternative way of locating the polyp or its removal site. To facilitate re-identification of the site (difficult identification during surveillance examinations), the polypectomy site can also be marked as outlined above in cases of difficult localisation after an endoscopic intervention.

*Alternative procedures to remove polyps* (open or laparoscopic resection, rendezvous procedures, TEM, transanal removal) may be considered in individual cases. Removed

flat and sessile polyps should be marked with a pin or dye for identification. Fixing on a cork plate is also mandatory for these flat polyps.

Endoscopic full-thickness resection (eFTR) is a reserve procedure ([546]) in which the area to be removed is pulled into a hollow cylinder attached to the tip of the endoscope by means of pincers; and, in principal, a snare removal as well as a closure of the defect in the colon wall using a larger clip is performed simultaneously. Possible indications include: residual adenoma tissue, recurrent adenomas, submucosal non-neoplastic polyps, etc. Low-risk early cancer, either in the primary intention or (after receiving the results of the EMR histology) in the secondary intention to ensure R0 resection (see section 6.4 Approach for $pT_1$ Cancer) can be yet another indication. The limitations are: size ≥3 cm, failure to mobilise the lesion into the cylinder, inadequate accessibility of the equipment during the endoscopy, and operator errors concerning the technology used. The available data are insufficient for a final assessment at this time. Little is known about the complication rates as well. For this reason, this treatment method can only be carried out in isolated clinical cases in specialist centres. Widespread use of this method cannot (yet) be recommended.

*Complications*

Concerning the published complication rates associated with colonoscopy, reference is made to a review of the ASGE [547] and to a review related specifically to colonoscopy screening [548]. The S2K guideline on quality requirements for gastrointestinal endoscopy [415] provides an overview of the most relevant German [549-557] and international larger-scale studies [558-567]. In a large, prospective German study, independent factors for the risk of perforation included polyps larger than 1 cm as well as localisation in the right colon, and for the risk of bleeding, only polyp sizes >1 cm [557]. The risk of serious bleeding (requiring transfusion or surgery, recurrent secondary bleeding) was 0.9%; the risk of perforation was 1.2% in the right colon and 0.4% in the left colon.

For details on prophylactic measures to prevent (secondary) bleeding after endoresection and on polypectomy under dual platelet inhibition, reference is made to the S2K guideline on quality requirements for gastrointestinal endoscopy [415].

## 6.3.      Histological Examination

| 6.8. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | The histological examination of each polyp is mandatory. The histological reporting of polyps shall follow WHO criteria [568] with a statement about the completeness of 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 intraepithelial neoplasia); serrated lesions are subclassified as hyperplastic polyps, sessile serrated adenomas, mixed_polyps (with IEN grade) and traditional, serrated adenomas (with IEN grade) [569, 570]. | |
| | Strong consensus | |

**Background**

In recent years, molecular genetic findings have shown that other paths of cancer development exist alongside the "classic adenoma-carcinoma sequence". On the one hand, there is the so-called "serrated pathway in colorectal carcinogenesis", whose precursor lesion is considered to be the relatively new entity of the sessile serrated adenoma (SSA). On the other hand, there is a "mixed type" which combines molecular characteristics of the two other carcinogenesis pathways and whose precursor lesions can be traditional serrated adenoma (TSA) or villous adenomas. The primary key mutation for the alternative serrated pathway lies in the BRAF gene with a disruption of apoptosis, followed by senescence with (CpG) methylation and consecutive gene silencing (e.g. hMLH1, MGMT, p16) and the development of generally high-grade microsatellite instability (MSI-H) ([571], [572]).

Since the serrated pathway in colorectal carcinogenesis may progress more rapidly, the knowledge and diagnosis of precursor lesions is of vital importance. The new entities sessile serrated adenoma (SSA) and traditional serrated adenoma (TSA) were first defined in 2010 ([573]). Hyperplastic polyps (HP) are formally classified as non-neoplastic lesions and are thus "innocent". Based on current data and on the relatively similar, but not identical, morphology of hyperplastic polyps and sessile serrated adenomas, it must, however, be assumed that SSAs were misclassified as hyperplastic polyps in the past. For lesions >0.5 cm, the "misclassification rate" is around 30% ([571]).

**Sessile serrated adenomas (SSA)**

Sessile serrated adenomas are typically >5 mm, located in the right hemicolon and have a flatter profile. They do not protrude into the intestinal lumen as polyps do. SSAs are relatively difficult to recognise during endoscopy; they can be delimited from their surroundings by means of a layer of mucus (known as a mucus cap). Owing to their morphology and localisation, they could be a considerable cause of so-called interval cancer. Meanwhile, it is undisputed that SSAs are precursor lesions of the "serrated pathway in colorectal carcinogenesis". The differential diagnosis of HP and SSA is based on the typical overall appearance of the SSA with L- and T-shaped branching at the base of the crypt, serration down to the base of the crypt, the presence of dilated, frequently "angular" basal crypts and occasional "inverted crypts" extending from under the lamina muscularis mucosae.

**Traditional serrated adenomas (TSA)**

Unlike SSAs, traditional serrated adenomas protrude into the intestinal lumen similar to polypoid lesions. They combine the serrated architecture of hyperplastic polyps with the IEN of classic adenomas. They account for around 1% of all colorectal adenomas and are located predominantly in the left hemicolon and rectum. From a molecular perspective, TSAs are characterised by a high number of K-RAS gene mutations.

**"Mixed polyp"**

The term "mixed polyp" is used to summarise a heterogeneous group of lesions that may contain elements of serrated adenomas, hyperplastic polyps and tubular, tubulovillous or villous adenomas.

**Risk assessment of serrated lesions**

While it is not known how long it takes for serrated lesions to undergo malignant transformation, the presence of serrated lesions in itself, however, appears to indicate an increased risk for developing colorectal neoplasms. Analogous to oesophageal and

pulmonary tumours, serrated lesions are a sign of cancerisation of the colon. They indicate that the affected person has a predisposition to develop (pre-)neoplastic lesions with a carcinogenic potential in multiple sites inside the colon.

Numerous studies have shown that serrated "polyps" are associated with synchronously and metachronously advanced colorectal neoplasms in the sense of indicator lesions. A meta-analysis ([574]) summarises the results of nine studies with 34,480 patients. Serrated polyps were detected in 15.6% of the patients. When serrated polyps were detected, the patient had a 2.05-fold risk of developing advanced neoplasia. The diagnosis of proximal serrated polyps was associated with a 2.77-fold risk increase. When polyps were large serrated polyps (>1 cm), the risk increased 4-fold. Serrated lesions thus appear to be lesions that indicate an increased risk of advanced colorectal neoplasia. Patients with large serrated adenomas in the proximal hemicolon are particularly at risk of developing advanced colorectal neoplasia.

Only few data on the long-term course of serrated lesions are available, which do not provide for a conclusive evaluation. The risk of developing colorectal cancer depending on the presence of adenomas in the follow-up was investigated in a population-based randomised study ([575]). The risk of colorectal cancer was increased 2.5-fold in patients with a large serrated polyp, 2-fold in patients with advanced (conventional) adenomas and was 0.6% for patients with non-advanced adenomas. The authors concluded that a large serrated adenoma can be considered an independent risk factor for colorectal cancer, even after correcting the risk with the histology, size and multiplicity of accompanying adenomas.

A retrospective national population-based case control study conducted by Erichsen [576] in a total of 272,342 colonoscopies showed that SSAs with cytological markers of dysplasia were associated with the development of adenocarcinomas. Women with SSAs were at a higher risk of developing colorectal cancer than men: an SSA increased the risk of colorectal cancer fivefold in women, compared to twofold in men. Patients with an SSA proximal to the left flexure were found to have the highest risk of developing colorectal cancer.

In summary, at present it can be assumed that patients with large serrated adenomas have an increased risk of developing colorectal cancer, comparable to the risk of advanced conventional adenomas.

Regarding follow-up recommendations after polypectomy, the histological work-up of removed lesions is of crucial importance. Consequently, it is mandatory to histologically examine all removed lesions. For this reason, the concept of removing and discarding small polyps (Resect and Discard) proposed by individual experts is rejected ([577]).

| 6.9. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | In case of cancer, the histology report has to contain the following characterisations:<br><br>· a measure of the depth of infiltration (pT category), for sessile polyps the submucosal invasion in µm,<br><br>· the histological differentiation grade (grading),<br><br>· presence or absence of lymphatic vessel infiltration (L classification),<br><br>· and an assessment of the resection margins (R classification) with regard to the local removal in healthy tissue (for depth and on the sides). | |
| Level of Evidence<br><br>**3a** | Source: [578] | |
| | Strong consensus | |

| 6.10. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | The extent of tumour budding can be rated as an additional parameter. | |
| | Strong consensus | |

| 6.11. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Concerning further therapeutic consequences for completely removed pT1 cancer, a final classification into "low-risk" (G1, G2 and no lymph vessel invasion (L0)) or "high-risk" (G3, G4, and/or lymph vessel invasion (L1)) shall be performed. | |
| Level of Evidence<br><br>**3a** | | |
| | Consensus | |

| 6.12. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | Tumour cell budding greater than 1 can also be rated as "high-risk". | |
| | Consensus | |

**Background**

The necessity of a statement on the distance of the tumour from the resection in healthy tissue in patients with pT1 cancer is disputed.

**Tumour grading and budding**
The degree of tumour differentiation is defined according to the rules of the WHO (WHO 2010) which state that the degree of tumour differentiation is governed by those parts of the tumour that are most difficult to differentiate. The tumour invasion front should not be taken into consideration. However, daily practice has shown that the tumour invasion front in particular is characterised by a phenomenon known as tumour budding. This phenomenon refers to individual tumour cells or also tumour cell clusters at the invasion front which are usually poorly differentiated and have characteristics similar to those of stem cells. These cells are also genetically different from those found in the primary tumour. However, a standardised definition of how to assess or grade tumour bedding has not yet been developed. From now on, a proposal made by Japanese authors is to be implemented: according to this proposal, tumour budding is to be defined as histological proof of tumour cell clusters (five cells or fewer) of dedifferentiated or isolated tumour cells at the invasion front. Here, the invasion front should undergo microscopic analysis with 200-fold magnification and the degree of budding should be determined as grade 1 with 0-4, grade 2 with 5-9 or grade 3 with >9 buddings or tumour cell clusters. In several studies, grade 2 or 3 tumour budding, i.e. >4 buddings or clusters at the invasion front, was considered an additional parameter indicating an increased risk of lymph node metastases ([579], [580], [581]).

Since the analyses on tumour budding originate mainly from Japan and tumour budding grading is not yet standard practice in Germany, the grade of recommendation to take tumour budding into account in the risk assessment of T1 cancers was lowered to "can".

A checklist to ensure standardised histopathological analysis of colorectal polyps should be used ([578]).

## 6.4.     Approach for pT1 Cancer

| 6.13. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation **A** | In the context of an endoscopically R0-removed polyp with a pT1 cancer, no additional oncological resection shall be performed if there is a low-risk situation with a cancer-free polyp base (R0). In the high-risk situation, radical surgical therapy shall be performed, even if the lesion has been completely removed. | |
| Level of Evidence **3a** | Sources: [582-584] | |
| | Consensus | |

| 6.14. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | With incompletely removed low-risk pT1 cancer, a complete endoscopic or local surgical removal has to follow. If an R0 situation cannot be achieved or it is doubtful that a pT1 situation exists, an oncological-surgical resection shall be performed. | |
| Level of Evidence<br><br>**3a** | Sources: [582-584] | |
| | Strong consensus | |

**Background**

The prognosis of pT1 cancer varies widely depending on the situation. The major determinant of a risk stratification into a low-risk and a high-risk group is the probability of lymph node metastases. As a whole, the group of T1 cancer has a lymph node metastasis rate (N+) of 0-20% [582-584]. There are a number of prognostic criteria for estimating the rate of metastases [585-588]; in this context, the risk of lymph node metastases in the low-risk situation is defined as around 1% or less [582, 583, 589], [585, 586, 590-594], [595].

*The following factors are important for the risk stratification of pT1 cancer*:

- Grading: G1 and G2 are considered low-risk criteria (G1 well differentiated, G2 moderately differentiated, G3 poorly differentiated, G4 undifferentiated).
- Invasion in lymphatic vessels (L classification) or blood vessels (V classification): The absence of invasion (L0 V0) determines the low-risk category. Proof of vascular invasion (V classification) should be mentioned, however, its significance for local therapy has not been conclusively confirmed.
- Tumour cell budding, i.e. the presence of isolated, "scattered" tumour cells at the tumour invasion front (see Recommendation 6.12).
- Submucosal invasion, as measured in biopsies removed during surgery or polypectomy (especially with *sessile/flat lesions*). In this context it has proven useful to divide the submucosa into three layers for surgical biopsies. In biopsies of sessile polyps removed during endoscopic polypectomy, however, only the measurement of the depth of submucosal invasion in μm is useful, since the submucosal layer is not available as a total layer and/or no muscularis propria is present. With 0-6%, the so-called early invasive forms (sm1 = submucosal invasion ≤1000 μm) have a low risk of N+ [490, 582-585]. In contrast, the risk of lymph node metastases in sm3 cancer is around 20% [490, 596].
  Caution: The measurement of submucosal infiltration in *pedunculated/stalked polyps* in μm is not useful and/or is misleading, because the thickness of the submucosal layer depends on the length of the stalk. In practice, the classification of polyps according to Haggitt [597, 598] is difficult to perform. With the exception of advanced stalk invasion (>3000 μm) [599], T1 cancer in pedunculated polyps is classified as sm1.

- In multivariate analyses, lymphatic vessel invasion is given the highest significance as a risk factor for the presence of lymph node metastases. An L+ status is associated with a 20% rate of N+ ([600]). For L0 and G2, a submucosal invasion depth of 1000 µm to 2000 µm appears to increase the rate of lymph node metastases (N+) by only 1% to 2% ([601], [602]).

**Important additional comments on the resection (R) status:**

For endoscopically/locally removed low-risk T1 cancer, the reliable assessment of complete removal (R0) is an absolute prerequisite for a follow-up without oncological resection. Where possible, stalked lesions should be removed in one piece. For sessile/flat lesions and en-bloc removal, the lateral and basal margins can be assessed histopathologically; for piecemeal removal, only the basal margins can be reliably assessed by histology. The necessity of a safety distance of 1 mm to the base is controversial [585]; here, the endoscopic literature does not provide conclusive information. In patients with a low-risk situation and a confirmed R0 status (see below), a subsequent radical surgical resection according to oncological criteria is not required.

As a rule, endoscopic cancer therapy in the context of polypectomy is performed without prior knowledge of the cancer diagnosis. Removal using the piecemeal technique appears adequate here [603]. Here, the evaluation of the lateral R situation is performed macroscopically during endoscopy, the evaluation of the vertical infiltration is done histologically (basal R0). However, early (2-6 months) endoscopic re-examination of the local R0 situation by means of a biopsy is necessary.

In selected cases of an incomplete resection, endoscopic full-thickness resection (eFTR) can help achieve a curative R0 situation in low-risk tumours through secondary endoscopic resection of the removal site (see also section 6.2.1 Endoscopic Resection).

In every case of a definitive Rx basal or R1 basal or unclear vertical resection margin, surgical resection (usually performed as an oncological resection) is required in operable patients!

Randomised studies comparing endoscopic and surgical procedures in T1 cancer are not available. Retrospective studies show that relapses in the form of local recurrences or distant metastases can be expected in around 3% of cases following endoscopic treatment of low-risk T1 cancer ([604]; [595]). For this reason, the oncological situation should be discussed with the individual patient, and surgical risks associated with the oncological resection should be discussed and weighed against the risks of endoscopic local therapy alone.

Care should be taken with sessile lesions, especially if a cancer diagnosis was already confirmed by biopsy prior to the therapy. In this case, a situation is frequently present in which the lesions cannot be treated adequately using endoscopic means. Endoscopic warning signs include: ulceration, depressed lesions, contact bleeding and absence of the lifting sign when injecting under the lesion. Any such known malignant lesions should only be removed endoscopically in centres with sufficient expertise in primary assessments and endoscopic resection techniques.

For known or suspected T1 cancer, endoscopic removal as an en-bloc resection is the optimal procedure for oncological reasons. The method of choice for lesions located in the rectum is ESD (see 6.2.1 Endoscopic Resection).

| 6.15. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | After complete removal (R0) of low-risk (pT1, low-grade (G1, G2, L0)) cancer, endoscopic surveillance examinations of the local resection site shall be performed after six months.<br><br>A complete colonoscopy shall be performed after three years. | |
| Level of Evidence<br><br>**4** | | |
| | Strong consensus | |

**Background**

The above recommendations serve to enable the recognition of local recurrences. A complete colonoscopy for the early detection and treatment of recurrences should be performed according to the recommendations for adenoma surveillance.

## 6.5.　Polyp Management (Follow-Up)

| 6.16. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | After removal of small single, non-neoplastic polyps, no endoscopic surveillance should be performed. | |
| Level of Evidence<br><br>**3b** | Sources: [605-607] | |
| | Consensus | |

**Background**

Patients with small (<1 cm) hyperplastic polyps and a negative family history do not appear to have an increased risk of developing colorectal cancer. Here, the general recommendations for CRC prevention apply, i.e. colonoscopy screening every 10 years [605-607]. Exceptions include non-neoplastic polyposis syndromes (hyperplastic, juvenile, Peutz-Jeghers and SSA polyposis) with an increased risk of malignant transformation [608].

| 6.17. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | The timing of the surveillance colonoscopy after complete removal of neoplastic polyps (adenomas) shall depend on the number, size and histology of the removed adenomas. | |
| Level of Evidence<br><br>**2b** | Sources: 619 | |
| | Strong consensus | |

| 6.18. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | For patients who have 1 or 2 adenomas <1 cm without higher-grade intraepithelial neoplasia, a surveillance colonoscopy should be performed after 5-10 years. | |
| Level of Evidence<br><br>**3b** | Sources: [210, 609, 610] | |
| | Strong consensus | |

| 6.19. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | If, however, no or only 1-2 adenomas <10 mm without a mostly villous histology or HGIEN are discovered during this surveillance colonoscopy, the next surveillance colonoscopy should be performed after 10 years. | |
| Level of Evidence<br><br>**3b** | Sources: [210, 609, 610] | |
| | Consensus | |

| 6.20. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | For patients who have 3-4 adenomas, or one adenoma that is ≥1 cm, or an adenoma with a mostly villous histology or HGIEN, the first surveillance colonoscopy should be performed after 3 years. | |
| Level of Evidence<br><br>**3b** | Sources: [611] | |
| | Consensus | |

| 6.21. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | For patients with adenomas with high-grade intraepithelial neoplasia and histologically confirmed complete removal, a surveillance colonoscopy should be performed after three years. | |
| Level of Evidence<br><br>**1b** | Sources: [611] | |
| | Strong consensus | |

| 6.22. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | In adenomas > 5 mm with histologically non-confirmed complete removal even if macroscopically the removal was complete, a control should be performed after 6 months. | |
| Level of Evidence<br><br>**5** | Expert opinion | |
| | Consensus | |

| 6.23. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | In case of ≥5 adenomas of any size, the control interval should be <3 years. | |
| Level of Evidence<br><br>**5** | Expert opinion | |
| | Consensus | |

| 6.24. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | After removal of large adenomas in piecemeal technique, a short-term control of the removal area shall be performed after 2-6 months. | |
| Level of Evidence<br><br>**3b** | Source: [612-616] | |
| | Consensus | |

| 6.25. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | After complete removal of a traditional serrated adenoma or sessile serrated adenoma, the follow-up should be the same as for classic adenomas. | |
| Level of Evidence<br><br>**3b** | Sources: [576, 617, 618] | |
| | Consensus | |

**Background**

After removal of adenomas, interval adenomas are again detected in around 50% of the patients ([619]). Surveillance examinations after polypectomy account for around 20% of all colonoscopies and are thus an important cost factor ([620]). The target structure of polypectomy follow-up is cancer on the one hand, and advanced adenoma on the other hand. After removal of adenomas, so-called interval cancer is diagnosed in 0.7% to 0.9% of patients within 3 years at surveillance colonoscopies [429].

**Table 9: Follow-Up Intervals After Polypectomy**

| Starting situation | Interval of surveillance colonoscopy |
|---|---|
| 1 or 2 small tubular adenomas (<1 cm) without a villous component or high-grade intraepithelial neoplasia | 5-10 years |
| 3 or 4 adenomas or ≥1 adenoma ≥1 cm or villous component or high-grade intraepithelial neoplasia | 3 years |
| ≥5 adenomas | <3 years |
| Serrated adenomas | As for classic adenomas |
| Removal in piecemeal technique | Control of the removal site after 2-6 months |

This is caused by missed lesions (miss rate), incomplete polypectomies and the occurrence of rapidly growing tumours [428, 430, 432, 621]. The definition of surveillance intervals after polypectomy depends on the patient's individual risk. The risk depends fundamentally on the number, size and histology of the removed adenomas [619]. The risk of cancer is not significantly increased in patients with 1 or 2 small tubular adenomas [210], [609], [610]. Therefore, surveillance colonoscopy after 5 to 10 years seems sufficient. If only 1 or 2 small tubular adenomas are again detected during the surveillance colonoscopy, there is no significantly increased risk, so that the next surveillance colonoscopy should then be repeated after 10 years. After removal of 3 or 4 adenomas or at least 1 adenoma ≥10 mm or with a mostly villous histology (not tubulovillous adenomas!) or high-grade intraepithelial neoplasia, surveillance colonoscopy should be performed after 3 years due to the increased risk of advanced neoplasia. These recommendations are based on the data of the National Polyp Study, in which an examination after 3 years showed a similar rate of advanced neoplasia as after 1 year [611]. A pooled analysis showed that patients with 5 or more adenomas have a markedly increased risk of advanced neoplasia of 24.9% [619], especially if 1 of the adenomas is ≥10 mm [622]. For this reason, a shorter surveillance interval appears appropriate in these cases.

The follow-up interval of the second surveillance colonoscopy depends on the findings of the index colonoscopy and the first surveillance colonoscopy. There are no relevant data available from randomised studies, only from retrospective analyses. A possible algorithm is shown in the table above. It must be taken into account that patients diagnosed with advanced adenomas in the index colonoscopy continue to be at an increased risk of advanced neoplasms, as are they if 1 or 2 tubular adenomas are diagnosed in the first surveillance colonoscopy ([623]) ([624]), ([625]), ([626]), so that another control examination after 3 years appears reasonable in this case. Again, randomised studies assessing different follow-up intervals after the removal of serrated adenomas have not been conducted. Only case control studies and case series were identified in the literature search. These studies identified a similar rate of advanced adenomas in the surveillance colonoscopy as after the removal of adenomas ([576]), ([617]), ([618]). For this reason, it appears reasonable that the same follow-up recommendations for non-serrated adenomas should apply after the removal of serrated adenomas (for details see section 6.3).

An incomplete endoscopic removal of adenomas is generally associated with an increased risk of interval cancer ([627]). The goal is therefore to achieve a complete removal which is pathologically confirmed. Consequently, it also appears useful to perform a control examination of the removal site after the removal of adenomas >5 mm for which a complete removal cannot be confirmed histologically. Even if no comparative data are available, it is recommended that the control should be carried out after around 6 months, analogous to the removal using the piecemeal technique. For smaller adenomas, the assessment of the completeness of the removal by forceps can be difficult to impossible for the pathologist. The clinical relevance of small adenomas is also unclear. For this reason, the endoscopic assessment of the completeness of the removal is decisive in these cases, and a repeated examination of the removal site is superfluous.

After removal of flat or sessile adenomas in piecemeal technique, the recurrence rate is significantly increased, especially with larger adenomas (9-28%) [612-616]. The use of argon plasma coagulation to remove remaining tissue to ensure a complete removal can be helpful [613, 616]. In this case, however, a complete histological examination cannot be performed. The special group of patients with removal of flat or sessile adenomas in

piecemeal technique should undergo surveillance endoscopy of the removal site after 2-6 months due to the higher rate of local recurrences ([628]).

Concerning the follow-up recommendations for HNPCC, FAP and CED patients see section 10.6.

## 6.6.　　Secondary Chemoprevention of Adenomas

| 6.26. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Secondary chemoprevention following polypectomy should not be performed outside of studies. | |
| Level of Evidence<br><br>**1b** | Sources: [80-82, 629-631] | |
| | *Strong consensus* | |

**Background**

Even though a limited preventive effect has been demonstrated for low-dose aspirin in several prospectively randomised studies with high levels of evidence (1b) [629, 630], an intake of aspirin to lower the risk of adenoma recurrences cannot be recommended owing to the limited effect (reduction of the adenoma recurrence rate by max. 35%) and the risks posed by taking the drug [632]. The same holds true for COX-2 inhibitors, for which a reduction in the adenoma recurrence rate of 24 to 45% has been shown [80-82]. The COX-2 inhibitors, however, have been associated with a significantly increased rate of cardiovascular side effects [633, 634] which outweigh their potential benefit [635]. The reduction of the adenoma recurrence rate of 12% with calcium appears to be too low to recommend the longer-term administration for this indication [631].

# 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 [636, 637] 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) [638].

In contrast, in the US [639, 640], 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 anocutanoeus line [641].

## 7.3.       Definition Interdisciplinary Tumor Conference

| 7.1. | Consensus-based Recommendation | 2013 |
|------|-------------------------------|------|
| **EC** | All CRC patients should be presented in an interdisciplinary tumor conference after they have completed their primary therapy (e.g. operation, chemotherapy).<br><br>Patients with the following constellations should already be presented before therapy:<br><br>- every rectal cancer<br>- every stage IV colon cancer<br>- metachronic distant metastases<br>- local recurrence<br>- 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 [642].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 [643].

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 [644].

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 10: 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. | Evidence-based 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 | • Digital-rectal examination | 5 | [645-647] |
| A | • Complete colonoscopy with biopsy | 4 | 645-647] |
| A | • In the case of an endoscopically non-transversible stenosis, complete colonoscopy 3-6 months postoperatively | 3b | [645-647] |
| 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-localed 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 [645-647]. 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. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | 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<br><br>**4** | [410] | |
| | Strong consensus | |

| 7.4. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | If the colonoscopy is incomplete for other reasons (e.g. adhesions), a CT- or MR-colonography should be performed. | |
| Level of Evidence<br><br>**4** | 410] | |
| | Strong consensus | |

**Background**

In this case a virtual colonography is a promising alternative [410]. 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 |
|---|---|---|
| **EC** | An abdominal ultrasound and a conventional chest x-ray in 2 levels should be the basic examination for pre-operative staging of CRC.<br><br>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. | |
| | 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%) [648-650]. 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%) [648, 651]. 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%) [648, 651].

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) [649, 650, 652].

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 [653, 654].

### 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 |
|---|---|---|
| **EC** | 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%) [655].

### 7.4.2.3. Relevance of PET-CT

#### 7.4.2.3.1. For Primary Diagnosis of Colorectal Cancer

| 7.7. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence **2b** | PET/PET-CT has no relevance in the diagnostic work up of newly diagnosed CRC. | |
| | De Novo: [656-671] | |
| | 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 [656, 661]. In some cases it was not better [657-659, 664]. The quality of the method used for comparison is not known. In recent studies with multidector spiral CT there was no significant detectable difference [657, 658].

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) [656-664].

In the studies the use of PET or PET-CT led to changes in therapeutic procedures in 2-27% of the cases [657, 658, 661, 664-671].

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. | Evidence-based 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: [672, 673] | |
| | Consensus | |

| 7.9. | Evidence-based 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: [674-676] | |
| | 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 [677]. 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 [673], 2 systematic reviews [678];[651], a prospective case control study [674], and a retrospective case series [676] 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 [679].

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 [672] 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 [673]. 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 [674]. 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 [680]. 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 [675] and a retrospective study [676] reached similar results.

## 7.4.3.  Tumor Markers

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

| 7.11. | Consensus-based Statement | 2013 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| **EC** | 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 [681-683].

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 |
|---|---|---|
| **EC** | 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. | Evidence-based 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 endoscopie ultrasound should be performed. | |
| Level of Evidence **2b** | De Novo: [684-692] | |
| | Strong consensus | |

| 7.15. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence **3** | CT is not suitable for staging ofT1-cancer. | |
| | De Novo: 684-692] | |
| | Strong consensus | |

| 7.16. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2b** | The accuracy of all imaging procedures for the evaluation of the lymph node status is very questionable. | |
| | De Novo: 686, 687] | |
| | Strong consensus | |

| 7.17. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 mesorectual infiltration especially the distance from the mesorectal fascia are of important prognostic relevance [684]. 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 [685]. Another prognostic factor is affected lymph nodes [684].

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 [686]. Its high sensitivity and specificity was confirmed in a more recent meta-analysis [687]. 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 [686]. 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) [688-692]. However, the accuracy of the CT was significantly lower in the lower third than in the upper two thirds [693]. If it is necessary to show the mesorectal fascia and its association with the tumor, the MRI is currently the most sensitive method [694]. The fascia cannot be demonstrated by endosonography [688].

When evaluating lymph nodes the sensitivity (55-73%) and specificity (74-78%) of all methods are currently insufficient [686, 687]. 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/EC | 2008 |
|---|---|---|
| Grade of Recommendation | In individual cases the following examinations may be useful: | Level of Evidence |
| 0 | • Sphincter manometry | 4 |
| EC | • Gynecologic examination | |
| EC | • 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 cytoscopy 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 |
|---|---|---|
| **EC** | 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 inconspicious preoperative evaluation.<br><br>If the pre-operative diagnostics are sufficient, the diagnostic benefit of intra-operative ultrasound to look for further metastases does not justify its effort. | |
| | 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) [695].

### 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 [696]. 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 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| **EC** | 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 [697, 698].

## 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 [699-701].

The extent of the colon resection is defined by the transsection 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 [702]. 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) [703, 704].

### 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 [705]. Accordingly if the vessel ist 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 metastazation also takes place via the major omentum in the direction of the gastric antrum and on to the pancreatic head [700]. 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 metastazation 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 metastazation 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 transsection 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 [706, 707].

### 7.5.2.2. Complete Mesocolic Excision (CME)

| 7.22. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [708, 709]. The higher radiality does not seem to be associated with an increased complication rate [710]. Previous data indicate an improvement of survival rate if CME is consistently performed [708].

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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**3a** | De Novo: [711-713] | |
| | 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 [711].

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 [712, 713]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**2a** | De Novo: [714, 715] | |
| | 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 [714, 715].

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

| 7.25. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | A LITT for the treatment of CRC liver metastases should only be performed as part of a clinical trial. | |
| Level of Evidence<br><br>**4** | De Novo: [716, 717] | |
| | 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 [716, 717]. 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) [636, 637]. 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 [718]. However, anatomical studies show that in many cases a deep anastomosis is also possible without central ligation [719]. 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) [720-723].

- 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) [724, 725].

- 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 [726].

- Protection of the autonomic pelvic nerves (hypogastric nerves, inferior and superior plexus [727, 728].

| 7.26. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**1b** | De Novo: [729-732] | |
| | Strong consensus | |

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

| 7.27. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**3b** | De Novo: [724, 733-737] | |
| | Strong consensus | |

**Background**

The reason for this procedure [736, 737] 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. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**1b** | [727, 738, 739] | |
| | Strong consensus | |

| 7.29. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**2b** | [725, 740-743] | |
| | Strong consensus | |

| 7.30. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**2b** | de Novo: [744, 745] | |
| | 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 anastamosis 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**1a** | de Novo: 746] | |
| | Strong consensus | |

| 7.32. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**1a** | Of the different reconstruction forms, the advantages of the functional results of a colon-J-pouch are best confirmed. | |
| | de Novo: [746, 747] | |
| | Majority consensus | |

| 7.33. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**1b** | Under functional aspects, the transverse coloplasty is inferior to the colon-J-pouch. | |
| | de Novo: [747, 748] | |
| | Majority consensus | |

| 7.34. | Evidence-based Statement | 2013 |
|---|---|---|
| Level of Evidence<br><br>**2a** | The side-to-end anastomosis may be as good as the colon-J-pouch. | |
| | de Novo: ] | |
| | 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 [746]. When constructing a J-pouch the loop length should not exceed 6 cm to prevent emptying problems [749]. 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 [747]. 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 [748]. Since studies with sufficient case numbers are still missing, definite conclusions on the role of side-to-end anastomosis cannot be made [750].

### 7.5.3.5.   Decision to Preserve the Sphincter

| 7.35. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [751]. Imaging procedures are not helpful in evaluating the response [752].

### 7.5.3.6. Approach in Case of Complete Response after Neoadjuvant Therapy

| 7.36. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [753]. 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. | Evidence-based 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: 709, 754, 755] | |
| | Consensus | |

#### Background

In rectal-exstirpation the preparation rate with insufficient lateral safety margins is classically increased [754]. The oncologic results are poorer compared to sphincter preserving interventions with comparable tumor stages [755]. The extralevatoric

"cylindrical" resection leads to better safety margins and should be viewed as the superior method even without randomized studies [709].

| 7.38. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**3b** | de Novo: [756] | |
| | 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 [756].

## 7.5.4.     Stoma-Construction

| 7.39. | Consensus-based Recommendation/ Consensus-based Statement | 2013 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| **EC** | Colostomies and ileostomies are equally good as deviation stomas. | |
| | Strong consensus | |

### Background

A protective stoma can reduce the morbidity especially of clinically relevant anastamosis insufficiencies and urgent relaparotomies [757]. If primary deviation stomas are avoided, the long-term rate of permanent stomata is by no means lower [758]. There are arguments for both types of protective stomas, even if recent meta-analyses favor ileostomies [759, 760].

| 7.41. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | Stoma construction should be discussed and planned with the patient as early as possible before the operation. | |
| | Strong consensus | |

| 7.42. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | The stoma position should be marked pre-operatively. | |
| | Consensus | |

| 7.43. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [761, 762]. Furthermore, a prospective study reported that pre-operative stoma counseling makes postoperative care easier [763].

### 7.5.5.    Local Excision of Rectal Cancers

| 7.44. | Evidence-based Statement | 2008 |
|---|---|---|
| Level of Evidence<br><br>**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. | |
| | [764-767] | |
| | 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 [768, 769]. There is much to suggest that for local excision the transanal endoscopic microsurgical methods are superior to open transanal excision using a spreader [770, 771].

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 [772-775].

| 7.45. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**3b** | [772, 776] | |
| | 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 [772, 776]. If the patient refuses radical revision surgery in this situation, an adjuvant radiotherapy may be considered.

## 7.6.        Laparoscopic Surgery

| 7.46. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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.[6] | |
| Level of Evidence<br><br>**1a** | de Novo: [777-781] | |
| | Strong consensus | |

| 7.47. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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 [777]. In the incisional hernias, adhesion-related revision operations, or regional and systemic tumor relapses [778, 779]. 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 [780]. This study demonstrates oncologic safety of laparoscopic surgery for both colon and rectal cancer [781]. No strict criteria have been validated for defining special laparoscopic expertise that is without doubt necessary.

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

---

[6] 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-telemanipulation-system - the only "robot" established in clinical routine - has been used in several series for laparoscopic total mesorectal excisions [782, 783]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | 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:<br><br>- PCI (peritoneal cancer index) < 20<br>- No extraabdominal metastases<br>- Possibility of macroscopic complete removal or destruction of all tumor manifestations<br>- Therapy at a specialized center<br><br>These procedures should preferably be performed as part of a trial | |
| Level of Evidence<br><br>**2a** | de Novo: [784-787] | |
| | Strong consensus | |

**Background**

So far, there is only one completed randomized study comparing systematic chemotherapy and cytoreductive surgery with HIPEC [785]. This study demonstrated also long-term that surgical therapy of peritoneal carcinosis leads to significantly better disease-specific survival [786]. 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 [787] 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 [696]. 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 [788]. 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 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| **EC** | 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| **EC** | A multimodal two-stage procedure should be chosen in case of multiple synchronic 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**4** | de Novo: [789, 790] | |
| | 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 [789]. 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%) [790]. 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 |
|---|---|---|
| **EC** | Prophylactic colectomy or proctocolectomy in HNPCC mutation carriers shall not be performed.<br><br>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. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | After cancer resection in addition to the usual follow-up-colonoscopic must be performed in the same interval as preoperatively. (see also Chapter 5.2.2.1) | |
| Level of Evidence<br><br>**2a** | Evidence from update literature search: [274, 275, 289-292] | |
| | Strong consensus | |

**Background**

Since regular screening nearly always detects cancers in stage UICC I/II or even as premalignant adenomas [274, 275] 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 extracolic 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 extracolic 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. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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.<br><br>In attenuated FAP with only minimal involvement of the rectum, an ileorectostomy is recommended (see also 5.2.2.2) | |
| Level of Evidence<br><br>**3b** | 307] | |
| | Strong consensus | |

### 7.7.9. Cancers in Ulcerative Colitis

| 7.57. | Evidence-based Statement | 2008 |
|---|---|---|
| Level of Evidence<br><br>**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* [398].

## 7.8.        Postoperative Histopathological Examination

| 7.58. | Evidence-based 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: [568, 704, 791-803] | |

**Background**

Increasingly and especially after neoadjuvant radiochemotherapy, the degree of remission achieved is histologically classified according to Dworak [803].

| 7.59. | Consensus-based Recommendation | 2008 |
|---|---|---|
| **EC** | 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 |
|---|---|---|
| **EC** | 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) [804-807]. 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 [808, 809]. 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 [810]. 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 [811-814]. 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 |
|---|---|---|
| **EC** | 12 or more lymph nodes shall be removed and examined. | |
| | Strong consensus | |

| 7.62. | Conssensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | The ratio of tested and affected lymph nodes should be documented. | |
| | Strong consensus | |

| 7.63. | Consensus-based Statement | 2013 |
|---|---|---|
| **EC** | 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 [704]. The so-called INTACC-study with 3491 patients also showed that the prognosis correlates with removed/examined lymph nodes [815]. 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 [816].

This effect was demonstrated in numerous cohorts [817-820]..

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 [821-823].

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 [824].

## 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 |
|---|---|---|
| **EC** | Analogous to the quality evaluation of the resection in rectal cancer, the quality of the colon cancer resection should also be categorized as follows:<br><br>Grade 1 (good): intact mesorectum<br>Grade 2 (moderate): mesorectal surface irregularities<br>Grade 3 (poor): defects down to the muscularis propria or the tumor<br><br>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 appropiate, 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 [825, 826].

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

| 7.65. | Consensus-based Recommendation | 2013 |
|-------|-------------------------------|------|
| **EC** | 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 quantitively. | |
| | 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)

| R0 wide | R0 narrow |
|---|---|
| distance > 0,1 cm | distance ≤ 0,1 cm |
| CRM negative | CRM positive |

**distance of tumour from resection margin**
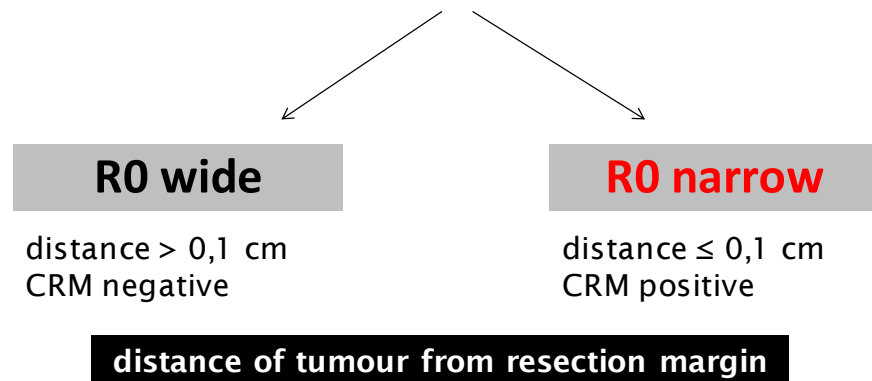
Taking into account continuous primary tumour spread, satellites, involvement of lymphvessels, venous infiltration, perineureum infiltration, lymphnode metastases

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+ [685, 827].

Whether a safety margin of less than 2mm leads to a poorer prognosis is controversial [828, 829].

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

| 7.66. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | 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:<br><br>The quality of the resection specimens is graded by the integrity of the mesorectal fascia in 3 categories:<br><br>• Grade1 (good): mesorectal fascia is intact<br>• Grade 2 (moderate): intramesorectal surface tearing<br>• Grade 3 (poor): tearing down to the muscularis propria or the tumor<br><br>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 . [830].<br><br>Therefore, the pathohistological report must describe the radicality in the levator musculature region. The following categories should be used:<br><br>• Grade 1 (good): levator musculature included in resection, no opening of the intestine or tumor<br>• Grade 2 (moderate): muscularis propria intact, no opening of the intestine or tumor<br>• Grade 3 (poor): parts of the muscularis propria are missing or opening of the intestine or tumor<br><br>The analysis has to be performed by a pathologist. | |
| | 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 ($P < 0.05$) [831]. 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 [827]

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 [825, 830].. 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. | Evidence-based Recommendation/ EC[7] | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Psychooncological care should be included in the overall therapy concept. | |
| Level of Evidence<br><br>**1b** | [833-860] | |

| 7.68. | Consensus-based Recommendation/ EC[8] | 2013 |
|---|---|---|
| **EC** | 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%) [835-838]. For the CRC patient group the numbers are similar [839, 840]. Advanced disease stage, marked functional impairment, and high somatic discomfort are associated with a high risk of psychological disorders [841. 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 [840, 842]. 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 [843].

A large proportion of psychological disorders in tumor patients is not correctly diagnosed and is insufficiently treated [837, 844, 845]. 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 regularly

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[7] Taken from the interdisciplinary S3-guideline for the diagnostics, therapy and follow-up of breast cancer. 832.          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**

[8] Taken from the interdisciplinary S3-guideline for the diagnostics, therapy and follow-up of breast cancer. 803. Ibid.

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 [[836, 846, 847]. 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 [848], 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 onocologic expert centers, or by including practicing physicians or psychological psychotherapists with psycho-oncologic qualification [849-851]. 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 [834, 845, 852-860].

In addition, look at the S3-Guideline Psychooncology,

AWMF     -Registernummer:     032/051OL:     http://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/

# 8. Adjuvant and Neoadjuvant Therapy

## 8.1. Adjuvant Therapy of Colon Cancer

### 8.1.1. Indication for Adjuvant Therapy of Colon Cancer

R0 resection of the primary tumour is a prerequisite for adjuvant therapy. The basis for the indication for adjuvant therapy after quality-controlled tumour resection [861] is a histopathological determination of the stage, especially the determination of the pN status. To determine a pN0 status, 12 or more regional lymph nodes should be examined (UICC 2002). Immunocytological findings of isolated tumour cells in bone marrow biopsies or lymph nodes as well as cytological tumour cell findings in peritoneal lavages do not serve as an indication for adjuvant therapy outside of clinical studies.

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

**Contraindications for adjuvant chemotherapy of colon cancer**

- Performance status worse than 2 (ECOG)
- Uncontrolled infection
- Liver cirrhosis Child B and C
- Severe coronary heart disease, cardiac insufficiency (NYHA III and IV)
- Preterminal kidney failure and end-stage renal disease
- 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 | 2017 |
|---|---|---|
| **EC** | Adjuvant therapy should not be omitted solely for reasons of age. However, there is insufficient evidence to support the application of adjuvant chemotherapy in patients aged over 75 years. | |
| | Strong consensus | |

**Background**

Analyses of a Canadian database, which examined patients (n= 2,801) in Ontario between 2002-2008, show that 68% of patients aged 70-79 years and even 24% of patients aged >80 years in stage III were receiving adjuvant therapy [862]. In this retrospective analysis, all age groups benefited from adjuvant chemotherapy. However, the administration of adjuvant therapy was associated with the Charlson Comorbidity Index, so that only "medically" fit elderly patients received adjuvant therapy.

Due to the small sample sizes, the reliability of data from prospective, randomised studies on the impact of adjuvant chemotherapy in elderly patients is limited. This was due to an age limitation as part of the inclusion criteria in most of these studies. For example, patients aged >75 years could not be enrolled in the MOSAIC study [863]. While the NSAPB C-07 study had no age limitation, only 396 of the original 2,409 patients were older than 69 years. For this reason, pooled analyses of clinical studies have to be carried out in order to assess the impact of age on the use of adjuvant chemotherapy. Pooled analyses of the NSABP-C08, XELOXA, X-ACT and AVANT studies showed that treatment with FOLFOX/XELOX can be discussed in all age groups [864]. The hazard ratio for adjuvant therapy with oxaliplatin was 0.78 for overall survival in patients aged >69 years, whereas younger patients had a significantly stronger benefit from oxaliplatin-based therapy with an HR of 0.62. However, elderly patients exhibited a higher rate of adverse drug reactions. The NO16968 study yielded comparable data. In an exploratory analysis, the benefit of XELOX versus the comparative arm 5-FU/FA (bolus regimen) was also maintained in patients aged >69 years (n= 409 of 1888) [865]. The hazard ratio for the 7-year OS was 0.91 (0.66-1.26) in patients aged >69 years compared to 0.80 in patients aged <70 years. This reduced benefit of adjuvant therapy in elderly patients was also evident in an analysis of the ACCENT database. While the administration of capecitabine was also shown to be effective in elderly patients, the combination of fluoropyrimidine and oxaliplatin was not [866]. The age of the patient, therefore, has no predictive value in itself [867]. However, in elderly patients the benefit of adjuvant therapy is lower, while the toxicity is higher.

| 8.2. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation **B** | Adjuvant chemotherapy should be initiated as soon as possible postoperatively. | |
| Level of Evidence **3b** | Sources: [868-870] | |
| | Strong consensus | |

| 8.3. | Evidence-based Statement | 2017 |
|---|---|---|
| Level of Evidence **1b** | In the randomised studies, adjuvant chemotherapy was initiated within 8 weeks. | |

**Background**

Randomised studies on this question do not exist. In a retrospective analysis of cohort studies [868], an inverse correlation was found between the start of adjuvant chemotherapy and survival. This was also confirmed in another retrospective analysis of cohort studies [869] and in a retrospective register analysis [870].

A small retrospective study (n=186) suggests that starting adjuvant therapy later than 60 days after the surgery can lead to a reduction in overall survival [871]. This important question was also studied in 1,053 patients with stage III colon cancer (surgery between 2000-2005) [872]. In 648 patients (61%), adjuvant chemotherapy was commenced within 16 weeks of surgery. Patients who received adjuvant chemotherapy later than 12 weeks after surgery were found to have a poor socioeconomic status and more comorbidities. The mortality in patients who received adjuvant chemotherapy within 12-16 weeks of surgery was 1.4 times higher than in patients who received the treatment within 8 weeks of surgery. The mortality rate in patients who did not receive adjuvant chemotherapy within 16 weeks was more than twice as high compared to patients who received the treatment within 8 weeks. In this patient population, the cancer-specific mortality increased by 76%.

Another retrospective analysis (1997-2012) assessed whether the start date of adjuvant therapy (< or >8 weeks) or the need for follow-up surgery have an impact on the prognosis [873]. The need for follow-up surgery was found to be a significant factor for the delay in adjuvant therapy (OR 2.3). No difference in survival was found between patients who had no delay in adjuvant therapy but underwent follow-up surgery and patients who had neither a delay in adjuvant therapy nor required follow-up surgery. However, patients with a delay in adjuvant therapy who did not require follow-up surgery were found to have a significantly worse prognosis than patients who had neither a delay in adjuvant therapy nor required follow-up surgery (colon: HR 1.16; rectum: HR 1.17). Overall survival was also worse in patients who had both a delay in adjuvant therapy and required follow-up surgery compared to patients who had neither.

### 8.1.3.        UICC Stage III

| 8.4. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | For patients with R0 resected stage III colon cancer, an adjuvant chemotherapy shall be performed. | |
| Level of Evidence<br><br>**1a** | Source: [874-877] | |
| | Strong consensus | |

**Background**

Various randomised studies have demonstrated a significant survival benefit for patients with stage III colon cancer due to adjuvant chemotherapy [878, 879]. Meta-analyses and pooled analyses (Gill et al.) in 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 in the prognosis of patients with lymph node positive disease (stage III) [874-877].

## 8.1.4.        UICC Stage II

| 8.5. | Evidence-based Recommendation | 2017 |
|------|-------------------------------|------|
| Grade of Recommendation<br><br>**0** | For patients with curatively resected stage II colon cancer, an adjuvant chemotherapy can be performed. | |
| Level of Evidence<br><br>**1 b** | Sources: [880-884] | |
| | Strong consensus | |

**Background**

The absolute benefit of adjuvant therapy in UICC stage II without risk factors is between 2 and 5% for the five-year survival. Studies and pooled analyses of studies of patients with stage II colon cancer did not show a significant survival benefit from postoperative adjuvant chemotherapy [880-883]. A pooled analysis of seven randomised studies which compared adjuvant chemotherapy to surgery alone merely demonstrated a significant improvement of the disease-free five-year survival (DFS) (72% vs. 76%; p=0.049) in the univariate analysis. This benefit could not be shown for the five-year overall survival in stage II colon cancer (80% vs. 81%; p=0.1127). Furthermore, the individual studies differed considerably concerning therapy modalities and included small sample sizes [875]. In a population of 43,032 Medicare patients (>66 years; 18,185 patients in stage III, 57% received adjuvant chemotherapy), 6,234 patients in stage II had no (19% with adjuvant chemotherapy) and 18,613 patients had at least one unfavourable prognostic criterion (21% with adjuvant chemotherapy). The five-year survival rates in these three groups were 44%, 69% and 57%. While chemotherapy had no impact on survival in both stage II groups, chemotherapy in stage III significantly improved survival (5-year survival rate: 48.9% vs. 35.2%) [885].

The British QUASAR study is the largest individual published study concerning this issue [884]. In this study, after a median observation period of 5.5 years, the relative risk for death from any cause was significantly lower in the treatment 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 around 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 dosages of folinic acid). The relative risk for the isolated subgroup of stage II colon cancer was not significantly reduced; the effect, however, was the same in all subgroups, leading to the assumption of a survival benefit for all prognosis groups. Considering the significance of this study for the so-defined "high-risk-situation" (see below), no recommendations can be derived, since data on the T-category and/or degree of vascular invasion are merely available for around 20% of all patients. Of these 20%, only very few patients actually exhibited a T4 or V1 status.

At this time, there are no convincing data available concerning the use of oxaliplatin in stage II: The effect of adjuvant postoperative chemotherapy (FOLFOX4 versus LV5FU2) in stage II was reported in a subgroup analysis [886]. Regarding stage II, there was neither a significant improvement in disease-free survival nor an overall survival benefit

for patients additionally treated with oxaliplatin and having a stage II tumour. Taking into account all currently available randomised and controlled studies, a recommendation for an obligatory use of adjuvant chemotherapy in stage II cannot be given [887-889]. However, in view of the positive results of the currently largest study, the QUASAR study, a benefit of adjuvant therapy in stage II patients without risk factors cannot be completely excluded – regardless of the methodological shortcomings of this study. For this reason, therapy should at least be taken into consideration in this stage [884]. In any case, the benefits and risks of such a therapy should always be discussed with the patient.

### 8.1.5.     UICC Stage II with Risk Factors

| 8.6. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | In stage II adjuvant chemotherapy should be taken into consideration in selected risk situations (T4, tumour perforation/tears, surgery under emergency conditions, number of examined lymph nodes too small). | |
| Level of Evidence<br><br>**3b** | Sources: [704, 879, 890] | |
| | Strong consensus | |

**Background**

The factors listed above have been identified as unfavourable for the prognosis. It thus appears possible that patients with these risk factors may also benefit from adjuvant chemotherapy in stage II cancer. Nonetheless, there are no prospective data available concerning the association of these risk characteristics and the benefit of adjuvant chemotherapy. Therefore, before initiating adjuvant chemotherapy, a thorough discussion with the patient about the advantages and disadvantages of adjuvant chemotherapy against the backdrop of the current data situation should be carried out in this subgroup.

Several studies found that a poor prognosis was associated with certain risk situations such as T4 tumour, tumour perforation, operation under emergency conditions as well as too few examined lymph nodes [891, 892]. In a retrospective study conducted in 1,306 patients with a stage II tumour, a multivariate analysis showed that T4 category was associated with poor disease-free survival (HR 1.75) [893]. In the study conducted by Moertel (n=318), T4 category in stage II had no additional prognostic relevance [887]. However, prognostic relevance was demonstrated in a study conducted by Burdy (n=108) [894], in the Erlanger analysis (n=305) [891] and in the meta-analysis published by Gill [875].

A significantly lower five-year survival rate was observed after emergency surgery, 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 [895]. Cancer-specific survival after five years was reduced from 74.6% to 60.9% with evidence of anaemia, to 51.6% with evidence of stenosis, and to 46.5% with evidence of perforation (p<0.001) [896]. In several studies, the number of examined lymph nodes was also found to be an independent prognostic factor [704, 890]. 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 [890]. 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 tumours of N0 status showed the best overall survival if more than 20 lymph nodes were analysed [704]. In a study of 3,592 cases of colorectal cancer, an English working group [897] identified 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 tumour 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 [898] 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 in whom only 1-7 lymph nodes were examined. This result was independent of tumour stage and other patient or tumour characteristics. Even if study results are heterogeneous with regard to the exact number of lymph nodes to be examined, experts believe that at least 12 lymph nodes should be analysed, even if this number cannot be achieved at all times. In this context, please also refer to the section "Surgical Treatment of Colorectal Cancer".

A study in which patients with stage II tumours and high-risk characteristics represented a small subgroup showed no benefit of adjuvant chemotherapy compared to surgical therapy alone [879]. In contrast, the MOSAIC study included a high-risk population consisting of patients with stage II tumours with T4 status, tumour perforation, ileus, poorly differentiated tumour, blood vessel invasion and/or less than 10 lymph nodes examined. For this high-risk population, postoperative adjuvant FOLFOX4 chemotherapy resulted in a non-significant improvement of disease-free ten-year overall survival by 3.7% percentage points in comparison to 5-FU/FA chemotherapy. There was also no significant improvement of the ten-year overall survival (75.4% vs. 71.7%). In the FOLFOX4 group, 48 of 212 patients died, compared to 53 of 222 patients in the 5-FU/FA group [886]*.

| 8.7. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | For patients in stage II, the microsatellite status has to be determined prior to establishing an indication for adjuvant chemotherapy. Additional parameters (e.g. level of CEA protein, level of differentiation of the tumour, 18q loss, isolated tumour cells in lymph nodes or in bone marrow, DNA ploidy and TS/p53 expression, lymph and blood vessel invasion, molecular genetic analyses) may not be used as an indication for adjuvant chemotherapy. | |
| Level of Evidence<br><br>**3b** | Sources: [899-902] | |
| | Strong consensus | |

| 8.8. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | If microsatellite instability (MSI-H) is present, adjuvant chemotherapy should not be performed in stage II. | |
| Level of Evidence<br><br>**2a** | | |
| | Strong consensus | |

**Background**

It has been demonstrated in some, but not in all studies, that a number of the prognostic parameters mentioned in recommendation 8.7. have a prognostic relevance for colorectal cancer. However, there are no prospective studies available on the benefit of adjuvant chemotherapy in the presence of one or more of these factors. In some studies, the degree of differentiation was rated as an independent prognostic factor not only in stage III [795, 903], but also in stage II and III [875]. In contrast, an analysis by Hermanek demonstrated that the degree of differentiation only has additional prognostic relevance in a subgroup of stage III cancer (any T N2 M0) [904].

In several studies, loss of the 18q allele was also shown to have independent prognostic relevance in stage II [905-909]. However, a study of patients with stage II colon cancer (n=70) came to the conclusion that 18q loss did not have any prognostic relevance [910]. A recently published meta-analysis unequivocally demonstrated a negative prognostic relevance of DNA aneuploidy. Five years after surgery, patients with aneuploid colorectal cancer exhibited a significantly higher mortality rate than patients with diploid tumours. This was true for all subgroups studied, and in particular for stage II. However, the studies were designed retrospectively [911].

Microsatellite instability (MSI) can be detected in 10-15% of all cases of sporadic colorectal cancer. The results of an Italian study of 718 patients indicate that patients with mismatch repair protein (MMRP)-negative tumours have a better long-term prognosis than patients with MMRP-positive cancer. This positive prognostic effect was seen in both stage II and stage III (757). A supplementary study of the PETACC-3 study (5-FU vs. FOLFIRI) analysed the impact of the microsatellite status on the prognosis of stage II/III tumours (n=1,254 patients). The tumours were categorised as MSI-high (MSI-H) (3 or more markers unstable) or MS-stable (MSS) using 10 markers. In stage II, patients with MSI-H tumours had a significantly better RFS and OS than patients with MSS tumours (HR 0.26 and 0.16). In contrast, only a slight improvement in RFS was seen in stage III (HR 0.67), but no significant impact on OS [912].

Concerning the impact of the MS status on the effects of adjuvant chemotherapy, only retrospective analyses of prospectively randomised studies or register analyses are available. In the Italian study, adjuvant chemotherapy was shown to improve the prognosis of patients with MMR protein-positive tumours [913]. A study conducted by Sinicrope demonstrated that microsatellite instability and DNA diploidy were also associated with a better prognosis [914]. In 570 patients with stage II (55%) and stage III (45%) analysed jointly in the IMPACT study, adjuvant chemotherapy led to an

improvement in survival; however, with high-grade microsatellite instability, adjuvant chemotherapy resulted in decreased survival [899]. A study of 876 patients with stage III tumours revealed that the microsatellite status had no prognostic relevance for the group that had not received adjuvant chemotherapy (5-year survival rate: 43% versus 36%), while a significantly higher survival rate was demonstrated for the patients with MSI-positive tumours who had undergone chemotherapy [915]. An additional analysis of 5 prospective studies showed that MSI tumours have a significantly improved DFS and a tendency for improved OS after surgical therapy alone. However, in contrast to the group with MMS tumours, a DFS benefit due to 5-FU-based therapy was not observed in the group with MSI tumours. In patients with stage II MSI tumours, adjuvant 5-FU therapy even resulted in a reduction of OS [900]. A Spanish study (stage II/III) and a Korean study (stage II) also demonstrated that patients with MSI tumours did not benefit from adjuvant 5-FU therapy [901] [902]. In contrast to this, a retrospective Australian study showed that adjuvant chemotherapy also improved the prognosis for MSI tumours [916]. The prognosis of patients with MSI-H colon cancer was also not influenced by the therapeutic arm in the PETACC-3 study; in other words, in the group of patients treated with 5-FU, MSI-H tumours retained their prognostic advantage over MSI-L/S tumours [912].

The data of the MOSAIC study (n=2,246) (*FU/LV vs. FOLFOX*) were additionally analysed with regard to the effects of the mismatch repair status (MMR) and the BRAF mutation after a median follow-up of 9.5 years. The 10-year OS was 79.5% in the FU/LV group vs. 78.4% in the FOLFOX4 group for stage II (HR 1.00), and 59.0% vs. 67.1% for stage III (HR 0.80; p=0.016). Defective MMR (dMMR) was identified in 9.4% of the study population. No significant improvement of survival was observed in the dMMR group (stage II/III) with FOLFOX4 (HR 0.41; 95% CI: 0.16-1.07) [886].

More recent studies have analysed additional parameters:

- Immunohistochemical analysis of the CDX2 gene product, a regulator of intestinal development. CDX2-negative tumours (6.9% of all CRCs) were found to have a significantly poorer prognosis in this retrospective study. A marked improvement of the five-year DFS for CDX2-positive (80-87%) vs. CDX2-negative tumours (49-51%) was also shown for stage II. In the CDX2-negative group (recruited from the studies NCBI-GEO, NCI-CDP, NSABP C-07 and Stanford TMAD), adjuvant chemotherapy compared to surgical therapy alone increased the DFS from 56% to 91% in stage II and from 37% to 74% in stage III ([917])

- Circulating tumour DNA (ctDNA). In the group of patients who had not received postoperative adjuvant chemotherapy, ctDNA was detected in 14/178 patients (7.9%) postoperatively; of these, 11 (79%) suffered a recurrence in the median follow-up of 27 months. Recurrence was detected in only 16/164 patients (9.8 %) with negative ctDNA ([918]).

- The effect of local inflammation (measured in the section as the degree of tumour infiltration by chronic inflammatory cells (CIC), lymphocytes, plasma cells and macrophages) and systemic inflammation (measured in the blood as the neutrophil-to-lymphocyte ratio (NLR)) on the prognosis was determined. An increased CIC value significantly improved the 5-year OS (low: 69.7%; high: 83.7%), while a high NLR value reduced the survival rate (low: 82.5%; high: 60.5%) ([919]).

## 8.1.6.    Chemotherapy Protocols

### 8.1.6.1.    Stage III
**Oxaliplatin in combination with 5-FU/Folinic Acid (FA)**

| 8.9. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | For adjuvant chemotherapy of stage III colon cancer, a therapy containing oxaliplatin shall be given. | |
| Level of Evidence<br><br>**1b** | Sources: [865, 886, 920, 921] | |
| | Strong consensus | |

**Therapy schemes**

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

**Modified FOLFOX6 scheme**: Oxaliplatin (85 mg/m$^2$ as a 2-hour infusion; day 1), folinic acid (400 mg/m$^2$ as a 2-hour infusion, day 1) + 5-FU (400 mg/m$^2$ as an IV bolus, day 1; then 2400 mg/m$^2$ as a continuous 46-hour IV infusion). 1 cycle lasts 2 weeks, 12 cycles total.

**XELOX**: Oxaliplatin 130 mg/m$^2$ on day 1; capecitabine 2x1,000mg/m$^2$/day, day 1-14, repeated on day 22. 1 cycle lasts 3 weeks, 8 cycles total.

**Background**

Several randomised studies have demonstrated a significant reduction of the recurrence rate and an increase in overall survival when a combination of 5-FU and folinic acid was administered [876, 878, 879].

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. In the study population as a whole, FOLFOX4 chemotherapy demonstrated a significant improvement in disease-free survival compared to LV5FU2 chemotherapy (73.3% vs. 67.4%, p=0.003) (10-year survival) [886, 920]*. 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) (250 deaths in the FOLFOX group (n=672) vs. 293 deaths in the 5-FU/FA group (n=675)). Four years after therapy, the rate of peripheral sensory neuropathy was 12% (grade I), 2.8% (grade II), and 0.7% (grade III) [886, 920, 922, 923]*.

The NSABP C-07 study included 2,407 patients with stage II (28.6%) or stage III tumours 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 [921]. When choosing between the different regimens, 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, the rate of level 3 and 4 diarrhoea was three-fold higher 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 chemotherapy-induced enteropathy [921]. While showing comparable efficacy, 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 preference is given to the modified FOLFOX6 scheme, which consists of a 46-hour continuous infusion of 5-FU after an initial 5-FU bolus on day 1. This way, the patient is spared the 5-FU bolus and the pump change on day 2 of the FOLFOX4 therapy.

After a follow-up of nearly 7 years, data of the NO16968 study (*FU/LV vs. XELOX)* show that the addition of oxaliplatin improves the 7-year OS from 67% to 73%. This long-term analysis thus confirms that the combination of the oral prodrug capecitabine in combination with oxaliplatin also plays a role in the adjuvant chemotherapy of stage III colon cancer [865]. A meta-analysis of 8,734 patients (NSABPC-08, XELOXA, X-ACT, and AVANT studies) showed no difference between DFS and OS relative to the administered fluoropyrimidine (5-FU/leucovorin vs. capecitabine). A multivariate analysis confirmed the results of the MOSAIC study, which showed that the addition of oxaliplatin is associated with a survival benefit [924].

Regarding the duration of adjuvant chemotherapy see 8.1.6.3.

| 8.10. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Oxaliplatin-based therapy should not be performed in patients aged over 70 years. | |
| Level of Evidence<br><br>**2b** | Sources: [863, 925-928] | |
| | Consensus | |

**Background**

Even though 40% of all CRC patients are older than 75 years, only between 1-5% of randomised patients are aged ≥75 years in the adjuvant therapy studies. Whether adjuvant chemotherapy has a positive effect in patients aged ≥75 years was analysed on the basis of data from 5,489 patients from 4 data registers with UICC stage III CRC. The use of adjuvant chemotherapy in this group of patients led to an improvement in postoperative survival. The combination of 5-FU and oxaliplatin only led to an improved survival trend (HR 0.84; CI 0.69-1.04; p=NS), corresponding to an absolute improvement of survival of 5 percentage points after 3 years. An additional analysis of the data

registers showed that more side effects were observed in elderly patients treated with oxaliplatin [925].

Retrospective analyses of the MOSAIC study [863] assessed the significance of supplementing the adjuvant therapy by oxaliplatin on the endpoints DFS (disease-free survival), TTR (time to recurrence) and OS (overall survival) in elderly patients. As a limiting factor it must be mentioned that patients aged >75 years could not be enrolled in the MOSAIC study. As a result, the subgroup of patients aged >69 years in the MOSAIC study accounted for only 315 of the total study population of 2,246 patients. This subgroup analysis did not show an advantage for oxaliplatin. With 1.10 (95% CI: 0.73-1.56), the HR for OS was even to the advantage of the 5-FU/FA regimen alone. For DFS and TTR, the HR was 0.93 (95% CI: 0.64-1.35) and 0.72 (95% CI: 0.47-1.11), respectively. However, the significance level was not achieved, which may be due to the small sample size.

A similar analysis of the American NSABP C-07 study [926] showed no advantage for the FLOX therapy (5-FU bolus regimen plus oxaliplatin) compared to FU/FA therapy alone (HR 1.03; 95% CI: 0.77-1.36; p=0.87) in patients aged >69 years with regard to DFS. The same was found for overall survival (HR 1.18; 95% CI: 0.86-1.62; p=0.30). Here, the oxaliplatin/age interaction on OS was significant with a p-value of 0.039. 396 of the original 2,409 patients were older than 69 years. These data are supported by smaller, retrospective analyses. A Danish working group was able to retrospectively identify 191 patients aged >69 years who received adjuvant therapy with fluoropyrimidine (FP) or with FP plus oxaliplatin at a centre [927]. Here, too, the administration of oxaliplatin was associated with a shorter DFS (HR 0.58, p=0.016) and a shorter OS (HR 0.49; p=0.003) with an altogether higher toxicity (HR 3.69; p=0.001). A Canadian analysis of 90 patients aged >65 years showed that the benefit of adjuvant oxaliplatin therapy decreased with age [928].

The NO16968 study (FU/FA vs. XELOX) [865] was unable to demonstrate a negative effect of age on DFS or OS in the subgroup analysis. However, it is unclear to what extent this is related to capecitabine as a combination therapy drug.

A pooled analysis which assessed the effect of oxaliplatin in elderly patients [864] did not show a negative effect of age on the administration of oxaliplatin after adjusting for comorbidities. In the analysis of 904 patients from the NSABP C-08, XELOXA, X-ACT, and AVANT studies who received either fluoropyrimidine (FP) monotherapy or FP plus oxaliplatin, the interaction test for age and oxaliplatin was negative with regard to OS and DFS.

In summary, oxaliplatin should only be part in the adjuvant therapy in well-justified exceptions, for example, for patients without comorbidities.

**Monotherapy with Fluoropyrimidines**

| 8.11. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | In case of contraindications against oxaliplatin-containing regimens, monotherapy with fluoropyrimidines shall be given. Here, oral fluoropyrimidines should be preferred over infusional schemes. Bolus regimens may no longer be used due to higher toxicity. | |
| Level of Evidence | Sources: [924, 929-934] | |

| 8.11. | **Evidence-based Recommendation** | **2017** |
|---|---|---|
| **1 b** | | |
| | Strong consensus | |

**Oral 5-FU Prodrugs:**
Capecitabine 2 x 1,250 mg/m$^2$ body surface area p.o. day 1-14, every 3 weeks.
1 cycle lasts 3 weeks, 8 cycles total.

**Background**

1,987 patients with stage III colon cancer were either randomised to the Mayo Clinic scheme (983 patients) or were given capecitabine monotherapy (1,004 patients) over a period of 24 weeks each (X-ACT study). The primary study objective 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 did not show a significant difference, but a trend towards the superiority of capecitabine was found (81.3% vs. 75.6%; p=0.05) [929]. A meta-analysis of 8,734 patients (NSABPC-08, XELOXA, X-ACT, and AVANT studies) did not show a difference in DFS and OS in connection with the administered fluoropyrimidine (5-FU/leucovorin vs. capecitabine) [924].

Even through a randomised study with UFT + folinic acid versus 5-FU/FA [935] did not detect a difference in overall survival and disease-free survival and Japanese meta-analysis of three studies even found a significant improvement of overall survival and DFS [936], 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/m$^2$ as a 2-hour infusion, day 1 and 2) plus 5-FU (400 mg/m$^2$ as a bolus, then 600 mg/m$^2$ as a 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/m$^2$ as a 1-2-hour infusion) plus 5-FU (2,600 mg/m$^2$ as a 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 a long-term infusion over 12 weeks total (300 mg/m$^2$/day)

**Background**

Compared to the 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 favour of the infusional route [930, 931]* [932, 933]. A comparison of a

12-week therapy with the protracted venous infusion (PVI) of 5-FU (300 mg/m²/day) versus a 6-month Mayo scheme showed no significant difference in recurrence-free survival (RFS) and in overall survival, while demonstrating lower toxicity for PVI 5-FU [934]. Beginning adjuvant chemotherapy within a period of 8 weeks after surgery showed a significant survival benefit [937]. The optimal duration of chemotherapy was 6 months [932, 938, 939].

| 8.12. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation  **A** | Monoclonal antibodies or irinotecan may not be used in the adjuvant therapy of colon cancer. | |
| Level of Evidence  **1b** | Sources: [940-942] | |
| | Consensus | |

### Background

Adjuvant therapy with an irinotecan-based protocol cannot be recommended on the basis of the data obtained from phase III studies [940], [941], [942].

Several studies have assessed the significance of monoclonal antibodies in the adjuvant situation. In the N0147 study, patients (N=1,863) with KRAS wild type tumours received adjuvant therapy with either mFOLFOX6 or mFOLFOX6 + cetuximab (12 cycles every 2 weeks). No positive effect of the adjuvant cetuximab therapy was demonstrated after a follow-up of 28 months: no difference was observed in either DFS (74.6% vs. 71.5%) or overall survival (87.3% vs. 85.6%). Significantly increased toxicity was observed in the cetuximab group. In the subgroup of patients aged over 70 years, the addition of cetuximab led to a marked decrease of DFS (86.2% vs. 72.5%). [943]. The addition of cetuximab to FOLFOX4 chemotherapy also did not improve the oncological outcomes in the PETACC-08 study [944].

The NASABP C-08 study compared the modified FOLFOX6 scheme (12 cycles every 2 weeks) with FOLFOX6 + bevacizumab. Bevacizumab was administered for 1 year in total. Patients with curatively resected colon cancer in stage II or III (75%) were enrolled in the study; patients aged over 70 years accounted for only 15.1% of the population. After a median follow-up of 5 years, this study did not show a significant improvement of DFS for the additional use of the antibody (75.1% vs. 77.9%), not even after a separate analysis of stage II and stage III. Overall survival was comparable in both groups [945]. The AVANT study (n=3,451) used a similar therapeutic design as the NSABP C-08 study. The primary endpoint was DFS. In this study, XELOX plus bevacizumab was tested as an additional third therapeutic arm. More serious side effects were reported in the groups treated with bevacizumab than in the group receiving FOLFOX therapy alone (25.5% vs. 20%). Within 60 days of starting the therapy, 2 patients died in the FOLFOX group, 4 patients in the FOLFOX4 plus bevacizumab group, and 6 patients in the XELOX plus bevacizumab group. The DFS was not improved by the addition of bevacizumab. A negative impact of the bevacizumab therapy on overall survival was even observed (HR for bevacizumab-FOLFOX4 vs. FOLFOX4 1.27 (p=0.02), bevacizumab-XELOX vs. FOLFOX4 1.15 (p=0.21)) [946]. The large QUASAR 2 study (Kerr) compared two therapeutic groups

with one another after curative therapy of stage II high-risk or stage III colon cancer (capecitabine vs. capecitabine plus bevacizumab). No difference in the 3-year DFS was established after a median follow-up of 4.92 years (75.4% vs. 78.4%). [947].

The intensification of postoperative chemotherapy by means of antibody therapy does not improve survival compared to combination chemotherapy alone. Monoclonal antibodies therefore have no role in the adjuvant therapy of colon cancer.

### 8.1.6.2.        Stage II

| 8.13. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | If patients with stage II tumours receive adjuvant chemotherapy, fluoropyrimidines should be administered as monotherapy. | |
| Level of Evidence<br><br>**1b** | Sources: [863, 886] | |
| | Consensus | |

**Background**

At present there is no evidence to suggest that the addition of oxaliplatin leads to an improved efficacy of an adjuvant therapy in stage II (see section 8.1.4 UICC Stage II). Subgroup analyses of the MOSAIC study were conducted to assess the effectiveness of adjuvant chemotherapy with the FOLFOX4 scheme in stage II and in older patients (70-75 years, N=315). 2,246 patients with a history of curative resection of stage II (N=899) or III colon cancer were enrolled in the MOSAIC study and received postoperative adjuvant therapy with either LV5FU2 or FOLFOX4 for 12 cycles. High-risk stage II was defined as: T4 tumour, tumour perforation, ileus, poorly differentiated tumour, blood vessel invasion or less than 10 lymph nodes examined. For the entire stage II population, the additional administration of oxaliplatin did not improve DFS or overall survival. The same was found for the subgroup of high-risk tumours and the group of older patients [863]. This outcome was also confirmed in the long-term analysis of the MOSAIC study for high-risk stage II: the addition of oxaliplatin did not lead to a prognostic improvement compared to LV5FU2 chemotherapy [886].

There are no randomised studies in patients with stage II colon cancer available for the oral 5-FU prodrug capecitabine. Stage II is characterised by a higher drug non-compliance than stage III [948].

### 8.1.6.3. Duration of adjuvant therapy

| 8.14. | Evidence-based Recommendation | new 2019 |
|---|---|---|
| Grade of Recommendation<br><br>**A**<br><br><br>**B** | A) In the adjuvant setting the accumulating (neuro-)toxicity shall be weighed against the therapeutic benefit.<br><br>B) In case of a low risk of recurrence (T1-3 N1) therefore a combination of oxaliplatin and capecitabine (CAPOX/XELOX) should be given for three months. | |
| Level of Evidence<br><br>**1b** | Sources: [949-952] | |
| | A) Strog consensus<br>B) Consensus | |

| 8.15. | Evidence-based Recommendation | new 2019 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Patients with a high risk of recurrence (T4 or N2) should continue to receive an oxaliplatin-based therapy (FOLFOX or CAPOX/XELOX) for 6 months. | |
| Level of Evidence<br><br>**1b** | Sources: [949-952] | |
| | Consensus | |

**Background**

Regarding the duration of adjuvant chemotherapy, the prospective, systematically pooled analysis of 6 randomised phase III studies (SCOT, TOSCA, Alliance/SWOG 80702, IDEA France, ACHIEVE, HORG; n=12,834 patients, median follow-up 39 months) of the IDEA ("International Duration Evaluation of Adjuvant Therapy") was presented at the 2017 ASCO Annual Meeting [953]. This study has now been published as full paper (einfügen Literaturstelle 953). This study was designed to demonstrate the non-inferiority of a 3-month vs. 6-month adjuvant FOLFOX/XELOX chemotherapy. Non-inferiority was assumed if the 95% confidence interval (CI) of the hazard ratio (HR) was below 1.12. 40% of the patients received XELOX. It has to be emphasised that there was no randomisation concerning CAPOX/XELOX or FOLFOX-therapy. The primary endpoint was disease-free survival (DFS). No data of overall survival are available yet.

The occurrence of grade 3/4 neurotoxicity was significantly lower after 3 than after 6 months (FOLFOX: 3% vs. 16%; XELOX: 3% vs. 9%). The 3-year DFS rate was 74.6% (3 months) vs. 75.5% (6 months) (HR 1.07; 95% CI: 1.00-1.15). Non-inferiority was thus

not demonstrated for the study as a whole, but for the subgroup of patients with stage T1-3 N1 receiving 3 months of XELOX therapy.

The 3-month vs. 6-month DFS HRs were 1.16 (1.06-1.26) for FOLFOX and 0.95 (0.85-1.06) for XELOX. Thus an inferior outcome was demonstrated for a three month FOLFOX treatment whereas there was non-inferiority for a three month XELOX treatment compared to a six month XELOX treatment.

The 3-month vs. 6-month DFS HRs were 1.01 (0.90-1.12) in the T1-3N1 subgroup and 1.12 (1.03-1.23) in the T4 or N2 subgroups. The non-inferiority was thus not shown for the whole study group but for the subgroup with T1-3 N1 and XELOX treatment. The 3-year DFS (%) for the three and six month therapy for the different subgroups were:

N1: 79.7 vs. 80.8%

N2: 61.6 vs. 61.8%

T1-3: 79.0 vs. 79.3%

T4: 58.1 vs. 61.4%

T1-3N1: 83.1 vs. 83.3%

T4 or N2: 62.7 vs. 64.4%

There is no difference in the N2 subgroup so that for this group a therapy duration of 3 months may be discussed.

The main criticism of the IDEA data relates to the heterogeneity of the 6 individual studies and the fact that results were only significant for subgroups. The French substudy [954] suggested superiority of the 6-month regimen, but only 10% of the patients were treated with XELOX. 6 months of chemotherapy were also found to be better than 3 months (still with a power of 72% instead of 80%) in the TOSCA study [955]. Patients with rectal cancer and high-risk stage II colon cancer were also enrolled in the SCOT study [956]. The difficulties with coming to a conclusion among the authors of the IDEA-trial is illustrated in the discussion of the results in the papeer of Sobrero et al. (954). No consensus could be achieved concerning a 3 month adjuvant therapy for patients with N2-cancers.

The data of a large-scale register study from Korea [957] (n=61,315; stage II: 20,525; stage III: 25,170) were also presented at the 2017 ASCO Annual Meeting. In contrast to the IDEA study, adjuvant chemotherapy <3 months in colon cancer was shown to be significantly worse; in addition, the harder endpoint OS instead of DFS was reported (HR FOLFOX/CAPOX 2.15; HR FL/CAP 3.72).

## 8.2. Perioperative Therapy of Rectal Cancer

### 8.2.1. Neoadjuvant Therapy

#### 8.2.1.1. Stage I

| 8.16. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Preoperative therapy may not be performed in UICC stage I (cT1-2N0). | |
| Level of Evidence<br><br>**2b** | Sources: [958, 959] | |
| | Strong consensus | |

**Background**

Rectal cancers in UICC stage I (T1/2N0) show a low rate of local recurrence and distant metastases when the treatment consists of radical surgery alone with adequate total mesorectal excision (TME) for tumours in the lower/middle third of the rectum or partial mesorectal excision (PME) for tumours in the upper third of the rectum (3% local recurrence and less than 10% distant metastases after 10 years [958]. For this reason, this early tumour stage has been excluded from modern, randomised studies assessing the role of neoadjuvant radiochemotherapy in locally advanced rectal cancer (cT3/4 and/or cN+) [960] [961] [962] [963] [964].

Nevertheless, randomised studies on preoperative short-term pre-radiation with 5x5 Gy versus surgery alone included tumour stage I. While long-term results of the Swedish study showed a significant benefit regarding local control for the additional radiation for UICC stage I as well (4.5% versus 14% after 13 years, p=0.009), the concept of TME had not yet been implemented in this study and the local recurrence rates in the study arm receiving surgery alone was unacceptably high [965]. The more recent Dutch TME study also showed a numerically significant reduction of the local recurrence rate for UICC stage I in the study arm with preoperative short-term radiotherapy (<1% vs. 3% after 10 years without preoperative radiotherapy, p=0.027) [958]; however, the local recurrence rates in this stage were low in both study arms. These low local recurrence rates in stage I were also confirmed in the most recent British study of short-term radiotherapy (MRC-CR07) (1.9% after 3 years with pre-radiation vs. 2.8% with immediately surgery, n.s.) [959].

For patients with deep-seated T1N0 high-risk cancer (G3/4, L1, V1, diameter larger than 3 cm, sm3) or with T2N0 tumours who refuse an extirpation, radio(chemo-)therapy followed by local excision/transanal endoscopic microsurgery or a wait-and-see strategy for clinically complete remission can be a treatment option [966-970]. This procedure, however, has not yet been validated and requires further prospective studies.

### 8.2.1.2. Stage II/III

| 8.17. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | For UICC stages II and III (cT3/4 and/or cN+) neoadjuvant radiochemotherapy or short-term radiotherapy should be performed for tumours in the lower and middle third of the rectum. | |
| Level of Evidence<br><br>**1b** | Sources: [958, 960, 961, 971-975] | |
| | Consensus | |

| 8.18. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | Primary resection can be performed in patients with rectal cancer in UICC stage II/III in the following exceptions:<br><br>- cT1/2 tumours in the lower and middle third with potential lymph node involvement in imaging procedures<br>- cT3a/b tumours in the middle third with only limited infiltration into perirectal adipose tissue on the MRI (cT3a: <1 mm, cT3b: 1-5 mm) and without suspected lymph node metastases or extramural vascular invasion (EMVI) in imaging procedures with adequate quality assurance of the MRI diagnostics and TME surgery. | |
| | Strong consensus | |

**Background**

A tumour is classified as rectal cancer if its aboral border is less than 16 cm away from the anocutaneous line, as measured by rigid rectoscopy [976]. Studies on the neoadjuvant therapy of rectal cancer have not used a standardised definition of the rectal third based on the distance of the lower border of the tumour to the anocutaneous line. In addition to the definition of ≤6 cm for the lower third, 6 to ≤12 cm for the middle third, and 12 to ≤16 cm for the upper third [961] [977] [978], the distances 0-5 cm, >5-10 cm and >10-15 cm have also been used as limits [958] [959].

A German study on adjuvant and neoadjuvant radiochemotherapy (50.4 Gy in 28 fractions, 5-fluorouracil 1,000 mg/m²/day 1–5 in the first and fifth week of RT) of rectal cancer (up to 16 cm from the anocutaneous line) in UICC stage II and III (CAO/ARO/AIO-94) demonstrated a significant reduction of the local recurrence rate in the neoadjuvant arm (6% vs. 13% in the postoperative arm after 5 years, p=0.006) [960] [961]. The rate of postoperative complications was not increased for preoperative radiochemotherapy in comparison to immediate surgery; overall acute and chronic toxicity were significantly lower in the preoperative radiochemotherapy arm. For deep-seated tumours for which the surgeon had established an obligatory indication for extirpation prior to randomisation, the rate of sphincter-retaining surgical procedures was doubled by pretreatment in comparison to immediate surgery (19% for immediate surgery, 39% after neoadjuvant radiochemotherapy, p=0.004). In 2004, this study established neoadjuvant radiochemotherapy as a new standard for locally advanced

rectal cancer in UICC stage II and III. Meta-analyses confirmed an improvement in local control by preoperative radiotherapy (with a biologically equivalent dose, BED, >30 Gy) compared to surgery alone or postoperative radiotherapy [974] [975]. For conventional fractionated preoperative radiotherapy (1.8-2 Gy single dose up to 45-50.4 Gy total dose), the simultaneous combination with 5-fluorouracil-containing chemotherapy was shown to be significantly superior with regard to local control in two randomised studies (HR 0.54, 95% CI 0.41-0.72) [962] [963] [964] [979]. This was confirmed in meta-analyses [971] [972] [973].

However, the improvement in local control did not translate into an improvement in disease-free survival and overall survival in any of these studies/meta-analyses. Long-term results in particular of the Swedish and Dutch studies on short-term preradiation showed a significantly decreased disease-related quality of life for a number of items after preradiation with 5x5 Gy compared to surgery alone (e.g. frequency of stool in patients without a stoma as per EORTC QLQ-CR-29: mean point score after surgery alone 19.4 vs. 26.3 after 5x5 Gy + surgery, p=0.006 [980] and a deterioration in functional results (sexual function: erectile dysfunction 30% after surgery alone vs. 50% after 5x5 Gy + surgery; faecal incontinence requiring pads: 37% after surgery alone vs. 56% after 5x5 Gy + surgery after a 14-year follow-up period [981] [982] [983] - however with an outdated radiation technique and radiation volumes).

For this reason, criteria for possible omission of preoperative radio(chemo)therapy in UICC stage II and III must be defined:

A problem of every neoadjuvant therapy is the potential "overstaging" and, thus, the resulting "overtreatment" of patients who have been misdiagnosed with lymph node positive tumour (cN+). The difficulty in imaging diagnostics for cN+ is due, among other reasons, to the occurrence of reactively enlarged lymph nodes and frequent micrometastases in healthy lymph nodes. Since the sensitivity and specificity for the evaluation of lymph node involvement are thus limited for all staging methods (MRI/endorectal ultrasound/pelvic CT: sensitivity 77%, 57%, 79%; specificity 76%, 80%, 76%) [984], primary surgery is considered an expedient option for cT1/2 tumours showing a questionable cN+ status (thus, formally UICC stage III) during imaging.

The extent of infiltration into perirectal adipose tissue can be used as further selection criterion for primary surgery in wall-penetrating cT3 tumours in the middle third of the rectum. For radial tumour infiltration below 5 mm (cT3a/b) determined in thin-layer MRI and an adequate distance to the mesorectal fascia, a risk of local recurrence comparable to that of stage I can be assumed for adequate TME [985]. Therefore, neoadjuvant radio(chemo)therapy can be omitted in this constellation if no additional risk factors (e.g. deep-seated tumour, confirmed lymph node involvement, EMVI) are present and the centre can provide high-quality MRI and TME surgery [986].

| 8.19. | **Consensus-based Recommendation** | 2017 |
|---|---|---|
| **EC** | The radial distance of the primary tumour measured in the thin-layer MRI (or lymph node involvement in imaging procedures) from the mesorectal fascia (mrCRM) may not be used as a deciding factor for primary surgery outside of studies. | |
| | Consensus | |

**Background**

A number of study groups have assessed the radial distance of the tumour (or involved lymph node) to the mesorectal fascia (= later circumferential resection margin, CRM) as a selection criterion for primary surgery without neoadjuvant therapy [987] [978]. If the distance is more than 1 mm (mrCRM-), a pathologically confirmed CRM-negative resection (pCRM >1 mm) is also achieved without pretreatment with adequate TME in more than 90-95% of cases. The Mercury Study Group reported a negative predictive value of MRI of 94% for the circumferential resection margin in primary surgery (pCRM- in 192 of 205 patients with mrCRM-). The absolute number of local recurrences after a median follow-up of 62 months in the group of 205 patients with negative mrCRM who underwent surgery alone was 7% (14/205) [987].

Both the mrCRM as determined by thin-layer MRI and the pCRM as determined by histopathology undoubtedly have a high prognostic value for local control as well as for disease-free survival and overall survival [987] [685]. However, subgroup analyses of large, randomised studies confirm that preoperative radiotherapy resulted in a further significant improvement of the local recurrence rate, especially when a pCRM-negative resection was achieved [958] [827]. A multivariate analysis within the scope of the British MRC-CR07 study on risk factors for locoregional recurrence identified the lymph node status, preradiation with 5x5 Gy, the position of the tumour relative to the anterior quadrants and the quality of surgical TME as independent prognostic factors, while pCRM was only confirmed as a significant factor in the univariate analysis [827]. An indication for neoadjuvant radio(chemo)therapy versus primary surgery based exclusively on the selection criterion mrCRM- therefore requires further quality-controlled, prospective studies.

The OCUM study group is assessing a risk-based indication for preoperative radiochemotherapy, which is carried out only for the mrCRM+ constellation within the scope of this non-randomised, prospective observational study for tumours >/=6 cm from the anocutaneous line irrespective of the T and N category, while patients with tumours in the lower third (<6 cm) from category T3 upwards receive neoadjuvant therapy. Of the 642 already enrolled patients, 389 (61%) have undergone primary surgery; the rate of pCRM- in these patients was 98% [978]. However, in the group with primary surgery, a total of 192 patients (49%) had early cT1-2 tumours and in 96 patients (25%) the tumour was located in the upper third of the rectum. Long-term results on local control and survival are not available yet.

| 8.20. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Rectal cancer in the upper third without a risk constellation for a local relapse shall be treated by primary surgery and receive adjuvant therapy as for colon cancer. | |
| Level of Evidence<br><br>**1b** | Sources: [965, 988] | |
| | Strong consensus | |

| 8.21. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | In case of a risk constellation in the upper third of the rectum (e.g. T4, mrCRM+, definite and extensive lymph node involvement in imaging procedures) preoperative radio(chemo)therapy can be performed. | |
| | Consensus | |

**Background**

The following arguments speak in favour of treating the upper third of the rectum (defined variably as >10-15 cm, or >12-16 cm from the anocutaneous line, as measured by rigid rectoscopy) in the same way as colon cancer: Data from the American studies on adjuvant therapy which originally established postoperative radiochemotherapy for the treatment of locally advanced rectal cancer were based exclusively on rectal tumours with a distance of up to 12 cm between the distal edge of the tumour and the anocutaneous line [989] [990]. While the more modern studies on neoadjuvant radiotherapy/radiochemotherapy included tumours in the upper third, the Swedish and Dutch studies on short-term preradiation versus surgery alone showed no significant improvement of the local recurrence rate by additional radiotherapy for tumours located in the upper third of the rectum (defined here as >10-15 cm from the anocutaneous line) (8% vs. 12% for surgery alone after 10 years, p=0.3, in the Swedish study; 3.7% vs. 6.2% after 5 years, p=0.12, in the Dutch study) [965] [988]. In the British MRC CR07 study, however, the 3-year local recurrence rate for tumours >10-15 cm from the anocutaneous line after preradiation was 1.2% vs. 6.2% after primary surgery (HR 0.19; 95% CI: 0.07-0.47) [959]. All in all, the local recurrence rate decreased with increasing distance to the anocutaneous line in all studies; it is thus justified to forgo general preradiation for tumours in the upper third of the rectum or to only establish a selective indication for this therapy in patients with risk factors for a local recurrence or with R1 resection (e.g. cT4, mrCRM+, cN2).

| 8.22. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | Neoadjuvant radiotherapy can be performed either as short-term radiation with 5x5 Gy followed by immediate surgery or as conventional fractionated radiochemotherapy (1.8-2.0 Gy to 45-50.4 Gy) with an interval of 6-8 weeks until surgery is performed. | |
| Level of Evidence<br><br>**1b** | Sources: [991][994][992-995] | |
| | Strong consensus | |

| 8.23. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | For T4 tumours, proximity of the tumour to the mesorectal fascia (<1-2 mm) or distal tumours with intended sphincter preservation, preoperative radiochemotherapy should be performed. | |
| | Strong consensus | |

| 8.24. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | For patients in whom downsizing of the tumour is attempted, short-term radiotherapy with a longer interval of up to 12 weeks to surgery (with and without neoadjuvant chemotherapy) can be performed. | |
| Level of Evidence<br><br>**1b** | Sources: [996-998] | |
| | Consensus | |

**Background**

In two randomised studies, pre-operative short-term radiation with 5x5 Gy over five consecutive days, immediately followed by surgery, was compared to preoperative, conventional fractionated 5-fluorouracil-based radiation radiochemotherapy (45 to 50.4 Gy in 25-28 fractions), followed by surgery after 4-8 weeks. A Polish study found a significantly superior result in relation to downsizing and downstaging (pCR rate 16% vs. 1%, p<0.001) as well as a significantly lower rate of CRM+ resections (4% vs. 16% after 5x5 Gy, p=0.02) after adjuvant radiochemotherapy; however, with an increased acute toxicity compared to short-term radiation (18% grade 3-4 toxicity vs. 3% after 5x5 Gy, p<0.001). The rate of sphincter-preserving surgical procedures (primary endpoint: 58% vs. 61% after 5x5 Gy), the local (16% local recurrences after 4 years vs. 11% after 5x5 Gy) and systemic tumour control (34.6% metastases after 4 years vs. 31.4% after 5x5 Gy), as well as late toxicity (grade 3-4 7% vs. 10% after 5x5 Gy) showed no significant difference in both arms [992] [993] [994]. These results were confirmed by the Australian Trans-

Tasman study. Here, the primary endpoint, namely the rate of locoregional recurrences, showed no significant difference in both arms either (3-year results: 7.5% after 5x5 Gy vs. 4.4% after radiochemotherapy, p=0.24) [991]. The postoperative complications were similar in both study arms (53.2% after 5x5 Gy vs. 50.4% after radiochemotherapy); acute toxicity during radiochemotherapy was higher (e.g. grade 3-4 diarrhoea 1.3% vs. 14.2%, p<0.001) [999]. Within the first 12 months, no sigificant differences in the disease-related quality of life was established between the two study arms based on the EORTC questionnaires QLQ-C30 and OLC-C38 [995].

In principle, both fractionation schemes could thus be used for preoperative radiotherapy. In constellations in which tumour shrinkage prior to surgical procedures is desirable (e.g. T4 tumours, proximity of the tumour to the mesorectal fascia, distal tumours with an intention to preserve the sphincter), conventional fractionated radiochemotherapy with an interval before surgery should be preferred over short-term radiation immediately followed by surgery.

However, newer studies have shown that marked tumour regression is also observed with a longer interval between short-term radiotherapy and surgery. In the randomised Stockholm III study, surgery was performed either immediately after the administration of 5x5 Gy or after 4-8 weeks: the rate of ypT0 tumours was 2.1% following immediate surgery and 11.8% after a longer interval [996] [997]. A Polish phase III study compared conventional fractionated 5-fluorouracil-based radiochemotherapy (partly including oxaliplatin) with short-term radiotherapy followed by 3 cycles of neoadjuvant chemotherapy with FOLFOX-4 and surgery in week 12 in patients with clinically fixed T3 or T4 tumours. No significant difference was found in relation to the primary endpoint, the R0 resection rate, in both study arms (71% vs. 77%, p=0.07), nor in the local control and disease-free survival. The acute toxicity across all grades (1-4) was significantly lower in the arm with short-term RT and neoadjuvant chemotherapy (75% vs. 83%, p=0.006); the incidence of higher-grade 3-4 toxicity (diarrhoea, neutropenia) was similar in both arms overall (23% vs. 21%) [998]. Another randomised phase III study (RAPIDO) assessed short-term radiotherapy with 5x5 Gy, followed by six cycles of CAPOX and surgery in week 22-24 versus conventional radiochemotherapy with capecitabine and surgery in week 14-16 in high-risk patients as defined by MRI (T4, mrCRM+, N2, EMVI+) [1000]. Recruitment for this study was completed in June 2016; results are not available yet.

| 8.25. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>A | Neoadjuvant radiochemotherapy shall include oral capecitabine or infusional 5-fluorouracil. | |
| Level of Evidence<br><br>1b | Sources: [972, 973, 1001-1003] | |
| | Strong consensus | |

**Background**

For conventional fractionated preoperative radiotherapy (1.8-2 Gy single dose to 45-50.4 Gy total dose), the simultaneous combination with 5-fluorouracil-containing

chemotherapy was shown to be significantly superior to radiotherapy alone in terms of local control, but not in relation to disease-free survival and overall survival in two randomised studies (EORTC 22921, FFCD 9203) [962] [963] [964]. This has been confirmed in meta-analyses [972] [973]. In the EORTC 22921 and FFCD 9203 studies, patients in the preoperative combination arms received 5-fluorouracil as a bolus infusion 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. In the German CAO/ARO/AIO-94 study, 5-fluorouracil without modulation was administered with folinic acid in the first and fifth week of radiation at a dose of 1,000 mg/m²/day as a 120-hour infusion [960].

Two subsequent, prospectively randomised studies assessed the replacement of infusional 5-fluorouracil by oral capecitabine [1001] [1002] [1003] (see evidence table in the Guideline Report). The German phase III study started as an adjuvant study in 2002 and was extended by a neoadjuvant stratum after publication of the CAO/ARO/AIO-94 study in 2004. In the adjuvant stratum, after having undergone resection, patients first received two cycles of capecitabine at a dose of 2,500 mg/m²/day over a period of 14 days (repeated on day 22), followed by radiochemotherapy (1.8 Gy to 50.4 Gy) with capecitabine 1,650 mg/m²/day throughout the period of radiotherapy and another three cycles of capecitabine. Patients in the 5-fluorouracil arm received two 5-FU bolus cycles after surgery (500 mg/m²/day 1-5, repeated on day 29), followed by radiotherapy with infusional 5-FU at a dose of 225 mg/m²/day throughout the period of radiotherapy and two additional 5-FU bolus cycles. In the neoadjuvant stratum, radiochemotherapy was carried out with capecitabine, followed by surgery and five adjuvant cycles of capecitabine at the same doses as in the adjuvant stratum. The neoadjuvant cohort in the infusional 5-FU arm underwent preoperative radiochemotherapy analogously to the CAO/ARO/AIO-94 study (1,000 mg/m²/day as a 120-hour infusion in the first and fifth week). Following surgery, four 5-FU bolus cycles were administered (500 mg/m²/day 1-5, repeated on day 29). Overall survival was defined as the primary endpoint of the study (non-inferiority limit 12.5%). In 392 evaluable patients and after a median follow-up of 52 months, the 5-year survival was 76% in the capecitabine arm and 67% in the 5-fluorouracil arm (p=0.0004 for non-inferiority). In the neoadjuvant stratum (n=161 patients), signs of an increased anti-tumour effect were observed in the capecitabine group: pathological complete remission (pCR) was more frequent in the capecitabine arm (14% vs. 5%, p=0.09) and more patients had node-negative tumours in the resection (71% vs. 57%, p=0.08) [1001]. The results of the American NSABP R04 study, which assessed the use of oxaliplatin (see below) in addition to neoadjuvant radiochemotherapy with infusional 5-fluorouracil (225 mg/m²/day during RT) versus capecitabine (1,650 mg/m²/day during RT) in a 2x2 factorial design, was confirmed by the German study with regard to surgical results, pCR rates and the tolerability of the therapy [1002]. The rate of locoregional recurrences after 3 years (4.0% vs. 3.9%) as well as disease-free survival (66.4% vs. 67.7%) and overall survival (79.9% vs. 80.8%) after 5 years was nearly identical in the arms with infusional 5-FU and capecitabine [1003].

A large number of phase II studies have shown pCR rates of up to 30% for neoadjuvant 5-fluorouracil-based or capecitabine-based radiochemotherapy including oxaliplatin (summary: [1004]). The significance of these combination therapies was subsequently assessed in a total of seven randomised phase III studies [1002] [1003] [1005] [1006] [1007] [1008] [1009] [977] [1010] [1011]. These studies differed mainly in the administration route and dosage of 5-fluorouracil/capecitabine and oxaliplatin during simultaneous radiochemotherapy. Five of the studies assessed the significance of oxaliplatin only during neoadjuvant radiochemotherapy; in two studies, randomisation also included adjuvant chemotherapy with or without oxaliplatin [977] [1009]. The studies also differed with regard to the chosen primary endpoint (pCR rate [1007], local

control [1003], disease-free survival [977] [924] [1011], overall survival [1006] [1010]), and the resulting sample size calculations and their follow-up periods. The German CAO/ARO/AIO-04 [977] and Chinese FOWARC [1011] studies determined a significant improvement of the pCR rate as the secondary endpoint after neoadjuvant radiochemotherapy including oxaliplatin, while five additional individual studies showed no significant difference in the pCR rates. A meta-analysis including the ACCORD 12, STAR-01, NSAPB R-04 and CAO/ARO/AIO-04 studies described a significant increase in the pCR rate (HR 1.20; 95% CI, 1.01-1.42; p=0.04), but also a significant increase in grade 3-4 acute toxicity (HR 2.29; 95% CI, 1.31-4.00, p=0.004) after neoadjuvant radiochemotherapy with oxaliplatin [1012].

The German CAO/ARO/AIO-04 study demonstrated a significant improvement of disease-free survival (as the primary endpoint). A meta-analysis of four studies with details on the disease-free survival described a marginally significant effect on this endpoint (HR 0.89; 95% CI: 0.78-1.00, p=0.05) [1013]. However, five of the seven individual studies showed no significant improvement of disease-free survival by including oxaliplatin; long-term results on the FOWARC study are still pending regarding this. All in all, an advantage of using oxaliplatin has not been confirmed.

| 8.26. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation **B** | Surgery should be performed 6-8 weeks after neoadjuvant radiochemotherapy. | |
| Level of Evidence **3a** | Sources: [1014-1017] | |
| | Consensus | |

| 8.27. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation **B** | After short-term radiotherapy (5x5 Gy), surgery should be performed either within 10 days after starting radiotherapy or after 4-8 weeks. | |
| Level of Evidence **3b** | Sources: [997, 1018] | |
| | Strong consensus | |

**Background**

In the prospective studies to establish preoperative radiochemotherapy, surgery was performed within 3-10 weeks (median: 5.4 weeks; EORTC 22921, FFCD 9203 [962] [964]) or 6 weeks (CAO/ARO/AIO-94 and CAO/ARO/AIO-04 [960] [977]) after completing neoadjuvant therapy. The recently published GRECCAR-6 study randomised 265 patients after neoadjuvant radiochemotherapy (45-50 Gy, infusional 5-FU or capecitabine) into

two arms with surgery after 7 weeks vs. 11 weeks [1014] (see evidence table in Guideline Report). There was no significant difference in the primary endpoint of this study, the pCR rate (15% after 7 weeks vs. 17.4% after 11 weeks, p=0.6); however, more postoperative complications occurred after surgery in week 11 (32% vs. 44.5%, p=0.04) and the quality of TME was worse (complete TME 90% vs. 78.7%, p=0.02). Long-term results on oncological endpoints have not yet been published for this phase III study. Two meta-analyses and a systematic review based on non-randomised data with secondary analyses of prospective studies or observational studies suggest that an interval exceeding the usual 6-8 weeks after radiochemotherapy appears to be associated with an increased pCR rate, with an otherwise consistent complication rate [1015] [1016] [1017] (see evidence table in the Guideline Report). Differences in the local recurrence rate, disease-free survival or overall survival were not observed. There is thus no higher level of evidence to support an increase in the interval between the conclusion of radiochemotherapy and surgery beyond the standard 6-8 weeks.

In the prospective studies to establish short-term radiotherapy with 5x5 Gy, surgery should be performed within one week of completing radiotherapy. A secondary analysis of the Dutch TME study showed that elderly patients (=/>75 years) in particular exhibited poorer survival if they underwent surgery more than 3 days (i.e. surgery on day 4-7) after completing radiotherapy [1018]. For this reason, a maximum interval of 10 days is recommended as the total treatment time (start of RT until surgery) for this group.

In the randomised Stockholm III study, surgery was performed either immediately after the administration of 5x5 Gy or after 4-8 weeks: the rate of ypT0 tumours was 2.1% after immediate surgery and 11.8% after a longer interval; there was, however, no difference in the rate of pCRM+ resection and abdominoperineal extirpation [997]. Postoperative complications were lower after 5x5 Gy and a longer interval than after immediate surgery, and there were no differences in the long-term results on oncological endpoints (local recurrences, distant metastases) [1019] (see evidence table in the Guideline Report). Another randomised, monocentric study from Poland with a total of 154 patients also revealed a significant improvement of tumour downstaging after a longer interval (4-5 weeks after 5x5 Gy), however, with an identical R0 resection rate, rate of sphincter-preserving surgical procedures and no significant difference in overall survival (primary endpoint) [1020]. The results of the systematic review by Bujko et al. do not allow for a definite conclusion owing to the heterogeneity of the included studies [1021]. On the whole, a total treatment time of 10 days should be pursued for sole preoperative radiotherapy with 5x5 Gy and surgery. However, according to the publication of the Stockholm III study, a longer interval until surgery of 4-8 weeks can also be pursued and is a particularly appropriate alternative to conventional fractionated radiochemotherapy in patients requiring downsizing who are unsuitable for or refuse chemotherapy. Regarding the addition of neoadjuvant chemotherapy after 5x5 Gy and a longer interval to surgery, see the background text in recommendation 8.24.. For patients showing clinically complete remission after neoadjuvant therapy and prior to planned surgery based on the digital rectal examination, the rectoscopy and thin-layer pelvic MRI, a "wait-and-see" strategy without radical surgery is being increasingly discussed. This treatment concept is currently being assessed in prospective studies and has not yet been validated. If the patient refuses to have surgery (at least in terms of an extirpation) in spite of being informed about the unclear data situation, close surveillance involving a digital rectal examination, rectoscopy and thin-layer MRI every three months during the first two years is to be recommended to facilitate early recognition and treatment of a local tumour growth ("re-growth").

Comment on performing an MRI after completion of neoadjuvant therapy: Due to insufficient data, this issue was not discussed by the working group. A case-by-case decision should be made as required.

| 8.28. | Consensus-based Recommendation | 2017 |
|---|---|---|
| EC | Neoadjuvant chemotherapy before or after radiochemotherapy (or as neoadjuvant therapy alone without radio(chemo)therapy) may not be performed outside of studies. | |
| | Strong consensus | |

| 8.29. | Consensus-based Recommendation | 2017 |
|---|---|---|
| EC | Short-term RT with 5x5 Gy followed by neoadjuvant chemotherapy and surgery within a reasonable period can be performed in case of synchronous metastases. | |
| | Consensus | |

**Background**

Until now, only few studies have tested neoadjuvant chemotherapy before or after radiochemotherapy, or as sole therapy without RT/RCT. A small, randomised phase II study from Spain (n=108) compared 4 cycles of induction chemotherapy with capecitabine/oxaliplatin followed by radiochemotherapy with capecitabine/oxaliplatin and surgery, with the "classical" sequence (radiochemotherapy, surgery, adjuvant chemotherapy) with otherwise identical substances and dosages (evidence table 3) [1022] [1023]. There was no difference in the primary endpoint, the pCR rate and oncological long-term endpoints (for which, however, this randomised phase II study was not sufficiently powered), but the study did find a significant improvement in the tolerability and practicability of induction chemotherapy compared to adjuvant chemotherapy. Phase III studies on this question have not been conducted.

A prospective cohort study of the "Timing of Rectal Cancer Response to Chemoradiation Consortium" in the USA assessed the administration of zero, two, four and six cycles of FOLFOX chemotherapy, followed by surgery 6, 11, 15 and 19 weeks after completion of radiochemotherapy (see evidence table in the Guideline Report) after neoadjuvant radiochemotherapy with infusional 5-fluorouracil. The pCR rate increased successively in the cohorts (18%, 25%, 30%, 38%) without a simultaneous increase in surgical complications [1024]. Two randomised phase II studies are currently (date of information: 04/2017) recruiting patients with the aim of assessing which sequence (neoadjuvant chemotherapy before or after radiochemotherapy) is superior in terms of efficacy, practicability and toxicity [1025] and CAO/ARO/AIO-12. Results are expected in 2018.

Phase II studies [1026] [1027] and the randomised FORWARC study [1011] have yielded R0 resection, downstaging and pCR rates for sole neoadjuvant chemotherapy without radio(chemo)therapy. A randomised phase III study (PROSPECT) in the US is currently assessing sole neoadjuvant chemotherapy (6 cycles of FOLFOX) versus standard radiochemotherapy with 5-FU/capecitabine in selected patients (cT1/2N1; cT3N0/N1

with mrCRM-, sphincter retention possible). Data on this study are expected in 2018/2019.

Regarding neoadjuvant chemotherapy after 5x5 Gy for primary rectal cancer without synchronous distant metastases, see the background text on recommendation 8.15. In case of a primary rectal tumour with synchronous, (potentially) operable metastases, radiotherapy with 5x5 Gy, followed by early effective systemic therapy and surgical treatment of the primary tumour/metastases within a reasonable time period, can be an expedient option [1028].

## 8.2.2.    Adjuvant Therapy

### 8.2.2.1.    Adjuvant Therapy of Rectal Cancer After Primary Surgery (Without Neoadjuvant Therapy)

| 8.30. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation  **A** | In UICC stage I (pT1/2N0), R0 resection may not be followed by adjuvant therapy. | |
| Level of Evidence  **1b** | Sources: [958] | |
| | Strong consensus | |

**Background**

In all randomised studies on the adjuvant therapy of rectal cancer, patients with UICC stage I following R0 resection were excluded due to an altogether low rate of local recurrences and distant metastases (3% or less than 10% after 10 years [958]).

| 8.31. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | In case of histopathologically confirmed risk factors for a locoregional relapse (e.g. R1 resection, intraoperative tumour tears, pCRM+, insufficient TME quality, pT4, pT3c/d, pN2, extranodal tumour growth in the mesorectum, pT3 in the lower third of the rectum) adjuvant radiochemotherapy should be performed. | |
| | Consensus | |

**Background**

Phase III studies performed in the 1970s and 1980s on the adjuvant, multimodal therapy of UICC stage II and III rectal cancer (pT3-4 and/or pN+, up to 12 cm from the anocutaneous line) showed a reduction of the local recurrence rate (absolute difference: 10-15%) as well as an improvement of overall survival through the addition of 5-fluorouracil-based simultaneous and adjuvant chemotherapy to postoperative radiotherapy compared to surgery alone or unimodal adjuvant therapy (absolute difference: 5-15%) [summary: [1029]]. However, the surgical principles of total mesorectal excision were not implemented in these outdated studies, and the local

recurrence rates after surgery alone were high. A pooled subgroup analysis of five of these early North American studies also suggests that especially patients with pT1-2N1 and pT3N0 tumours following R0 resection do not benefit from the additional radiotherapy [1030].

Regarding the value of adjuvant radiochemotherapy in patients with UICC stage II and III cancer, no modern studies with quality-controlled TME surgery have been conducted since the establishment of neoadjuvant radio(chemo)therapy. Since postoperative radiochemotherapy is less effective and is associated with considerably more side effects than preoperative radiotherapy (see background text on 8.18.) [960], the benefit/risk ratio of postoperative radiochemotherapy when strictly applied according to the TME principles has not been sufficiently clarified [1031]. A general recommendation in favour of postoperative radiochemotherapy for all patients with UICC stage II and III tumours can therefore not be given. This therapy should be reserved for patients with histopathologically confirmed risk factors for an increased risk of local recurrence (e.g. R1 resection, intraoperative tumour tear, pCRM+, inadequate TME quality, pT4, pT3c/d, pN2, extranodal tumours in the mesorectum, pT3 in the lower third of the rectum).

| 8.32. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | If no adjuvant radiochemotherapy is performed after primary R0 resection in stage II/III, adjuvant chemotherapy should be performed anologuous to the indication criteria and regimen for colon cancer. | |
| | Strong consensus | |

### Background

A systematic review of postoperative chemotherapy versus observation after curative resection of rectal cancer (including 21 randomised studies between 1975-2011 and a total of 9,785 patients) confirmed a significant reduction in the mortality rate (HR 0.83, 95% CI: 0.76-0.91) and the recurrence rate (HR 0.75; 95% CI: 0.68-0.83) after 5-fluorouracil-based adjuvant chemotherapy [1032]. However, the studies included in the review are very inhomogeneous and also involve studies with preoperative and postoperative radiotherapy, and do not allow for differential statements according to UICC stages.

The randomised QUASAR study on adjuvant chemotherapy (5-FU + folinic acid or levamisole) versus observation in patients with colorectal cancer and an unclear indication for chemotherapy (usually stage II) showed a significantly reduced recurrence rate (HR 0.68, 95% CI: 0.52-0.88) and an improvement of overall survival (HR 0.77, 95% CI: 0.54-1.00) [884] after a median follow-up of 5.5 years for the subgroup of patients with rectal cancer (n=948). However, 203 of these patients had also received preoperative radiotherapy and 264 patients had received additional postoperative radiotherapy. QoL surveys with regard to typical side effects of chemotherapy (diarrhoea, nausea, fatigue, anorexia, dry mouth) showed a significant deterioration in the therapy versus the observation arm for all categories, but were limited to the time of chemotherapy. Two randomised Japanese studies showed a significant advantage of postoperative chemotherapy (with tegafur-uracil for 1 year) versus observation with regard to disease-free and overall survival for patients with UICC stage III rectal cancer after TME and selective, extended lateral lymph node resection [1033] [1034].

The evidence for adjuvant chemotherapy in patients with rectal cancer (without neoadjuvant therapy and without an indication for postoperative radiochemotherapy) is thus considerably lower than for colon cancer. Even though no phase III studies involving the use of modern adjuvant combination chemotherapies as sole adjuvant therapy after primary resection of rectal cancer without neoadjuvant therapy are available, expert consensus recommends proceeding according to the indication criteria and schemes of colon cancer in this constellation.

### 8.2.2.2. Adjuvant Therapy of Rectal Cancer After Neoadjuvant Radiotherapy or Radiochemotherapy

| 8.33. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | A recommendation for or against adjuvant chemotherapy following neoadjuvant radiochemotherapy cannot be given on the basis of the available data for rectal cancer. | |
| Level of Evidence<br><br>**5** | Sources: [962, 963, 1035-1037] | |
| | Consensus | |

**Background**

Four randomised phase III studies on adjuvant chemotherapy versus observation after neoadjuvant radiotherapy or 5-fluorouracil-based radiochemotherapy have been carried out (see evidence table in the Guideline Report). None of these studies showed a significant improvement of disease-free survival or overall survival due to adjuvant 5-fluorouracil-based chemotherapy [962, 963, 1035-1037].

The four phase III studies differ considerably in the choice and method of administration of the neoadjuvant radio(chemo)therapy and adjuvant 5-fluorouracil-based therapy and partly use outdated and suboptimal 5-FU bolus regimens. Only the CHRONICLE study included the use of oxaliplatin in adjuvant chemotherapy, but was terminated prematurely owing to inadequate recruitment [1036]. The poor compliance regarding adjuvant chemotherapy in particular and the high rate of patients (27-28%) who were unable to undergo adjuvant therapy after surgery is striking in all studies. This is especially true for studies in which randomisation was carried out prior to neoadjuvant therapy and surgery [963] [1035]. Two of the four studies had to be terminated prematurely owing to inadequate recruitment and are thus underpowered for the primary endpoints [1036, 1037].

A meta-analysis based on individual patient data obtained in these four randomised studies also found no significant differences for the subgroup of patients with ypTNM stage II or III tumours after R0 resection (n=1,196) in disease-free survival (HR 0.91; 95% CI: 0.77-1.07, p=0.23) or overall survival (HR 0.97, 95% CI: 0.81-1.17, p=0.775) for patients with or without adjuvant chemotherapy. At best, subgroup analyses suggest a benefit of adjuvant chemotherapy for patients with rectal cancer in the upper third (here: 10-15 cm from the anocutaneous line) [1038]. However, patients with ypTNM stage 0-I following neoadjuvant therapy were excluded from this meta-analysis, since they were not included in two of the four individual studies. It is also problematic that patients with sole neoadjuvant, conventional fractionated radiotherapy were not excluded, even

though this therapy does not represent a neoadjuvant standard and the hazard ratios for disease-free and overall survival in this patient group are especially to the disadvantage of adjuvant chemotherapy, in other words, they adversely influence the results of the pooled analysis.

Further meta-analyses on the role of adjuvant chemotherapy following neoadjuvant radio(chemo)therapy including mainly non-randomised, retrospective series suggest a benefit of adjuvant chemotherapy for the subgroup of patients with downstaging [1039] or with ypN0 (less for patients with ypT0N0 or ypN+) [1040]. However, the evidence of these retrospective data and meta-analyses is to be considered low, and the risk for distortion high. The 10-year data of the initial observation of the randomised EORTC 22921 study certainly do not confirm that especially patients with downstaging (ypT0-2) after neoadjuvant therapy benefit from adjuvant chemotherapy [963].

A randomised phase II study from South Korea (ADORE) found a significant improvement in disease-free survival for patients with ypTNM stage II/III after neoadjuvant 5-fluorouracil-based radiochemotherapy for the adjuvant chemotherapy with FOLFOX versus a 5-FU/folinic acid bolus regimen [1041]. A subgroup analysis showed that this was particularly true for ypTNM stage III. The median age of the study patients was (only) 54 years; the compliance of adjuvant chemotherapy was exceptionally high and there was no sole observation arm. Two randomised phase III studies (CAO/ARO/AIO-04, PETACC-6) included oxaliplatin both in the neoadjuvant radiochemotherapy and in the adjuvant chemotherapy versus 5-fluorouracil monotherapies (see background text on recommendation 8_2). The CAO/ARO/AIO-04 study demonstrated a significant improvement of DFS in the oxaliplatin arm, but it remains unclear whether this is attributable to the neoadjuvant inclusion, adjuvant inclusion or both therapies [977]. The PETACC-6 study showed no benefit from including oxaliplatin [1009].

A clear recommendation for or against adjuvant chemotherapy following preoperative radio(chemo)therapy can thus not be given on the basis of the available phase III data and meta-analyses; furthermore, a subgroup that preferentially benefits from this approach can also not be identified. This also applies to the preoperative short-term radiotherapy followed by immediate surgery, since the phase III studies to establish preradiation with 5x5 Gy versus surgery alone did not generally include adjuvant chemotherapy, and the only phase III study of adjuvant chemotherapy following 5x5 Gy (SKRIPT) was underpowered and negative. However, owing to the partly suboptimal 5-FU bolus administration, the reduced compliance and the partly premature study terminations, these studies are methodologically limited.

One argument for adjuvant chemotherapy following neoadjuvant radiochemotherapy is that the large number of studies on the multimodal treatment of rectal cancer included adjuvant chemotherapy as a mandatory component, and that they thus represent well-established treatment modalities [960] [1001] [977]. If both the patient and the physician decide in favour of adjuvant chemotherapy after thoroughly discussing the advantages and disadvantages, the data suggest forgoing bolus 5-FU in adjuvant therapy in favour of capecitabine or infusional 5-FU (in this regard, compare the opinion of the AIO's working group for colon cancer/rectal cancer; http://www.aio-portal.de). Additional oxaliplatin administration post or perioperatively should be discussed and decided on a case-by-case basis by the tumour board and with the patient.

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

The following part of the S3 guideline contains updated recommendations from 2017 on the tumour therapy of metastatic colorectal cancer (mCRC), which particularly reflect study findings from 2003-2016. Primary resectable metastases will be discussed, as well as the special situation of secondary resectability in a therapy concept that is primarily palliative. The availability of chemotherapeutic and biological substances are taken into account in a list containing comments on possible combinations depending on the goal of therapy and tumour- and patient-specific criteria. Dividing patients into subgroups is meant to simplify decision making. The decision about which therapeutic approach to take when metastases are diagnosed starts with an assessment of the patient's overall health (see

Patients in good overall health can undergo intensive therapy, i.e. surgery or chemotherapy. In patients with resectable tumour manifestations and a favourable risk constellation, resection of metastases should be the primary objective (see 9.7.1). Patients for whom surgical intervention is not a possibility should receive the most effective systemic chemotherapy available. Maximum shrinkage of the tumour should be the primary goal of therapy. The choice of the chemotherapy regimen depends mainly on the molecular pathological tumour profile. For patients with RAS wild type tumours, the localisation of the primary tumour is another important factor for the decision.

The therapeutic strategy for the treatment of the metastatic disease should be determined in the context of interdisciplinary tumour boards. Patients must be thoroughly informed about the available therapeutic options based on their individual requirements and must be involved in the decision. Aside from tumour therapy, which is outlined in the following, securing adequate analgesic therapy and nutrition, need-based psychosocial and psycho-oncological care, as well as supportive therapy schemes are integral constituents of a palliative care concept (see specific topic guidelines at http://www.leitlinienprogramm-onkologie.de/leitlinien/ and http://www.awmf-leitlinien.de).

Palliative medicine is defined as a therapeutic approach to improve the quality of life of patients and their families who are confronted with problems associated with a life-threatening disease. This is done be preventing and relieving suffering through the early recognition, careful estimation and management of pain and other issues of a physical, psychosocial and spiritual dimension.

Regarding aspects of palliative care irrespective of the underlying diagnosis, reference is made to the S3 Guideline for Palliative Care of the Guideline Program in Oncology (http://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/). Additional sources, as of 04/2017: S3 Guideline on Clinical Nutrition in Oncology, AWMF registration number: 073/006; S3 Guideline on Supportive Care, AWMF registration number: 032/054OL: http://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/).

Concerning therapy goals of tumour therapy, great value is increasingly attached to the disease- and therapy-related quality of life. As an easily measurable parameter, this aspect is increasingly recorded as a secondary endpoint in clinical studies. The wish of patients to be informed about all relevant and available measures (tumour-specific, supportive, psychosocial, psycho-oncological therapy options) and support offers (e.g. cancer counselling offices, self-help groups) has to be met. In addition,

complementary/unconventional treatment methods should be openly discussed with the patient, also to avoid unfavourable interactions with other therapeutic agents.
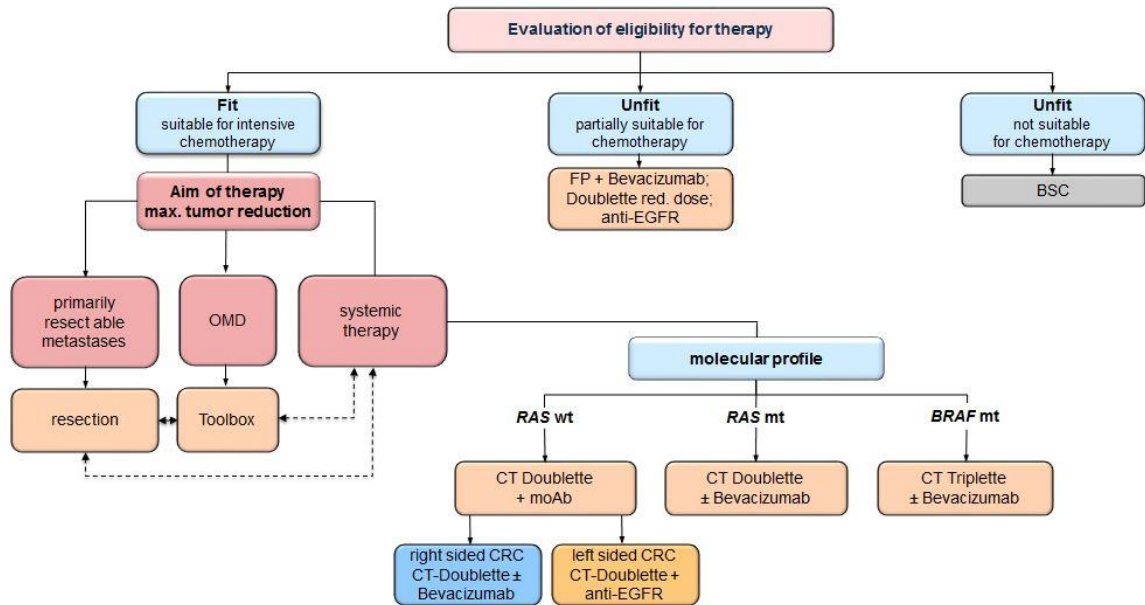


**Figure 3: Therapy algorithm in the treatment of mCRC**

## 9.1. Treatment Strategy

| 9.1. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | In principle, patients should have access to all treatment modalities, preferably at certified sites, during the course of their disease. | |
| | Consensus | |

| 9.2. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | If an indication for tumour 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. | |
| | Consensus | |

### Background

The therapeutic strategy is determined on the basis of characteristics related specifically to the patient and tumour. Presupposing the patient's willingness to undergo treatment (participatory decision making), the suitability for intensive or less intensive therapy is paramount with regard to patient-related characteristics (such as general health, comorbidities, life expectancy). In terms of tumour-related characteristics, the highest significance is given to the pathological and molecular biology of the tumour.

### Definition of Subgroups According to Clinical Situations/Therapy Goals:

| 9.3. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | To enable the choice of the optimal first-line therapy, a decision algorithm can be applied to assign the patients to defined treatment groups. Three decision-making levels can be distinguished:<br><br>- Overall health (tolerability of intensive therapy)<br>- Disease spread including localisation (therapeutic options are governed by the possibility of resectability or locoregional intervention)<br>- Molecular biology of the tumour (definition of the optimal targeted therapy) | |
| | Strong consensus | |

### Background

Owing to the changing molecular biology of the tumour during the course of the therapy and the resulting development of resistance, treatments administered in later therapy lines are markedly less effective and are therefore presumably unable to outweigh the possible effects of first-line therapy. In addition, there is a marked decrease in the number of treatable patients during the course of the therapy, as a result of which around 70% of initially treatable patients in second-line therapy and usually not more than 50% in third-line therapy are able to receive further treatment [1042, 1043]. Under first-line therapy, remission rates of 50-70% can be achieved with modern combination

therapies; in second-line therapy, remission rates drop to around 10-30 %, compared to less than 10% in third-line therapy.

### 9.1.1.    Categorisation According to Overall Health

The first decision level focuses on the patient. Presuming the patient is motivated to undergo treatment, this level looks at the *question of therapeutic tolerability*. Here, the patient's overall health and suitability for effective (intensive) therapy is at the foreground. This assessment is to be understood against the backdrop of the populations enrolled in the studies with a median age of 60-65 years and a predominantly good performance status (ECOG 0-1). The choice of the optimal treatment for the individual patient is thus made on the basis of the following categorisations:

1.    Not suitable for intensive therapy

2.    Suitable for intensive therapy

Additional details are provided in sections 9.6 and 9.7.

### 9.1.2.    Categorisation According to Disease Spread

The second level of decision making relates to the spread of the metastatic disease. It focuses on *local, locoregional or primarily systemic treatment approaches*. The following categorisations are therefore helpful when choosing the optimal treatment strategy:

1.    **Availability of a curative treatment option**
      a.    Resectable disease
      b.    Potentially resectable disease

2.    **Mostly palliative therapy concept**
      a.    Oligometastases
      b.    Presumably not/never resectable, disseminated disease

The criteria for categorisation are listed in 9.7.2.

### 9.1.3.    Categorisation According to the Molecular Biology of the Tumour

Sufficient knowledge of the molecular biology of the tumour provides the basis for an adequate therapy decision regarding the *optimal targeted therapy*.

Additional details are provided in section 9.8.

### 9.1.4.    Choice of Later Lines of Therapy

The choice of the optimal second-line therapy or later lines of therapy is governed by the molecular pathology of the tumour, the tumour localisation as well as the choice of, response to and toxicity of the previous therapy.

## 9.2.    Initial Molecular Biological Diagnostics Prior to Commencing Therapy

The primary goal consists, first, in the molecular pathological characterisation of the disease. This categorisation serves to assess the prognosis and to obtain predictive information regarding the choice of therapy. The molecular pathological examinations

of colorectal cancer essentially include an analysis of the mutation status of the RAS genes KRAS and NRAS (hotspot regions of exons 2, 3 and 4) and BRAF gene (hotspot region in exon 15), as well as an analysis of the microsatellite instability status (MSS, microsatellite stable; MSI-H, microsatellite instability high).

In patients in whom treatment is urgent (rapidly progressive or symptomatic disease), chemotherapy can be commenced and the most adequate targeted therapy can be implemented as soon as the results of the molecular biological testing are available.

## 9.2.1.  (ALL) RAS and BRAF Diagnostics Prior to First-Line Therapy

| 9.4. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | If possible, (All) RAS and BRAF mutations shall be determined prior to initiating first-line therapy. | |
| Level of Evidence<br><br>**1a** | Source: [1044] | |
| | Strong consensus | |

**Background**

Determining the status of RAS and BRAF mutations prior to initiating first-line therapy ensures that the patients receive the most effective therapy. The molecular pathological evaluation is thus an absolute prerequisite for treatment within the specified therapy algorithm.

### 9.2.1.1.  RAS Mutation

Around 50% of mCRC tumours are characterised by a KRAS or NRAS mutation [1045], [1046], [1044] [1047]. Up to 90% of the activating mutations in the K*RAS* gene are determined in codons 12 and 13. Around 70% of KRAS exon 2 mutations are found in codon 12, a further 30% in codon 13 [1048].

A retrospective analysis of the PRIME study showed that 17% of the tumours that had initially been classified as KRAS exon 2 wild type exhibited further RAS mutations in KRAS codons 61, 117 and 146 or in NRAS codons 12, 13 and 61. Like the KRAS exon 2 mutations, these other RAS mutations were associated with a resistance to panitumumab [1045]. The OPUS study also yielded similar results. Both studies suggest that the addition of an anti-EGFR antibody (panitumumab or cetuximab) to a FOLFOX chemotherapy regimen in patients with a RAS mutation is associated with a less favourable therapy outcome (PFS and OS) than chemotherapy alone [1045] [1049].

A post-hoc analysis of the CRYSTAL study identified 15% further RAS mutations in the population of KRAS exon 2 wild type tumours. This evaluation again showed that cetuximab was not effective against RAS-mutated tumours, but no negative impact on effectiveness parameters was observed here [1046].

The negative predictive value of the RAS mutation was confirmed for the first-line therapy in a meta-analysis of 9 studies [1044]. Compared to chemotherapy alone, the addition of an anti-EGFR antibody was not shown to improve PFS (HR 1.12, p=0.20) or OS

(HR 1.08, p=0.14). Similar data were also found for overall survival in the second-line therapy (OS: HR 0.93, p=0.482) [1050]. In patients with a KRAS mutation who had previously undergone intensive therapy, cetuximab did not provide a survival benefit compared to the best supportive care (BSC) (HR 1.01, p=0.97), while a highly significant prolongation of OS was observed in patients with KRAS wild type tumours (HR 0.55, p<0.001) [1051].

In summary, the RAS mutation can be considered a negative predictive marker with regard to the efficacy of an anti-EGFR therapy. Consequently, exclusion of a RAS mutation is essential prior to commencing an anti-EGFR therapy.

### 9.2.1.1.1.    Determination of the RAS Mutation Status

| 9.5. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | The RAS mutation status can be determined either in primary tumour tissue or in metastases. If the RAS mutation status cannot be determined in the tissue, consideration can be given to determining the RAS mutation status using circulating tumour DNA in blood. | |
| Level of Evidence<br><br>**3a** | Sources: [1052-1054] | |
| | Consensus | |

**Background**

As a general rule, a high concordance of the RAS mutation status in the primary tumour and in the metastatic tissue can be assumed. This applies especially for liver metastases (discordance rate of around 5-15%), but to a markedly lesser extent for lymph node metastases (discordance rate of 25%) [1052], [1053], [1054].

The RAS and BRAF mutation status can be determined as part of a **stepwise diagnostic process**. Here, the analysis of the BRAF gene is performed only after exclusion of a RAS mutation, since the mutual presence of RAS and BRAF mutations in the tumour is generally excluded. Alternative methods include, for example, diagnostic panel testing, which has the power to evaluate multiple mutations in one step.

The **localisation of the primary tumour** is of prognostic significance and – in addition to the RAS and BRAF mutation status – appears to be of predictive value [1055], [1056] [1057], [1058]. This information, especially in RAS wild type patients, should therefore be available prior to commencing treatment of metastatic CRC. Retrospective analysis of several large-scale studies on the first-line therapy of patients with RAS wild type tumours suggest that, in patients with a left-sided primary tumour, the addition of an anti-EGFR therapy to combination chemotherapy can lead to a marked improvement of overall survival compared to the latter alone or in combination with bevacizumab, while this is not the case for right-sided tumours. This is illustrated in more detail in section 9.8.2.

### 9.2.1.2.    BRAF Mutation
Activating mutations in the BRAF gene are reported in about 8-12% of patients with mCRC [1059], [1060]. Simultaneous mutations of RAS and BRAF genes are very rare (0.001%)

and are thus considered mutually exclusive [1061]. BRAF V600 mutations are the most common, and are associated with a very poor prognosis [1059].

BRAF V600 mutations occur more frequently with an MSI status than with an MSS status [1062]. Simultaneous BRAFV600 mutations and MSI are sporadic mismatch repair defects (dMMR). In contrast, BRAF V600 mutations are not observed in germ line mutations of MMR genes (Lynch syndrome) [1063].

Comparisons of the BRAF V600 mutation with the considerably less common BRAF mutations in codons 594 and 596 have shown that the BRAF V600 mutations are more commonly found in right-sided and primary mucinous carcinomas with peritoneal metastases. In contrast, the BRAF 594 and 596 mutations were more commonly associated with rectal and non-mucinous tumours without peritoneal metastases. The examined BRAF 594 and 596 tumours were all microsatellite stable and were also associated with considerably longer survival times (median 62.0 vs. 12.6 months; HR 0.36, p=0.002) [1064].

The clinical relevance of the BRAF mutation with regard to the optimal choice of targeted molecular biological therapy has not been fully elucidated (see also 9.8.4). Nevertheless, it is recommended to determine the BRAF V600 mutation at the time of the initial diagnosis of the metastatic disease. If a BRAF V600 mutation is diagnosed, intensified chemotherapy (e.g. with FOLFOXIRI + bevacizumab) can already be initiated early on owing to the poor prognosis. On the other hand, innovative treatment approaches for these patients in particular should be considered early on within the scope of clinical studies.

## 9.3. Pharmacogenetic Diagnostics Prior to First-Line Therapy

Several genetic tests that allow for a prediction of the toxicity of the drugs used in the treatment of mCRC are available. Nevertheless, the evidence confirming the benefit of these tests is still limited [1065]. Prospective validation studies are thus still pending.

### 9.3.1. UDP-glucuronosyltransferase

| 9.6. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>0 | The regular determination of UGT1A1 prior to palliative CTX with irinotecan is not recommended. It can, however, be determined, especially in case of Gilbert syndrome or other bilirubin conjugation disorders. | |
| Level of Evidence<br><br>3a | Sources: [1066] | |
| | Strong consensus | |

**Background**

The enzyme UDP-glucuronosyltransferase is responsible for the glucuronidation of SN-38, the active metabolite of irinotecan, to the inactive metabolite SN-38G. Benign unconjugated hyperbilirubinaemia (Gilbert's syndrome) is caused mainly by a variant in the UGT1A1 gene. More than 60 polymorphisms of the UGT1A21 gene have been

identified to date. UGT1A1*1 is the wild type allele, while *28, *93, *60, and *6 are among the most common polymorphic variants. The most common variant found in Caucasians is the UGT1A1*28 allele, which causes a reduction in gene expression of up to 70% and results in a marked increase in irinotecan toxicity.

The frequency of the *28 allele is 39% in Europeans, 16% in Asians and 43% in African patients. Around 10–20% Caucasians and African Americans are homozygous for *28, while this is the case for less than 5% of Asians [1067].

Increased rates of side effects, in particular neutropenia and diarrhoea, are observed in patients with a decreased metabolisation of SN-38 undergoing irinotecan therapy.

The currently available data are insufficient to support a general recommendation of pretherapeutic UGT1A1 genotyping ([1066]). In a meta-analysis of 12 clinical studies, UGT1A1*28 polymorphism was not identified as a reliable predictor of treatment effectiveness (response, PFS). When the UGT1A1*28 allele was present, no statistically significant result, but a trend towards a higher mortality risk was found in two models [1066].

In case of spontaneously increased serum bilirubin (especially with low conjugated bilirubin), Gilbert's syndrome may be present and, with this, an increased risk of irinotecan-associated side effects. According to the prescribing information for irinotecan, patients known to be homozygous for UGT1A1*28 should receive the typically indicated initial dose (taking into account the bilirubin value), but must be monitored for signs of haematological toxicity. In patients who show signs of haematological toxicity under the previous therapy, a reduced initial dose of irinotecan is to be considered.

## 9.3.2.  Dihydropyrimidine Dehydrogenase

| 9.7. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | Determining the DPD deficiency is a diagnostic option prior to fluoropyrimidine therapy. The regular evaluation of DPYD*2A polymorphism can be performed. | |
| Level of Evidence<br><br>**2b** | Sources: [1068, 1069] | |
| | Consensus | |

**Background**

Dihydropyrimidine dehydrogenase (DPD) is the key enzyme involved in the 5-FU metabolism. DPD inactivates around 80-90% of the administered 5-FU to 5,6-dihydrofluorouracil. The genetic polymorphism of the coding DPYD gene is the best described cause of DPD deficiency. Around 3-5% of Caucasians exhibit partial, and 0.2% exhibit complete DPD deficiency [1068]. Non-functional alleles include, among others, the variants DPYD*2A and DPYD*13, DPYD*9A and the SNP variant rs67376798.

With a frequency of 1-2%, DPYD*2A polymorphism is the most clinically relevant variant in the Western nations. In heterozygous carriers, a dose reduction of 5-FU is advised; in the much less common homozygous carriers, 5-FU is contraindicated owing to potentially life-threatening toxicity (neutropenia) [1069].

In the population analysis (n=2,038) of Deenen et al. [1068], testing of DPYD*2A polymorphism was shown to be cost-saving. However, when testing is focused solely on DPYD*2A, only 25% of all DPD-deficient patients are identified. Thus, a significant residual risk remains. Ultimately, the transferability of the study results to the German healthcare system must be considered.

# 9.4. Diagnostics Without an Immediate Relevance for First-Line Therapy

The determination of the microsatellite instability and of the HER2 amplification/ overexpression has no immediate relevance in first-line therapy. It can, however, become relevant for the course of treatment in later lines of therapy. Measuring these parameters can therefore be recommended.

## 9.4.1. Testing of Microsatellite Instability (MSI)

In mCRC, MSI testing is helpful, on the one hand, to establish an indication for human genetic counselling. On the other hand, it can be useful with regard to the treatment with immune checkpoint inhibitors when determining a strategy spanning various therapy lines.

While the guideline was being created, the MSI status was of no relevance yet for the choice of first-line therapy. However, data are available on pretreated patients which suggest a high efficacy of a treatment with the checkpoint inhibitor pembrolizumab in patients with microsatellite instability (MSI-H). However, in 82% (9/11) of the examined patients, a hereditary component was found (Lynch syndrome), so that the transferability of these findings to patients with a sporadic MMR defect still has to be demonstrated [1070].

**Background**

In patients exhibiting signs of familial colon cancer, the microsatellite analysis (through an analysis of the immunohistochemical expression of the DNA mismatch repair proteins MLH1, MSH2, MSH6 and PMS2 or microsatellite instability testing) and, where necessary, coupled with a methylation analysis of the MLH1 promoter/exon 1 area, or, if the latter is not available, by means of BRAF diagnostics (hereditary vs. sporadic) is imperative.

The selectivity of a BRAF mutation analysis to distinguish between spontaneous and hereditary colorectal cancer is around 50% [1071]; the selectivity of a methylation analysis is complete (~100%) [1072].

## 9.4.2. HER2/neu Amplification/Overexpression

At present, the relevance of HER2/neu amplification/overexpression for the choice of the first-line therapy has not been confirmed [1073]. However, initial data are available which suggest that HER2/neu amplification may be associated with resistance to anti-EGFR substances [1074], [1075]. In addition, the HERACLES study shows that patients with RAS-wt mCRC who were refractory to standard therapy (including cetuximab or panitumumab) and were found to have HER2 amplification/overexpression benefited from a treatment with trastuzumab plus lapatinib [1076] (see 9.8.6).

## 9.5.        Diagnostics During mCRC Therapy

No definite recommendations can be given on the diagnostics during therapy owing to lacking or controversial data.

### 9.5.1.       Therapy Monitoring during Therapy

Provided no anti-EGFR therapy was administered beforehand, repeated molecular testing of the RAS and BRAF mutation status (repeat biopsy) can be performed in patients with RAS/BRAF wild type mCRC during follow-on therapy. If the determination of the RAS or BRAF mutation status in the tissue is not possible, consideration can be given to determining the mutation status in the tumour DNA circulating in the blood [1077]. In individual cases, these analyses can deliver proof of an anti-EGFR resistance development on the basis of an expansion of RAS-mutated clones [1078], [1079], [1080]. They serve only to assess the course of the disease and do not replace the testing of the tumour tissue recommended at the start of the first-line therapy.

### 9.5.2.       Analyses to Establish an Indication for Targeted Therapies After Failure of First-Line Therapy

Proof of a microsatellite-unstable cancer (*MSI*) can support the process of establishing an indication for treatment with checkpoint inhibitors (see 9.4.1 Testing of Microsatellite Instability (MSI)). This approach has not yet been approved.

An indication for combination therapy with trastuzumab/lapatinib can likewise be considered for RAS wild type in the later course of treatment and after completing an anti-EGFR therapy in *HER2/neu* amplification/overexpression (see 9.4.2 HER2/neu Amplification/Overexpression). This approach has not yet been approved.

## 9.6.        Treatment of Patients Without an Indication for Intensified Therapy

According to the group categorisation outlined in point 9.1.1, two treatment groups can generally be distinguished:

(I)        Patients in whom intensive therapy is not suitable.
(II)       Patients in whom intensive therapy is suitable.

Patients in whom intensive therapy is not suitable include patients who do not qualify for primary surgery or intensive combination therapy on account of their overall health or who refuse intensified treatment owing to the associated side effects. The numerical age of the patients is not paramount in the assessment of the suitability for a therapy. The prevailing biological circumstances of the patient and tumour are decisive.

### 9.6.1. Primarily Resectable Disease in Patients With a Reduced Overall Condition

| 9.8. | Consensus-based Recommendation | 2017 |
|------|-------------------------------|------|
| **EC** | For primarily resectable metastases, the patient's ability to undergo surgery should be determined. If primary surgery is not an option, the possiblitiy of surgery / resectability should be verified in regular follow-ups (e.g. every 8 weeks). | |
| | Consensus | |

**Background**

For patients in whom intensive therapy is not a primary option, the possibility of administering bridging therapies with minimal side effects, e.g. therapy with a fluoropyrimidine, should be reviewed. Bevacizumab can be added to the therapy if rapid surgery is not the primary objective. For RAS wild type tumours, an anti-EGFR monotherapy is also an option.

As a general rule, the aim is to restore the patient's ability to undergo therapy and to achieve a status in which more intensive combination therapies are tolerated. It is important to regularly review and adapt the treatment concept based on the patient's overall health and motivation and on the tolerability and efficacy.

### 9.6.2. Primarily Unresectable Disease in Patients With a Reduced Overall Condition

| 9.9. | Consensus-based Recommendation | 2017 |
|------|-------------------------------|------|
| **EC** | Primarily palliative, symptomatic therapy has priority in patients with a reduced overall condition that precludes intensive chemotherapy. | |
| | Initial therapy with fluoropyrimidine + bevacizumab or dose-reduced doublet chemotherapy (+/- bevacizumab) can be performed. In case of RAS-WT tumours in the left hemicolon (from the left flexure) or in the rectum an anti-EGFR monotherapy can be performed. | |
| | Strong consensus | |

### 9.6.3. Poor Overall Condition Owing to the Cancer

| 9.10. | Consensus-based Recommendation | 2017 |
|-------|-------------------------------|------|
| **EC** | If the poor overall condition is mainly caused by the cancer, intensified therapy can also be performed in patients with a poor performance status (ECOG >1) after assessing all risks. | |
| | Consensus | |

## 9.7. Treatment of Patients With an Indication for Intensified Therapy

| 9.11. | Consensus-based Recommendation | 2017 |
|---|---|---|
| EC | In general, patients should have access to the most effective and still tolerable therapy. If there is a curative objective and no restrictions regarding the (potential) choice of therapy, the following parameters should in principle be considered in the decision-making process to determine the optimal multimodal approach:<br><br>a) surgical criteria (practicability of surgery, resectability including local ablative procedures),<br>b) prognostic criteria. | |
| | Strong consensus | |

**Background**

In patients with primarily resectable cancer, the fundamental question is to what extent primary resection (or intervention) can achieve a longer disease-free interval or, in the best case, healing. If unfavourable prognostic factors are present, neoadjuvant chemotherapy may be the better treatment option in individual cases.

In this regard, a distinction should be made between patients with synchronous and metachronous metastases [1081], [1082], [1083]. Compared to metachronous metastases, synchronous metastases are considered prognostically less favourable. In addition, synchronous metastases provide no information about the disease dynamics. The benefit of primary resection is thus less certain in this patient group than in patients with metachronous metastases. Additional prognostic factors that can be considered when making the decision include the number of metastatic lesions, the presence of extrahepatic metastases or the FONG score [1084].

### 9.7.1. Technically Primarily Resectable Disease

#### 9.7.1.1. Primarily Resectable Disease With an Oncologically Favourable Prognosis

| 9.12. | Consensus-based Recommendation | 2017 |
|---|---|---|
| EC | Primary resection of metastases shall be performed for resectable tumour manifestations and favourable prognostic criteria. | |
| | Consensus | |

#### 9.7.1.2. Evaluation of Resectability

| 9.13. | Consensus-based Recommendation | 2017 |
|---|---|---|
| EC | The evaluation shall be performed by a tumour board with the involvement of a surgeon with experience in the surgery of metastases. | |
| | Consensus | |

**Background**

The resectability of metastases should be assessed by an experienced organ surgeon (liver/lungs/peritoneum). The therapy concept as a whole and the integration of the possible resection into the therapy concept must be decided in the context of a multidisciplinary tumour board. To date, the criteria which characterise a surgeon as experienced in the surgical removal of metastases have not been clearly defined.

Regarding the surgical resectability of metastases, not only the size or number of metastases, but also the assessment of the combined consideration of clinical factors (overall health, localisation of metastases, size of the residual liver, disease-free interval, where applicable risk scores, etc.) is decisive. Risk scores, such as the score developed by Fong et al., can be helpful in the decision-making progress, but are not sufficient on their own [1084].

Following a resection of liver metastases, a 5-year survival between 25-35% can be achieved. Considerably fewer data are available on the resection of lung metastases. Nevertheless, a surgical procedure should be considered if an R0 resection status can be achieved [1052].

***Option of Seeking a Second Opinion***

It is very strongly recommended that a second opinion is sought, especially also concerning the surgical treatment of metastases. Where possible, second opinions should be given by certified centres with multidisciplinary tumour conferences.

### 9.7.1.3.    Primarily Resectable Disease With Unfavourable Prognostic Criteria

| 9.14. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | Primary systemic therapy can be performed for primarily resectable tumours and unfavourable prognostic criteria (e.g. brief disease-free interval or synchronous metastases). | |
| | Consensus | |

**Background**

Preoperative therapy can be used whenever the dynamics of the tumour are unclear, especially in the case of synchronous metastases, and a preoperative observation phase during chemotherapy is helpful to assess the speed and pattern of metastases formation.

### 9.7.1.4.    Optimal Timing of Resection

| 9.15. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | If disease stabilisation can be achieved by systemic therapy, resection shall be performed promptly (i.e. after 2-3 months). | |
| | Consensus | |

**Background**

For metachronous metastases, the disease dynamics can be assessed on the basis of the length of the disease-free survival (DFS). A longer DFS can be presumed to have a more favourable prognosis [1085]. In contrast, synchronous metastases are considered prognostically less favourable. Synchronous metastases are present if metastatic spread is already confirmed at the time of establishing the initial diagnosis of CRC. Primary chemotherapy can be recommended for a short DFS (<6 months) or in the presence of synchronous metastases. The evaluation of the disease dynamics and of the response to therapy are helpful in assessing the disease prognosis [1086].

### 9.7.1.5.   Approach for Very Small Metastases

| 9.16. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | Small metastases (≤1 cm) can be removed primarily, as they may otherwise disappear during initial chemotherapy and would no longer be identifiable by the surgeon intraoperatively. | |
| | Consensus | |

### 9.7.1.6.   Neoadjuvant Therapy of Resectable Liver Metastases

| 9.17. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation **B** | Neoadjuvant therapy of primarily resectable liver metastases should not be performed. | |
| Level of Evidence **2b** | Source: [1087] | |
| | Majority Agreement | |

**Background**

The clinical benefit of neoadjuvant/preoperative therapy has not been fully demonstrated for technically resectable metastases and favourable prognostic criteria. This has been studied in a systematic review [1087] with mostly retrospective, controlled observational studies; a randomised study [1088], [1089]; and several uncontrolled analyses. All in all, no influence on overall survival (OS) was shown. If there is no benefit, establishing an indication becomes obsolete, even if damage due to the preoperative therapy cannot be substantiated.

The EORTC-40983 study played a key role In the evaluation of the preoperative therapy. This study enrolled patients with mostly favourable risk factors (1-4 resectable liver metastases, 52% 1 liver metastasis, 26% 2 liver metastases, 65% metachronous metastases). For primarily resectable liver metastases, perioperative chemotherapy (6 cycles of FOLFOX4 both before and after surgery) was compared to surgery alone [1088]. Progression-free survival was the primary endpoint. The aim of achieving a prolongation of PFS with a hazard ratio of ≤0.71 by perioperative chemotherapy was just missed in the randomised patients (HR 0.79; 95% CI: 0.62-1.02; p=0.058). In addition, the analysis of the 5-year survival did not show a survival benefit. In the perioperative

chemotherapy arm, the 5-year survival rate was 51% (95% CI 45–58) compared to 48% (95% CI 40–55) in the group of patients who underwent primary surgery [1089]. One limitation was that the study had not been statistically designed (powered) to demonstrate a survival benefit.

The conclusions of the EPOC study apply to a patient population with more favourable prognostic criteria. Consequently, primary resection of metastases should be the primary goal in patients with a favourable prognosis (e.g. long disease-free interval for metachronous metastases) and technically feasible resectability (low number and good localisation of the metastases) (see also 9.7.1.1.). In patients with less favourable prognostic criteria, on the other hand, systemic therapy can be the primary approach (see 9.7.1.3.).

## 9.7.1.7.  Liver Resection After Chemotherapy

| 9.18. | Evidence-based Statement | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | Owing to insufficient evidence, the question of whether the segments in which metastases are no longer detectable also have to be resected in liver resection following chemotherapy can currently not be answered definitively. | |
| Level of Evidence<br><br>**4** | Sources: [1090-1098] | |
| | Consensus | |

### Background

The main concern in liver resection after chemotherapy is whether the segments in which metastases are no longer detectable also have to be resected. Only retrospective case series are available on this subject [1090], [1091], [1092], [1093], [1094], [1095], [1096], [1097], [1098]. The proportion of liver metastases that are no longer detectable on images taken during the course of chemotherapy varies between 6% and 24%.

Between 27% and 67% of the metastases that were no longer detectable during imaging were found intraoperatively either by macroscopy or ultrasound. The proportion of metastases with vital tumour cells in resected patients was 0% to 80%. Some of the patients received intra-arterial chemotherapy. The quality of the imaging procedures must also be considered. Regarding the detection of liver metastases, magnetic resonance imaging with liver-specific contrast agents as well as contrast-enhanced ultrasound offer the highest sensitivity [1099, 1100].

It is not entirely clear whether areas in which metastases are no longer detectable have to be resected. In any case, this constellation requires close monitoring. In the case series, the majority of patients received additive chemotherapy after resection of metastases (no statement on the optimal duration of therapy).

### 9.7.1.8. Adjuvant / Additive Therapy After Resection of Liver Metastases

| 9.19. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Adjuvant/additive chemotherapy should not be performed after resection of metastases. | |
| Level of Evidence<br><br>**2a** | Sources: [1101-1103] | |
| | Consensus | |

**Background**

The benefit of adjuvant/additive chemotherapy following R0 resection of metastases has not been established. Despite R0 resection of liver metastases, only around 30% of patients remain relapse-free in the long term. Regarding the question of the potential benefit of adjuvant therapy, a pooled analysis of two prospective, randomised studies as well as multiple retrospective analyses are available [1101], [1102], [1103], [1104], [1105], [1106], [1107], [1108], [1109], [1089]. The pooled analysis showed an improvement of the 5-year DFS (36.7% vs. 27.7%), which however just missed the significance level (p=0.058) ([1103]). Likewise, no significant improvement of the 5-year OS was achieved (52.8% vs. 39.6%) (p=0.095). In addition, the 5-FU bolus regimen that was used in both studies is presently no longer regarded as the standard. The benefit of adjuvant/additive chemotherapy administered according to current standards has not been established.

The retrospective analyses described an influence on DFS and partly on OS. However, due to a lack of randomisation, there is a considerable risk for an incorrect assessment, especially since the compared cohorts differed in terms of composition (e.g. sample size, age, extrahepatic metastases). In some studies, no impact on OS was found. Individual studies suggest a benefit in patients at higher risk of recurrence (e.g. according to the Memorial Sloan-Kettering Cancer Center Clinical Risk Score (MSKCC-CRS)). Overall, the amount of data available is unsatisfactory. A further meta-analysis included both perioperative and additive therapy, while a network meta-analysis compared various CTX regimens in particular; no conclusive statement on chemotherapy vs. no chemotherapy following R0 resection of liver metastases can therefore be made [1101], [1102].

### 9.7.2. Oligometastases

The term oligometastasis describes a limited spread of a potentially resectable or locally interventionally treatable metastasis formation, in which the spread is generally limited to e.g. 1-5 metastases and few organ systems (1-3 organs). Owing to the markedly poorer prognosis, metastases in lymph nodes, the brain or bones are not included in this categorisation.

No consensus on the definition and treatment of oligometastatic disease has been reached yet due to the lack of reliable data.

**Background**

A binding definition of oligometastasis is not available at the present time. In addition to the spread of metastasis, the concept also takes into account the possibility of local ablative or locoregional measures to treat the tumour in particular. Under favourable conditions, a curative treatment approach can also be considered in patients with oligometastases. This definition is based on the following assumptions:

a) The specific tumour biology appears to suggest a course in which the oligometastatic process shows a limited metastasis formation, at least for a relevant interval.

b) Surgical, local ablative or locoregional measures to treat the tumour can be administered in addition to systemic therapy.

c) The control of the localisation of the metastases is relevant for the prognosis, and the use of local ablative or resecting procedures may enable an interruption of the systemic therapy.

Where possible and reasonable, surgical resection should be the primary approach for locally treatable metastases. *Local ablative* procedures include: thermal ablation (RFA, MWA), radiotherapy (e.g. SBRT, brachytherapy) or electroporation (see section 9.13 Local Ablative Procedures).

*Locoregional* procedures include intra-arterial chemotherapy of the liver (HAI) or selective intra-arterial radiotherapy (SIRT) as well as cytoreduction with hyperthermal chemotherapy (HIPEC) (see also 9.14.1-9.14.3). Ultimately, a combination of surgical and ablative procedures is also possible. The indication for local ablative procedures should be established in multidisciplinary tumour conferences (see 9.14 Locoregional Procedures).

### 9.7.3. Primarily Unresectable Metastases

| 9.20. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | For primarily unresectable tumours, systemic tumour therapy shall be performed first. Depending on the tumour and patient characteristics, the most effective available therapy shall be used at the start of treatment. | |
| | Consensus | |

**Background**

In this context, maximum tumour shrinkage is the primary goal of therapy. This strategy is consistently pursued for patients with rapidly progressive or symptomatic, but also asymptomatic metastases. The best overall survival is achieved with a multimodal, possibly sequential, therapy concept. Therefore, the most effective systemic combination therapy available should be used primarily, taking into account the patient's preference and factors unrelated to the tumour (such as comorbidity) (intensified therapy). The possibility of secondary resection and/or the practicability of local ablative measures should be reviewed by multidisciplinary tumour conferences in regular follow-ups (e.g. every 2-3 months).

According to these guidelines, the primary tumour can first be disregarded in patients with a primary indication for systemic therapy. Exceptions may include symptomatic, stenotic tumour growth and/or relevant bleeding.

## 9.8. Selection of Systemic Therapy Depending on the Molecular Pathological Subgroup and the Tumour Localisation

The fundamental principle in the optimal treatment of mCRC is to select the most effective primary therapy based on factors related to the patient (such as motivation and toxicity profile) and unrelated to the tumour (such as the patient's overall health, comorbidity, etc.). Depending on the currently available findings, this decision can be made on the basis of the localisation and molecular pathology of the primary tumour.

### 9.8.1. RAS Wild Type

| 9.21. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Patients found to have a RAS wild type (RAS-wt) in an extended RAS analysis (KRAS and NRAS, exons 2-4) and with a left-sided primary tumour (colon cancer) shall preferably be treated with doublet chemotherapy plus anti-EGFR therapy in the first-line therapy of the metastatic disease. | |
| Level of Evidence<br><br>**1a** | Sources: [1110] | |
| | Consensus | |

**Background**

A direct comparison of anti-EGFR antibodies (cetuximab and panitumumab) with the anti-VEGF antibody bevacizumab was carried out in three randomised studies (FIRE-3, PEAK, CALGB 80405) in the first-line therapy of mCRC [1047], [1111], [1112]. The FIRE-3 study (phase III) compared FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab and evaluated ORR as the primary endpoint. The evaluation of the RAS wild type (wt) population showed no significant difference in ORR and PFS. In contrast, a marked survival benefit was observed in the cetuximab arm (HR 0.70, p=0.0059) [1047].

The PEAK study was conducted as a randomised phase II study and compared FOLFOX plus panitumumab to FOLFOX plus bevacizumab. Here, PFS was evaluated as the primary target criterion. In the subgroup of patients with RAS-wt tumours, the panitumumab arm was found to be superior with regard to PFS (HR 0.65, p=0.029) and OS (41.3 vs. 28.9 months). Given the low event rate (<50%), no statistical significance was achieved with regard to OS (HR 0.63, 0.058) [1111].

The CALGB/SWOG-80405 study (phase III) carried out a randomised comparison of (any) chemotherapy plus cetuximab versus chemotherapy plus bevacizumab. The choice of chemotherapy regimen, FOLFOX (76%) or FOLFIRI (24%), was left up to the participating centres. This study reported a significantly higher ORR in the cetuximab arm (69% vs. 54%, p<0.01). In contrast, no significant difference between the treatment arms was established with regard to PFS and OS [1112].

A meta-analysis based on the published results of the three comparative studies corroborated the superiority of the anti-EGFR treatment regarding ORR (odds ratio 1.46, p=0.004) and overall survival (HR 0.77, p=0.016). The PFS (HR 0.92, p=0.5) between the treatment arms was similar [1110].

As a therapeutic alternative associated with more side effects, treatment with the chemotherapy triplet with FOLFOXIRI (possibly + bevacizumab) can also be considered in these patients. The TRIBE study compared FOLFIRI plus bevacizumab to FOLFOXIRI plus bevacizumab in unselected patients. Compared to doublet chemotherapy, the triplet therapy was found to be superior with regard to ORR (65% vs. 54%; OR 1.59, p=0.013), PFS (12.3 vs. 9.7 months; HR 0.77, p=0.006) and OS (29.8 vs. 25.8 months; HR 0.80, p=0.03) [1113]. As anticipated, the treatment with FOLFOXIRI plus bevacizumab was accompanied by a significant increase in grade 3-4 side effects such as neutropenia, diarrhoea and peripheral neuropathy compared to the administration of FOLFIRI plus bevacizumab [1114].

While phase II studies suggest a high efficacy of triplet plus anti-EGFR therapy, there are no corresponding results available from phase III studies.

## 9.8.2.   Relevance of Tumour Localisation in the Treatment of RAS Wild Type Tumours

Retrospective analyses of clinical studies suggest that the localisation of the primary tumour is not only of relevance for the prognosis, but is also an important determinant in the therapeutic efficacy and should therefore be considered when making therapy decisions [1115], [1116], [1058]. Preclinical analyses support the various patterns of gene mutation and gene expression in right- and left-sided tumours [1117]. [1118]. The majority of analyses describe the splenic flexure as the dividing line [1057], [1055]. In principle, the line dividing right- and left-sided tumours would be drawn between the proximal two thirds and the distal third of the transverse colon. However, in light of the retrospective evaluations, the splenic flexure was used as the dividing line in the majority of analyses for pragmatic reasons [1057], [1055]. Correspondingly, the caecum, ascending colon and transverse colon are considered part of the right hemicolon, while tumours of the descending colon, sigmoid colon and rectum are considered left-sided. Right-sided tumours are less common than left-sided tumours (30% versus 70%), and more female and elderly patients are affected. They are characterised by a higher tumour mutation burden and a higher immunogenicity. From a molecular biological perspective, right-sided tumours exhibit a higher rate of CIMP (CPG-island methylation phenotype), BRAF mutations and microsatellite instability [1115].

The currently available data suggest that left-sided tumours largely benefit from a treatment with anti-EGFR substances. In first-line therapy, especially doublet chemotherapy regimens have been assessed. In combination with anti-EGFR substances, these regimens were shown to be markedly more effective in left-sided tumour in terms of ORR, PFS and OS than comparable combinations with bevacizumab or without monoclonal antibodies [1055], [1056].

Right-sided tumours, on the other hand, are characterised by a less favourable prognosis with a poorer response to standard therapies and anti-EGFR antibodies. In two studies (FIRE-3, CALGB 80405), the combination of doublet chemotherapy with the anti-EGFR antibody cetuximab was less effective than the combination of the same chemotherapy with bevacizumab [1055], [1057]. Due to the low sample size, the significance level was not achieved in the subgroup analysis.

In contrast to EGFR antibodies, there are no signs to suggest an efficacy of bevacizumab depending on the tumour localisation. In the NO16966 and AVF2107g studies, the addition of bevacizumab achieved longer survival periods than chemotherapy alone for right-sided tumours. The interaction tests for tumour localisation were negative [1058].

Based on the currently available data, doublet or triplet (+/- Bev) chemotherapy is recommended for right-sided primary tumours in the first-line therapy of the metastatic disease.

### 9.8.3.        RAS Mutation: Triplet / Doublet

| 9.22. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Doublet chemotherapy should be used primarily in patients with a RAS mutation. Whether triplet therapy is better than doublet therapy or whether bevacizumab should be used has not been confirmed. | |
| Level of Evidence<br><br>**3a** | Sources: [1113] | |
| | Consensus | |

**Background**

Anti-EGFR antibodies did not prove effective in patients with a RAS mutation and should therefore not be used [1045], [1046], [1049]. Prospective studies assessing the effectiveness of anti-VEGF substances in the first-line therapy of RAS-mutated mutation tumours are not available. A retrospective subgroup analysis of the FIRE-3 study showed comparable survival periods in patients with a KRAS mutation who received FOLFIRI plus bevacizumab or FOLFIRI plus cetuximab [1119]. In contrast, a retrospective analysis of the TML study regarding negative interaction tests suggests that the effectiveness of the treatment with bevacizumab in the second line of therapy was independent of the KRAS status [1120].

A subgroup analysis of the TRIBE study compared the effectiveness of triplet chemotherapy (FOLFOXIRI plus bevacizumab) with that of doublet chemotherapy (FOLFIRI plus bevacizumab) in patients with RAS-mutated tumours [1113]. Here, a higher effectiveness was reported for the triplet therapy with regard to overall survival (HR 0.88; 95% CI: 0.65-1.18), PFS (HR 0.78; 95% CI: 0.60-1.02) and the response rate (OR 1.55; 95% CI: 0.91-2.62). However, the significance level was not reached in any of the effectiveness measures. Consequently, a clear recommendation for the use of triplet chemotherapy for RAS-mutated tumours cannot be given.

## 9.8.4.    BRAF Mutation

| 9.23. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Patients with a BRAF mutation should primarily receive the most effective chemotherapy, e.g. triplet therapy, or be enrolled in a clinical study. | |
| Level of Evidence<br><br>**4** | Sources: [1064, 1121] | |
| | Consensus | |

**Background**

A BRAF V600 mutation is observed in 8-12% of mCRC patients. Women are more commonly affected, and the age of onset is usually higher. In around two thirds of affected patients, the tumour is located in the right hemicolon; increased mucinous subtypes are observed histologically.

A higher rate of lymph node metastases and peritoneal cancer is reported clinically. From a molecular pathological perspective, microsatellite instability and a "methylator phenotype" are common [1122], [1059]. The prognosis of patients with a BRAF V600 mutation is exceedingly poor; numerous studies have reported median PFS intervals of less than 6 months and median survival periods of less than one year [1061].

Triplet chemotherapy with the FOLFOXIRI regimen is currently recommended for patients with a BRAF V600 mutation. However, this recommendation is based on a subgroup analysis of only 28 patients with a BRAF mutation treated within the scope of the TRIBE study. Under treatment with FOLFOXIRI plus bevacizumab (n=16) versus FOLFIRI plus bevacizumab (n=12), considerably more favourable outcome data were observed in these patients: markedly prolonged OS (19.0 vs. 10.7 months; HR 0.54), longer PFS (7.5 vs. 5.5 months; HR 0.57) and a higher remission rate (56% vs. 42%; OR 1.87) [1064]. On the one hand, the results of this analysis can only be regarded as a basis for generating hypotheses owing to the low sample size; on the other hand, further analyses of the same working group have been published which support the effectiveness of FOLFOXIRI plus bevacizumab in patients with a BRAF mutation [1121].

Whether anti-EGFR substances are effective against BRAF mutations is the subject of controversial discussions. In this regard, two meta-analyses came to a different evaluation: In their analysis, Pietrantonio et al. found no significant increase in PFS (HR 0.88, p=0.33) or OS (HR 0.91, p=0.63) with the addition of anti-EGFR antibodies [1061]. Rowland et al., on the other hand, argue that the evidence is insufficient to definitively rule out that anti-EGFR antibodies have a different treatment effect in BRAF mutations than in BRAF wild type tumours [1123].

Ultimately, the available analyses are characterised by small sample sizes which do not allow for drawing definitive conclusions either in the individual nor in the joint meta-analysis.

The question of the significance of bevacizumab-based therapy versus cetuximab-based therapy was also addressed in a subgroup analysis of the FIRE-3 study. In 48 evaluable

patients with RAS-wt/BRAF-mut mCRC, OS was short and comparable in both therapy arms (median 12.3 vs. 13.7 months), regardless of whether cetuximab or bevacizumab had been given in combination with FOLFIRI [1124]. This analysis led to the hypothesis that, equally, neither an anti-EGFR nor an anti-VGEF strategy has the ability to improve the therapeutic outcome.

Owing to the poor prognosis of BRAF-mutated tumours, individual (as yet unauthorised) therapeutic approaches, for example with a BRAF inhibitor, MEK inhibitor and anti-EGFR antibody or, where possible, within the scope of a clinical study, can be considered for the second-line therapy [1125].

## 9.8.5.     MSI

Immune checkpoint inhibitors have been shown to be active in first clinical investigations in pretreated mCRC patients with microsatellite instability (MSI). In view of the currently limited data, however, a first-line therapy according to the RAS mutation status is first recommended in patients with MSI. In later therapy lines, the possibility of treatment with checkpoint inhibitors should be assessed.

**Background**

Mutations in the mismatch repair genes (MLH1, MSH2, MSH6 and PMS2) lead to faulty DNA replication, which in turn manifests as microsatellite instability (MSI) in variable lengths of the microsatellite DNA. Compared to proficient mismatch repair (MMRp), defective mismatch repair (MMRd) is responsible for a 10- to 100-fold increase in the mutation rate ([1071]). This causes increased immunogenicity and ultimately leads to the markedly increased lymphocytic infiltration of MSI tumours ([1126]). Upregulation of immune checkpoints, such as the programmed death (PD-1) pathway, has been shown especially for MSI tumours in the sense of an immune escape mechanism.

In colorectal cancer, MMRd occurs both within the scope of germ line mutations in one of the four mismatch repair genes (hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) as well as by somatic mutations or epigenetic silencing [1070].

First clinical data confirm the hypothesis that MSI tumours – in contrast to MSS tumours – respond well to a PD-1 blockade. A phase II study assessed 32 patients who had received at least 2 prior chemotherapy regimens [1070]. Of these, 11 patients were classified as MMRd and 21 as MMRp. Treated with the PD-1 inhibitor pembrolizumab, MMRd patients showed a significantly higher ORR (40% vs. 0%) and SD rate (50% vs. 11%) as well as a highly significant prolongation of PFS and OS compared to MMRp patients (medians were not achieved).

Immunological checkpoint inhibitors were not yet authorised for the treatment of mCRC at the time of creating this guideline.

## 9.8.6.     HER-2 Amplification

If HER-2 amplification is present in metastatic CRC, treatment according to the RAS and BRAF mutation status is first recommended. In refractory tumours, targeted molecular biological treatment based on the HER-2 status can then be considered. The effectiveness of a combination of trastuzumab and lapatinib in refractory cancer (KRAS wild type) was demonstrated in a multicentric proof-of-concept study (HERACLES). The combination of trastuzumab and lapatinib was not authorised for the treatment of colorectal cancer at the time of creating this guideline.

**Background**

Preclinical studies have shown that amplification of the HER-2 oncogene may be associated with resistance to anti-EGFR substances such as cetuximab [1075]. In addition, xenograft models have shown that a combination therapy of trastuzumab and lapatinib is effective in HER-2 amplification or overexpression, while no response to the individual substances was reported.

The HERACLES study was conducted as an open-label, multicentre, phase II proof-of-concept study [1076]. mCRC patients who were refractory to standard chemotherapy (including cetuximab or panitumumab) were enrolled in the study. Of 914 patients with KRAS exon 2 wild type, 48 patients (5%) with HER2-positive tumours were identified. The tumours were classified as HER2-positive either in case of an IHC score of 3+ or an IHC score of 2+ with a positive FISH test. For 27 patients enrolled in the study, the ORR was 30% (95% CI: 14–50), the SD rate 44% (95% CI: 25–63), the median PFS 21 weeks (95% CI: 16-32) and the median OS was 46 weeks (95% CI: 33-68).

## 9.9. Performance of First-Line Chemotherapy

The collective data from all currently available studies on the first-line therapy of metastatic colorectal cancer suggest that more effective and thus frequently more intensive treatment regimens are associated with a survival benefit (Table 11 - Table 17).

Consequently, all patients should be given access to the most effective first-line therapy. The strategy of sequentially offering all drugs that come into question during the course of the treatment was supported by older studies that did not involve the use of monoclonal antibodies (FOCUS, CAIRO); however, since these studies were performed in the "pre-antibody era", the survival periods were also markedly below 20 months owing to the limited therapeutic options. The studies are thus of limited value for the current therapy management.

### 9.9.1. First-Line Chemotherapy In a Good Overall Condition

| 9.24. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | For first-line chemotherapy, and under the condition of good overall health and high motivation, a fluoropyrimidine-based combination regimen with infusional 5-fluorouracil, such as FOLFIRI, FOLFOX or FOLFOXIRI, or with the oral fluoropyrimidine capecitabine (mainly with oxaliplatin, CAPOX) should be used primarily. | |
| Level of Evidence<br><br>**1a** | Sources: [1127], [1128] | |
| | Consensus | |

**Background**

A good overall condition of the patient is a prerequisite for intensive combination chemotherapy. Since the option of a less effective fluoropyrimidine monotherapy plus bevacizumab with markedly fewer side effects is theoretically available, it is important

to involve the patients in the discussion and to define their motivation regarding a potential prolongation of survival [1127], [1128].

| 9.25. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | The combination with an effective substance (anti-EGFR or anti-VEGF) should be based primarily on the main therapeutic goals, the molecular biological tumour characteristics and the tumour localisation (see 9.8.2). Therapeutic decisions should be based first and foremost on the treatment that can achieve the longest overall survival with acceptable tolerability. | |
| | Consensus | |

## 9.9.2. First-Line Chemotherapy In a Reduced Overall Condition From ECOG 2

| 9.26. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | In patients with a reduced overall condition, chemotherapy with fluoropyrimidine monotherapies (5-fluorouracil/folinic acid or capecitabine) usually in cmbination with bevacizumab can be used. | |
| | Consensus | |

**Background**

The AVEX study assessed the effectiveness of a combination of capecitabine plus bevacizumab in elderly patients (≥70 years) and compared it with capecitabine monotherapy within the scope of a phase III design [1128]. Mainly patients with a performance status ECOG 0 (46%) and ECOG 1 (45%) were enrolled. Patients with ECOG ≥2 accounted for less than 10% of the patient population. PFS was assessed as the primary endpoint. Treated with capecitabine plus bevacizumab, a significant prolongation of PFS (9.1 vs. 5.1 months; HR 0.53, p<0.0001; primary study endpoint) and an increase in ORR (19% vs. 10%; p=0.04) was achieved. Overall survival (secondary endpoint) was 16.8 months in the control arm and 20.7 months in the group treated with capecitabine and bevacizumab ((HR 0.79, 95% CI: 0.57–1.09; p=0.18); this difference was not significant. The tolerability of the treatment can generally be rated as good. The frequency of serious adverse events (SAEs) was 31% in the group receiving capecitabine monotherapy and 30% in the group receiving the combination of capecitabine and bevacizumab. Quality of life analyses were not carried out [1128].

These data are supported by a randomised phase II study conducted in patients for whom first-line therapy with irinotecan was not an option [1127]. The proportion of patients with ECOG 2 was again below 10% in this study. In this population, bevacizumab plus 5-FU/LV was compared to 5-FU/LV therapy alone. The addition of bevacizumab to 5-FU/LV led to a significant increase of PFS (9.2 vs. 5.5 months; HR 0.50, p=0.0002) and to a non-significant increase of OS (16.6 vs. 12.9 months; HR 0.79, p=0.16) and ORR (26.0% vs. 15.2%, p=0.055). The evaluation of the FACT-C score showed no negative effect of bevacizumab on the quality of life (QOL). The median time to worsening of the quality of life was 3.2 months in the bevacizumab arm and 2.3 months in the placebo arm (HR 0.66; p=0.016).

In summary, these study results suggest that first-line chemotherapy with fluoropyrimidine and bevacizumab is effective in elderly patients and in patients unsuitable for initial irinotecan-based therapy, and is thus a expendient therapeutic option for this patient population.

## 9.9.3.          FOLFOXIRI in First-Line Therapy

| 9.27. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | FOLFOXIRI ranks among the most effective chemotherapy regimens, but should only be used in patients with a good overall condition (ECOG performance status 0-1) owing to its increased risk of side effects. | |
| Level of Evidence<br><br>**1a** | Sources: [1113, 1114, 1129-1132] | |
| | Consensus | |

**Background**

A "meta"-analysis of two prospective, randomised studies, as well as two additional prospective, randomised studies are available [1129], [1130], [1131], [1114], [1113], [1132]. The meta-analysis compared FOLFOXIRI to FOLFIRI; the other two studies compared FOLFOXIRI + bevacizumab to FOLFIRI + bevacizumab. The data consistently show a higher response rate, prolonged PFS and OS, and in the studies that assessed this, a higher secondary R0 resection rate of liver metastases. The rate of grade 3-4 side effects was significantly higher in the group of patients treated with FOLFOXIRI plus bevacizumab than in the group treated with FOLFIRI plus bevacizumab. The most common side effects were neutropenia (50% vs. 20.5%, p<0.001), diarrhoea (18.8 vs. 10.6, p=0.01) and peripheral neuropathy (5.2 vs. 0%, p<0,001).

**Table 11: Randomised Studies on First-Line Therapy With FOLFOXIRI In Unselected Patients**

| Study | Regimen | N patients | ORR (%) | OR (p-value) | PFS (Mo) | HR PFS (p-value) | OS (Mo) | HR OS (p-value) |
|---|---|---|---|---|---|---|---|---|
| Falcone [1130] | FOLFOXIRI | 122 | 66* | na | 9.8 | 0.63 | 22.6 | 0.70 |
| | FOLFIRI | 122 | 41* | (0.0002) | 6.9 | (0.0006) | 16.7 | (0.032) |
| Souglakos [1129] | FOLFOXIRI | 137 | 43 | na | 8.4# | na | 21.5 | |
| | FOLFIRI | 146 | 33.6 | (0.168) | 6.9# | (0.17) | 19.5 | (0.337) |
| Loupakis [1114] | FOLFOXIRI + Bev | 252 | 65.1 | 1.64 | 12.1 | 0.75 | 29.8§ | 0.80§ |
| Cremolini [1113] | FOLFIRI + Bev | 256 | 53.1 | (0.006) | 9.7 | (0.003) | 25.8§ | (0.03)§ |

Key: *intention to treat analysis; #median time to progression; na, not available; §Cremolini et al. 2015

### 9.9.4. Combination of Chemotherapy With Anti-EGFR Substances

| 9.28. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | The addition of anti-EGFR antibodies (cetuximab or panitumumab) to chemotherapy significantly increases the effectiveness in relation to ORR, PFS and OS. Anti-EGFR antibodies may only be given if an all-RAS wild type in the tumour is confirmed. | |
| Level of Evidence<br><br>**1a** | Meta-analysis: see Guideline Report<br><br>Primary studies: [1041][1045][1040][1129][1056][1130][1131] | |
| | Consensus | |

**Background**

Monoclonal anti-EGFR antibodies such as cetuximab or panitumumab are only effective in patients with RAS wild type tumours (Table 12).

**Table 12: Randomised Studies on First-Line Therapy With anti-EGFR Substances in RAS-wt Patients**

| Study | Regimen | N patients | ORR (%) | OR (p-value) | PFS (Mo) | HR PFS (p-value) | OS (Mo) | HR OS (p-value) |
|---|---|---|---|---|---|---|---|---|
| CRYSTAL [1046] | FOLFIRI + Cet | 178 | 66.3 | 3.11 | 11.4 | 0.56 | 28.4 | 0.69 |
| | FOLFIRI | 189 | 38.6 | (<0.001) | 8.4 | (<0.001) | 20.2 | (0.0024) |
| OPUS [1049] | FOLFOX + Cet | 38 | 58 | 3.33 | 12 | 0.53 | 198 | 0.94 |
| | FOLFOX | 49 | 29 | (0.0084) | 5.8 | (0.0615) | 17.8 | (0.80) |
| PRIME [1045] | FOLFOX + Pani | 259 | 60 | NR | 10.1 | 0.72 | 26.0 | 0.78 |
| | FOLFOX | 253 | 47 | (0.003) | 7.9 | (0.004) | 20.2 | (0.04) |
| COIN# [1133] | FU/LV or Cape + Ox | 367 | 57 | | 8.6 | 0.96 | 17.9 | 1.04 |
| | FU/LV or Cape* + Ox + Cet | 362 | 64 | (0.049) | 8.6 | (0.60) | 17.0 | (0.67) |
| NORDIC# [1060] | FLOX | 97 | 47 | 0.96 | 8.7 | 1.07 | 22.0 | 1.14 |
| | FLOX + Cet | 97 | 46 | (0.89) | 7.9 | (0.66) | 20.1 | (0.48) |
| FIRE-3 [1134] | FOLFIRI + Cet | 199 | 65.3 | 1.33 | 10.3 | 0.97 | 33.1 | 0.697 |
| | FOLFIRI + Bev | 201 | 58.7 | (0.18) | 10.2 | (0.77) | 25.0 | (0.0059) |
| GALGB 80405 [1135] | FOLFOX/ FOLFIRI + Cet | 270 | 68.6 | 1.75 | 11.4 | 1.1 | 32.0 | 0.9 |
| | FOLFOX/ FOLFIRI + Bev | 256 | 53.8 | (<0.01) | 11.3 | (0.31) | 31.2 | (0.40) |
| PEAK [1111] | FOLFOX + Pani | 88 | 63.6 | NR | 13.0 | 0.65 | 41.3 | 0.63 |
| | FOLFOX + Bev | 82 | 60.5 | | 9.5 | (0.029) | 28.9 | 0.058 |

Key: *67% Cape-based therapy; #patients with KRAS wild-type tumours; Cet, Cetuximab; Pani, Panitumumab; Bev, Bevacizumab; Cape, Capecitabine; OR, Odds Ratio; ORR, objective response rate; PFS, progression-free survival; OS, overall survival;

In a randomised phase III study (CRYSTAL) with RAS-wt patients, the addition of cetuximab to FOLFIRI chemotherapy led to a prolongation of median survival from 20.2 to 28.4 months (HR 0.69, p=0.0024) [1046]. Comparable data were described in the PRIME study. In this randomised phase III study, the addition of panitumumab to the FOLFOX regimen resulted in a prolongation of OS from 20.2 to 26.0 months (HR 0.78, p=0.04).

In a meta-analytical evaluation (see Guideline Report) of the available studies, the addition of anti-EGFR antibodies to combination therapies in patients with KRAS wild type tumours resulted in a significant prolongation of PFS (HR 0.83, p=0.0001) and OS (HR 0.89, p=0.02).

In view of the study results, it was retrospectively postulated that anti-EGFR substances fail to achieve adequate efficacy in combination with a 5-FU bolus regimen or oral fluoropyrimidines. If one takes these studies (COIN and NORDIC) out of the meta-analytical evaluation, the therapeutic effects due to the addition of anti-EGFR antibodies are considerably stronger for PFS (HR 0.72, p<0.00001) and OS (HR 0.79, p=0.0003).

Compared to FOLFOX monotherapy, the use of panitumumab in the PRIME study in combination with FOLFOX led to a marked increase in grade 3-4 side effects, such as skin toxicity (36% vs. 2%), diarrhoea (18% vs. 9%), fatigue (9% vs. 3%) or hypomagnesaemia (6% vs. <1%). The rate of grade 3 infusion reactions after administration of the human IgG2 antibody panitumumab was 0.3% [1136]. Similar side effects were also reported in the CRYSTAL study. Compared to the administration of FOLFIRI alone, the combination of FOLFIRI plus cetuximab led to an increase in grade 3-4 side effects, such as acneiform exanthema (16.2% vs. 0%) or diarrhoea (15.7% vs. 10.5%). The rate of grade 3-4 infusion reactions after administration of the chimeric IgG1 antibody cetuximab was 2.5% [940].

Regarding the use of anti-EGFR substances depending on the localisation of the primary tumour, see 9.8.2.

**Table 13: Summary of Meta-Analyses on Anti-EGFR Substances - OS**

| OS (KRAS wt) | Studies | HR | (95% CI) | p |
|---|---|---|---|---|
| CT +/- anti EGFR all | Douillard, Maughan, Tveit, van Cutsem, Ye<br><br>[1136], [1133], [1060], [1137], [1138] | 0.89 | 0.80-0.98 | 0.02 |
| CT +/- anti-EGFR (no bolus or oral regimen)* | Douillard, van Cutsem, Ye<br><br>[1136], [1137], [1138] | 0.79 | 0.69-0.90 | 0.0003 |
| * without Tveit (bolus 5-FU), without Maughan (oral fluoropyrimidine) | | | | |

**Table 14: Summary of Meta-Analyses on Anti-EGFR Substances - PFS**

| PFS (KRAS wt) | Studies | HR | (95% CI) | p |
|---|---|---|---|---|
| CT +/- anti EGFR all | Bokemeyer, Douillard, Maughan, Tveit, van Cutsem, Ye [1139] [1136], [1133], [1060], [1137], [1138] | 0.83 | 0.76-0.91 | 0.0001 |
| CT +/- anti-EGFR (no bolus or oral regimen)* | Bokemeyer, Douillard, van Cutsem, Ye [1139], [1136], [1137], [1138] | 0.72 | 0.63-0.82 | <0.00001 |

\* without Tveit, 2012  (bolus 5-FU), without Maughan, 2011  (oral fluoropyrimidine)

## 9.9.5.        Combination With Anti-VEGF Substances

| 9.29. | Evidence-based Statement | 2017 |
|---|---|---|
| Level of Evidence **1a** | According to a meta-analysis of the study data, the addition of bevacizumab to an infusional combination chemotherapy significantly increases the effectiveness in relation to PFS, but not to ORR and OS. On the other hand, the addition of bevacizumab to monochemotherapy with a fluoropyrimidine significantly increases the effectiveness in relation to ORR, PFS and OS. | |
| | Meta-analysis: see Guideline Report<br><br>Primary studies: [1127, 1128, 1140-1146] | |
| | Consensus | |

**Background**

The effectiveness of an anti-VGEF treatment with bevacizumab was assessed in numerous studies on the first-line therapy of mCRC (Table 15). The study population included patients with an unselected molecular pathology. In the meta-analytical evaluation of all available studies, the addition of bevacizumab to fluoropyrimidine-based chemotherapy (monotherapy or combination therapy) led to a significant increase of PFS (HR 0.71, p<0.00001) and OS (HR 0.85, p=0.0008).

When limiting the analysis to fluoropyrimidine monotherapy (5-FU bolus or infusional 5-FU, capecitabine), the addition of bevacizumab resulted in a highly significant prolongation of PFS (HR 0.57, p<0.00001) and OS (HR 0.83, p=0.03).

If one excludes the no longer common 5-FU bolus regimen (IFL) from the analysis and focuses the evaluation on infusional combination chemotherapies, the addition of bevacizumab led to a significant prolongation of PFS (HR 0.79, p<0.0001), but not of overall survival (HR 0.92, p=0.18).

**Table 15: Randomised Studies on First-Line Therapy With Bevacizumab In Unselected Patients**

| Study | Regimen | N pat. | ORR (%) | OR (p-value) | PFS (Mo) | HR PFS (p-value) | OS (Mo) | HR OS (p-value) |
|---|---|---|---|---|---|---|---|---|
| Hurwitz (Phase III) [1140] | IFL + Bev IFL | 402 411 | 44.8 34.8 | (0.004) | 10.6 6.2 | 0.54 (<0.001) | 20.3 15.6 | 0.66 (<0.001) |
| Stathopoulos (Phase III) [1141] | IFL + Bev Bev | 114 108 | 36.8 35.2 | (n.s.) | NR | NR | 22 25 | 1.05 (0.139) |
| ARTIST (Phase III) [1142] | mIFL + Bev mIFL | 142 72 | 35.3 17.2 | (0.013) | 8.3 4.2 | 0.44 (<0.001) | 18.7 13.4 | 0.62 (0.014) |
| N016966 (Phase III) [1143] | FOLFOX/XELOX + Bev FOLFOX/XELOX | 699 701 | 47 49 | 0.90 (0.31) | 9.4 8.0 | 0.83 (0.0023) | 21.3 19.9 | 0.89 (0.077) |
| ITACa (Phase III) [1144] | FOLFOX4/ FOLFIRI + Bev FOLFOX4/ FOLFIRI | 176 194 | 50.6 50 | (0.865) | 9.6 8.4 | 0.86 (0.182) | 20.8 21.3 | 1.13 (0.317) |
| Kabbinavar (Phase II) 2003 [1145] | 5-FU/LV 5-FU/LV + Bev 5 mg/kg 5-FU/LV + Bev 10 mg/kg | 36 35 33 | 17 40 24 | | 5.2 9.0 7.2 | | 13.8 21.5 16.1 | |
| Kabbinavar (Phase II) 2005 [1127] | FU/LV + Bev FU/LV | 104 105 | 26.0 15.2 | (0.055) | 9.2 5.5 | 0.50 (0.0002) | 16.6 12.9 | 0.79 (0.16) |
| AVEX (Phase III) [1128] | Cape + Bev Cape | 140 140 | 19 10 | (0.04) | 9.1 5.1 | 0.53 (<0.0001) | 20.7 16.8 | 0.79 (0.18) |
| MAX (Phase III) [1146] | Cape + Bev Cape | 157 156 | 38.1 30.3 | NR (0.16) | 8.5 5.7 | 0.62 (<0.001) | NR | 0.88 (0.314) |

Key: Cape, Capecitabine; Bev, Bevacizumab; OR, Odds Ratio; ORR, objective response rate; PFS, progression-free survival; OS, overall survival

In summary, it can be said that an increase of overall survival was achieved in the meta-analytical evaluation of the available studies when bevacizumab was added to fluoropyrimidine monotherapy; this was not the case when it was added to infusional combination chemotherapy.

In the marketing authorisation study, the addition of bevacizumab to the IFL regimen led to an increase of grade 3-4 side effects such as diarrhoea (32.4% vs. 24.7%), hypertension (11% vs. 2.3%) or thrombotic events (19.4% vs. 16.2%) compared to treatment with IFL alone. An increase of grade 3-4 bleeding events (3.1% vs. 2.5%) and gastrointestinal perforations (1.5% vs. 0%) was additionally observed, however with an altogether lower frequency [1140]).

The following bevacizumab-specific side effects were described for the addition of bevacizumab to an oxaliplatin-based treatment regimen (FOLFOX or XELOX) in the NO16966 study: venous thromboembolic events (8% vs. 5%), arterial thromboembolic events (2% vs. 1%), bleeding events (2% vs. 1%), hypertension (4% vs. 1%) [1143].

Compared to capecitabine monotherapy, the addition of bevacizumab to treatment with capecitabine was associated with comparably fewer side effects. The following grade 3-4 side effects were described in the AVEX study: hand-foot syndrome (16% vs. 7%), diarrhoea (7% vs. 6%), venous thromboembolic events (6% vs. 4%), bleeding events (0% vs. 0%), hypertension (0% vs. 1%) [1128].

**Table 16: Summary of Meta-Analyses On Bevacizumab - OS**

| OS | Studies | HR | (95% CI) | p |
|---|---|---|---|---|
| CT +/- Bevacizumab (all available studies) | Hurwitz, Guan, Kabbinavar, Passardi, Saltz, Tebbutt, Cunningham [1140], [1142], [1127], [1144]. [1143], [1146], [1128] | 0.85 | 0.78-0.94 | 0.0008 |
| CT +/- Bevacizumab (only currently applied standard regimen)* | Passardi, Saltz, Tebbutt, Cunningham [1144], [1143], [1146], [1128] | 0.92 | 0.83 – 1.03 | 0.13 |
| Fluoropyrimidine +/- Bevacizumab | Cunningham, Kabbinavar,Tebbutt [1128], [1127], [1146] | 0.83 | 0.70-0.98 | 0.03 |
| Infusional combination CT +/- Bevacizumab | Guan, Saltz, Passardi [1142],[1143], [1144] | 0.92 | 0.81-1.04 | 0.18 |

*without Hurwitz, Guan, Kabbinavar (no 5-FU bolus or short-term regimen)

**Table 17: Summary of Meta-Analyses On Bevacizumab - PFS**

| PFS | Studies | HR | (95% CI) | p |
|---|---|---|---|---|
| CT +/- Bevacizumab all | Hurwitz, Guan, Kabbinavar, Passardi, Salz, Tabbutt, Cunningham [1140], [1142], [1127], [1144], [1143], [1146], [1128] | 0.71 | 0.65-0.77 | <0.00001 |
| CT +/- Bevacizumab (only currently applied standard regimen)* | Passardi, Saltz, Tebbutt, Cunningham [1144], [1143], [1146], [1128] | 0.75 | 0.68-0.82 | <0.00001 |
| Fluoropyrimidine +/- Bevacizumab | Cunningham, Kabbinavar, Tebbutt [1128], [1127], [1146] | 0.57 | 0.48-0.66 | <0.00001 |
| Infusional combination CT +/- Bevacizumab | Guan, Saltz, Passardi [1142], [1143], [1144] | 0.79 | 0.71-0.88 | <0.0001 |
| *without Hurwitz, Guan, Kabbinavar (no 5-FU bolus or short-term regimen) | | | | |

## 9.9.6.  Combination of Anti-EGFR and Anti-VEGF Substances

| 9.30. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | Combination therapy with an anti-EGFR antibody plus a VEGF signalling pathway inhibitor may not be used. | |
| Level of Evidence<br><br>**1b** | Sources: [1147-1149] | |
| | Strong consensus | |

**Background**

Three prospective studies consistently show that polychemotherapy in combination with anti-EGFR antibodies and with bevacizumab is associated with a reduced PFS and increased toxicity compared to polychemotherapy in combination with bevacizumab. Oxaliplatin-containing therapy was administered in all three studies; irinotecan-based therapy was additionally administered in one study [1147], [1148], [1149].

### 9.9.7. Duration of Induction Therapy

| 9.31. | Consensus-based Recommendation | 2017 |
|---|---|---|
| **EC** | Where possible, oxaliplatin-based induction therapy (FOLFOX, CAPOX, FOLFOXIRI) should be performed over a period of 4-6 months before de-escalating to an oxaliplatin-free therapy.<br><br>Not only allergic reactions but also the development of peripheral polyneuropathy, the incidence and severity of which increases with the cumulative dose of oxaliplatin, is a limiting factor for the use of oxaliplatin. | |
| | Consensus | |

**Background**

Due to oxaliplatin-induced polyneuropathy, FOLFOX or CAPOX can generally not be administered for longer than 4-6 months. In the MACRO study and in the CAIRO3 study, 6 cycles of CAPOX (4.5 months) were administered prior to commencing maintenance therapy [1150], [1151]. In the AIO KRK-0207 study, maintenance therapy was initiated after 6 months of induction therapy [1152]. In the TRIBE study, the duration of the induction therapy was also limited to a maximum of 12 cycles of the biweekly chemotherapy, following which maintenance therapy with 5-FU plus bevacizumab was administered and continued up to progression [1058].

The optimal duration of an induction therapy with FOLFIRI is not clear. For this reason, this treatment can be continued until an optimal response is achieved. In any case, an initial treatment duration of at least 4-6 months will also be aimed for here.

For patients receiving initial monochemotherapy with a fluoropyrimidine, this treatment should be continued until the disease progresses.

### 9.9.8. Maintenance Therapy and Therapy Interruption

| 9.32. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | After induction chemotherapy, the treatment can be paused or de-escalated to maintenance therapy. | |
| Level of Evidence<br><br>**1a** | Sources: [1152-1157] | |
| | Consensus | |

**Background**

After 4-6 months of oxaliplatin-based induction therapy, it should be verified whether maintenance therapy can be carried out to decrease toxicity and increase quality of life, or whether an interruption in therapy is possible.

### 9.9.8.1. Maintenance Therapy vs. Continuation of Induction Therapy

The question of whether maintenance therapy has an impact on overall survival compared to the continuation of induction therapy was evaluated in three meta-analyses and one systematic review [1153], [1154], [1155], [1156]. These consistently show that, compared to continuous therapy, maintenance therapy can be carried out without a significant impact on OS. Compared to continuous chemotherapy with an interruption of therapy, the difference in OS was minimal (HR decreased by 0.10), but partially significant. The rate of side effects appears to be partly lower for intermittent therapy or interrupted therapy. A trend towards a better quality of life was observed in the interruption arm; however, this parameter has only been assessed in few studies and yielded different scores.

### 9.9.8.2. Maintenance Therapy vs. Therapy Interruption

Based on the data of the AIO KRK-0207 study and of the CAIRO3 study, maintenance therapy compared to therapy-free periods enables a prolonged progression-free survival, but has no impact on overall survival ([1152], [1157]).

Following induction therapy with doublet/triplet chemotherapy plus bevacizumab, maintenance therapy with fluoropyrimidine plus bevacizumab is considered the preferred treatment option. Maintenance therapy with bevacizumab alone, on the other hand, is not recommended [1152]. Compared to bevacizumab monotherapy or therapy interruption, the continuation of treatment with maintenance therapy with fluoropyrimidine plus bevacizumab did not lead to a decrease in the global quality of life score (GHS/QoL) [1158].

If one opts for a therapy interruption following induction chemotherapy, this should be carried out as a "controlled break" and should involve a planned follow-up visit based on corresponding staging diagnostics.

## 9.10. Second-Line Therapy

### 9.10.1. Performance of Second-Line Chemotherapy

| 9.33. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Second-line therapy is usually markedly less effective than first-line therapy. Within the scope of the sequential use of active substances, the choice of second-line therapy should be based primarily on the effectiveness and side effects of the prior therapy. | |
| Level of Evidence<br><br>**1b** | Sources: [1159-1161] | |
| | Strong consensus | |

**Background**

Where possible, metastatic CRC patients should be given access to all available medicines during the course of the treatment. The significance of an effective second-

line therapy for overall survival has been analysed in several phase III studies. For example, a second-line therapy with irinotecan after failure of fluorouracil monotherapy resulted in a significant benefit in overall survival in comparison with BSC (OS 9.2 vs. 6.5 months) [1161] or infusional 5-FU/FA [1160] (OS 10.8 vs. 8.5 months).

In a comparison of irinotecan with infusional 5-FU, pain-free survival was longer under the treatment with irinotecan (10.3 vs. 8.5 months), with an otherwise comparable tolerability and quality of life in the two treatment arms [1160]. In the direct comparison with best supportive care, irinotecan significantly increased the time without worsening of the performance status. In the quality of life analysis, the treatment with irinotecan achieved better outcomes in all aspects (except diarrhoea) [1161].

Combination therapy with oxaliplatin and fluorouracil after failure of an irinotecan-containing protocol in first line-therapy was superior to 5-FU/FA or oxaliplatin monotherapy both in terms of the response rates achieved and time to progression [1159]. The combination therapy of 5-FU/FA with oxaliplatin and/or irinotecan, which show response rates (CR + PR) of 40-55% in first-line therapy, achieve response rates of 4% (FOLFIRI) to 15% (FOLFOX) and a progression-free survival of around 2.5-4.2 months in second-line therapy. The median survival of patients for both therapy sequences (FOLFOX followed by FOLFIRI or FOLFIRI followed by FOLFOX) was around 20 months [1162]. As anticipated, the toxicity profile differed depending on the medicines used. Quality of life analyses from these studies are not available.

## 9.10.2.    Second-Line Therapy With Anti-VEGF and Anti-VEGFR Substances

Several randomised studies have confirmed the benefit of bevacizumab (E3200, TML, BEBYP), aflibercept (VELOUR) and ramucirumab (RAISE) in second-line therapy. The effects of the therapy are highly consistent. The evaluable studies consistently show that a significant increase of PFS and OS can be achieved by adding the anti-VEGF substances bevacizumab or aflibercept or the anti-VEGFR antibody ramucirumab to second-line chemotherapy. It should be noted, however, that the absolute increase in the survival is moderate in comparison with the median OS and generally ranges between 1-2 months.

The antiangiogenic therapy is associated with the typical side effects; for example, the following grade 3-4 side effects were observed with the addition of aflibercept to FOLFIRI compared to FOLFIRI monotherapy: hypertension (19.3% vs. 1.5%), haemorrhaging (2.9% vs. 1.7%), arterial thromboembolic events (1.8% vs. 0.5%) and venous thromboembolic events (7.9% vs. 6.3%). In addition, a potentiation of chemotherapy-associated toxicities, such as diarrhoea or stomatitis, was also observed in part [1163].

Similarly, an increase in side effects was also observed for the combination of the VEGFR inhibitor ramucirumab with FOLFIRI compared to FOLFIRI chemotherapy. The increase notably affected grade 3-4 side effects such as neutropenia (38% vs. 23%), hypertension (11% vs. 3%), haemorrhaging (1.9% vs. 1.5%) or gastrointestinal perforation (1.5% vs. 0.6%) [1164].

**Table 18: Randomised Studies on Second-Line Therapy With Anti-VEGF Substances**

| Study | Prior therapy | Regimen | N pat. | ORR (%) | OR (p-value) | PFS (Mo) | HR PFS (p-value) | OS (Mo) | HR OS (p-value) |
|---|---|---|---|---|---|---|---|---|---|
| E3200 (Phase III) [1165] | Fluoropyrimidine and irinotecan (0% Bev) | FOFOX4 + Bev | 286 | 22.7 | | 7.3 | 0.61 | 12.9 | 0.75 |
| | | FOLFOX4 | 291 | 8.6 | (<0.0001) | 4.7 | (<0.0001) | 10.8 | (0.0011) |
| TML (Phase III) [1166] | Chemotherapy (100% Bev) | Chemo-therapy + Bev | 409 | 5 | | 5.7 | 0.68 | 11.2 | 0.81 |
| | | Chemo-therapy | 411 | 4 | (n.s) | 4.1 | (<0.0001) | 9.8 | (0.0062) |
| BEBYP (Phase III) [1167] | Chemotherapy (100% Bev) | Chemo-therapy + Bev | 92 | 21 | | 6.8 | 0.70 | 15.5 | 0.77 |
| | | Chemo-therapy | 92 | 17 | (0.573) | 5.0 | (0.010) | 14.1 | (0.043) |
| Chinese (Phase II) [1168] | Oxaliplatin-based (0% Bev) | FOLFIRI + BEV | 65 | 47.7 | | 8.5 | NR | 15.2 | NR |
| | | FOLFIRI | 77 | 28.5 | (<0.001) | 5.1 | | 11.3 | |
| VELOUR (Phase III) [1163] | Oxaliplatin-based (30.4% Bev) | FOLFIR + Aflibercept | 612 | 19.8 | | 6.9 | 0.76 | 13.5 | 0.82 |
| | | FOLFIRI + Placebo | 614 | 11.1 | (0.0001) | 4.7 | (<0.0001) | 12.1 | (0.0032) |
| RAISE (Phase III) [1164] | Fluoropyrimidine and oxaliplatin (100% Bev) | FOLFIRI + Ramu-cirumab | 536 | 13.4 | | 5.7 | 0.79 | 13.3 | 0.84 |
| | | FOLFIRI + Placebo | 536 | 12.5 | (0.63) | 4.5 | (0.0005) | 11.7 | (0.0219) |

Key: Cape, Capecitabine; Bev, Bevacizumab; OR, Odds Ratio; ORR, Objective Response Rate; PFS, Progression-Free Survival; OS, Overall Survival;

## 9.10.3.    Second-Line Therapy With Anti-EGFR Substances

Randomised studies have confirmed the benefit of panitumumab and cetuximab in second-line therapy. These drugs can therefore be administered as per their marketing authorisation after completion of first-line therapy (Tables 4-5).

Two randomised studies (EPIC and 181) have confirmed the effectiveness of the anti-EGFR substances cetuximab and panitumumab in second-line therapy. Both studies show a significant increase of ORR and PFS when anti-EGFR substances are added to FOLFIRI chemotherapy in the second line of therapy. However, no significant increase in survival was achieved in either of the studies.

A typical side effect of anti-EGFR therapy is acneiform exanthema, the overall frequency of which was 81.2% in the EPIC study with a grade 3-4 incidence of 8.2%. An increase in chemotherapy-associated toxicity, such as diarrhoea (28.4% vs. 15.7%), was also observed for the addition of anti-EGFR substances [1169]. In the EPIC study, the administration of cetuximab was associated with a significant increase of the global health score. However, on a critical note, the usual instruments used to analyse quality of life, such as the EORTC QLQ-C30 questionnaire, do not include an exanthema-relevant score and are therefore not suitable for assessing such aspects [1169].

**Table 19: Randomised Studies on Second-Line Therapy With Anti-EGFR Substances**

| Study | Prior therapy | Regimen | N oat. | ORR | OR (p-value) | PFS | HR PFS (p-value) | OS | HR OS (p-value) |
|---|---|---|---|---|---|---|---|---|---|
| EPIC* [1169] | Fluoropyrimidine + Oxaliplatin | FOLFIRI + Cet  FOLFIRI | 648  650 | 16.4  4.2 | NR  (<0.0001) | 4.0  2.6 | 0.692  (<0.0001) | 10.7  10.0 | 0.975  (0.71) |
| 191** [1170] | Fluoropyrimidine-based therapy  (66% Oxaliplatin  19% Bev) | FOLFIRI + Pani  FOLFIRI | 303  294 | 35  10 | (<0.001) | 5.9  3.9 | 0.73  (0.004) | 14.5  12.5 | 0.85  (0.12) |

Key: *unselected patients; **KRAS wild type; Cet, Cetuximab; Bev, Bevacizumab; OR, Odds Ratio; ORR, Objective Response Rate; PFS, Progression-Free Survival; OS, Overall Survival

## 9.11. Therapy Sequence

| 9.34. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | In patients with RAS wild type tumours, the localisation of the primary tumour is an important determinant in the evaluation of the optimal therapy sequence (see 9.8.2.). In patients with left-sided mCRC and RAS wild type, first-line therapy should include the use of an anti-EGFR antibody in combination with chemotherapy. In this constellation, anti-VEGF therapy is only considered in the context of second-line therapy. | |
| Level of Evidence<br><br>**2b** | Sources: [1130][1131] | |
| | Consensus | |

| 9.35. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | In patients with right-sided mCRC and RAS wild type, no anti-EGFR antibodies should be used in combination with chemotherapy in first-line therapy. | |
| Level of Evidence<br><br>**2b** | Sources: [1130][1131] | |
| | Strong consensus | |

**Background**

Apart from the localisation of the primary tumour (see 9.8.2), there is currently no reliable evidence available that recommends an optimal sequence of molecular biological substances. The previously available data were obtained mainly (I) from theoretical molecular biological papers/considerations, (II) from more or less unplanned recordings of second-line therapies after first-line randomisation (FIRE-3, CALGB, PEAK) or (III) from equally unplanned retrospective analyses of the first-line situation in randomised second-line therapies (TML, VELOUR; PRIME, PEAK).

### 9.11.1.1. Continuation of Anti-VEGF Therapy in Second-Line Therapy

The clinical data of the TML study confirm that the continuation of an anti-VEGF therapy with bevacizumab after progression under a bevacizumab-based first-line therapy is an effective treatment strategy in unselected mCRC patients. In comparison with chemotherapy alone, patients who received bevacizumab plus chemotherapy in the second line of therapy showed a longer median overall survival of 11.2 months (95% CI: 10.4-12.2) for bevacizumab plus chemotherapy and 9.8 months (95% CI: 8.9-10.7) for chemotherapy alone (HR 0.81, p=0.0062) [1166].

The most commonly reported grade 3-5 side effects in the TML study were neutropenia (16% vs. 13%), diarrhoea (10% vs. 8%) and asthenia (6% vs. 4%). Under treatment with

bevacizumab plus chemotherapy, the following grade 3-5 side effects were more common compared to chemotherapy alone: bleeding/haemorrhaging (2% vs. <1%), gastrointestinal perforation (2% vs. <1%) and venous thromboembolic events (5% vs. 3%).

### 9.11.1.2. Continuation of Anti-EGFR Therapy in Second-Line Therapy

The CAPRI-GOIM study analysed KRAS wild type mCRC patients who received either FOLFOX plus cetuximab or only FOLFOX in a randomised comparison after first-line therapy with FOLFIRI plus cetuximab. The continuation of the cetuximab treatment beyond progression (experimental arm) led to a non-significant increase of PFS in the entire group of examined patients (6.4 vs. 4.5 months, p=0,19). In contrast, a significant increase of second-line PFS (HR 0.56, p=0,025) was reported for patients with KRAS, NRAS, BRAF and PIK3CA wild type tumours in the experimental arm. The significance level for overall survival (HR 0.57, p=0.056) was not achieved due to the small sample size (n=66) [1171].

### 9.11.1.3. Sequential Use of Anti-EGFR and Anti-VEGF Therapy

Retrospective, clinical investigations suggest that an anti-EGFR therapy is less effective if it is preceded by an anti-VEGF therapy ([1172]). Preclinical data support this hypothesis [1173] [1174]).

The FIRE-3 study showed a markedly prolonged anti-VEGF therapy in second-line therapy following initial anti-EGFR therapy than for the inverse sequence [1042]. While the combination of panitumumab with a combination chemotherapy in first-line therapy (PEAK study) was considerably more effective than the bevacizumab-based comparative therapy [1111]. This effect could not be reproduced in the second-line therapy (SPIRITT study) after prior bevacizumab therapy [1175]. Comparable data were also ascertained in the Prodige 18 UNICANCER GI study, which analysed KRAS wt mCRC patients who progressed under a bevacizumab-based chemotherapy. The continuation of bevacizumab in combination with a cross-over chemotherapy was associated with a (statistically non-significant) longer median PFS and OS than the treatment with cetuximab plus chemotherapy [1176]. At present, however, the results of this study are only available in the form of an abstract.

While the available data suggest that the sequence of an anti-VEGF therapy followed by an anti-EGFR therapy is unfavourable, a final assessment which also includes the tumour localisation is still pending.

The data of the 181 study (FOLFIRI +/- panitumumab) suggest that anti-EGFR therapy in second-line therapy is more effective in left-sided than in right-sided primary tumours [1177]. For left-sided RAS wild type tumours, this manifests in more favourable effectiveness parameters in relation to ORR (50% vs. 13%), PFS (8.0 vs. 4.8 months) and OS (20.1 vs. 10.3 months).

## 9.12. Chemotherapy in Later Lines of Therapy

The therapeutic activity of anti-EGFR antibodies, as well as of trifluridine/tipiracil and regorafenib was assessed in randomised, placebo-controlled studies performed in intensively pretreated patients who had completed the standard therapies.

### 9.12.1. Effectiveness of Anti-EGFR Antibodies

Two large randomised studies compared a treatment with best supportive care (BSC) plus anti-EGFR antibodies versus BSC alone in patients with mCRC refractory to

chemotherapy [1178], [1179]. A direct head-to-head comparison of cetuximab and panitumumab also yielded similar effectiveness and toxicity data [1180]. Regarding the RAS status of unselected patients, the addition of panitumumab to BSC led to a significant improvement of the response rate (10% vs. 0%) and PFS (HR 0.54, p<0.0001). However, no increase in survival was achieved (HR 1.00), which was explained by the high proportion of cross-over patients (76%) [1178].

Another study evaluated the addition of cetuximab to BSC [1179]. In a retrospective analysis of patients with KRAS wild type tumours, the addition of cetuximab led to an ORR of 12.8% vs. 0% and a significant prolongation of PFS (3.7 vs. 1.9 months; HR 0.40, p<0.001) and OS (9.5 vs. 4.8 months; HR 0.55, p<0.001). In contrast, no benefit was observed in the subgroup of patients with KRAS-mutated tumours [1051]. With minor worsening of the physical function and global health status scores (both p<0.05), the quality of life in the cetuximab group was upheld for a significantly longer period [1179]. When comparing cetuximab to BSC alone, the following grade 3-4 side effects were observed: infusion reactions (4.5% vs. 0%), rash (11.8% vs. 0.4%), hypomagnesaemia (5.2% vs. 0%) [1179]).

## 9.12.2.  Effectiveness of Trifluridine/Tipiracil

| 9.36. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Trifluridine/tipiracil should be used in patients who have received all available chemotherapies/antibodies or in whom these are not indicated. | |
| Level of Evidence<br><br>**1b** | Sources: [1181, 1182] | |
| | Consensus | |

**Background**

Trifluridine/Tipiracil (TAS102) was assessed in two randomised studies (phase II and phase III) in pretreated CRC patients and was compared to placebo [1182], [1181]. One inclusion criterion was prior treatment with at least two chemotherapy regimens with monoclonal antibodies. Both studies showed an increase of overall survival (OS 1.8 and 2.4 months, respectively). In the phase III study, the hazard ratio for the improvement of overall survival was 0.68 (95% CI: 0.58-0.81, p<0.001). The therapy was also effective in patients who had previously undergone FU therapy. The rate of side effects was classified as moderate. The following grade 3-4 haematological side effects were mainly observed: neutropenia (38% vs. 0%), febrile neutropenia (4% vs. 0%), anaemia (18% vs. 3%) and thrombocytopenia (5% vs. <1%).

### 9.12.3.        Regorafenib

| 9.37. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | Regorafenib can be used in patients previously treated with all available chemotherapies/antibodies. | |
| Level of Evidence<br><br>**1b** | Sources: [1183, 1184] | |
| | Consensus | |

**Background**

Regorafenib is a multikinase inhibitor that was tested against placebo in pretreated mCRC patients within the scope of the CORRECT study [1184]. The study achieved its primary endpoint and showed a significant survival benefit for regorafenib (OS: 6.4 vs. 5.0 months; HR 0.77; 95% CI: 0.64–0.94). These results were confirmed by the CONCUR study, which was conducted exclusively in Asian patients [1183]. The use of regorafenib was seen critically owing to the toxicity associated with the treatment. The most significant grade 3-4 side effects include hand-foot syndrome (17% vs. <1%), fatigue (10% vs. 5%) and diarrhoea (7% vs. 1%) [1184].

### 9.12.4.        Reinduction / Rechallenge

The reinduction of antineoplastic substances whose efficacy was demonstrated in earlier therapy lines is a proven therapeutic strategy in oncology; however, evidence supporting the clinical effectiveness of this approach is limited.

Santini et al. analysed the effectiveness of a rechallenge with cetuximab in a small study (n=39). In patients who had responded to a cetuximab-based first-line therapy with a CR, PR or SD >6 months and who progressed under a cetuximab-free window therapy, an ORR of 54% and a PFS of 6.6 months was achieved with repeated cetuximab-based therapy [1185]. However, owing to the very small sample size, these data can only be considered as a basis for generating hypotheses.

### 9.12.5.        Other Medicines

Other medicines that can be considered as per their marketing authorisation following completion of the standard therapies are currently not available. Mitomycin should not be used owing to its comparably low efficacy in this setting.

## 9.13.        Local Ablative Procedures

| 9.38. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | Local ablative procedures can be performed if non-resectable metastases are present or if the patient's overall condition does not allow resection, especially following prior resection of liver metastases. | |
| Level of Evidence<br><br>**3b** | Sources: [1186-1189] | |
| | Strong consensus | |

**Background**

Local ablative procedures are used primarily in settings where surgical resection is not possible owing to technical or patient-related factors. However, local ablative procedures can also be carried out in combination with a surgical resection [1186-1188]. In this context, it must be generally noted that the evidence on this topic is limited and that sufficiently large, prospective, randomised studies are missing.

For primarily resectable liver metastases with an indication for local ablative procedures owing to their size and localisation, these procedures should be offered a an alternative and discussed with a surgeon experienced in liver surgery and an experienced interventional radiologist within the scope of an interdisciplinary tumour board. The indication for local ablative procedures should be established in multidisciplinary tumour conferences. The best overall survival is achieved with a multimodal or sequential therapy concept. The possibility of secondary resectability or the practicability of local ablative measures should be reviewed in the context of regular, multidisciplinary tumour conferences based on the results of regular follow-ups.

In the absence of randomised studies comparing the thermal procedures available, the efficacy of radiofrequency ablation (RFA), microwave ablation or high-precision conformal, hypofractionated radiation, such as stereotactic radiation or [HDR] brachytherapy, are considered comparable. However, the indication for the various procedures varies depending on the localisation of the tumour or its proximity to blood vessels. The results of the CLOCC study suggest a potential benefit of RFA (plus surgical) therapy in addition to chemotherapy despite the small sample size [1189]. This study compared RFA (intraoperative, laparoscopic or percutaneous) in addition to chemotherapy (6 months) to chemotherapy alone in patients with unresectable liver metastases. This study showed a significant prolongation of both PFS (9.9 vs. 16.8 months; HR 0.57, p=0,005) and overall survival (45.6 vs. 40.5 months; HR 0.58, p=0.01) in the RFA/chemotherapy arm.

In view of the continued lack of prospectively controlled studies, LITT can currently not be recommended for the treatment of liver metastases in CRC outside of clinical studies.

### 9.13.1.    Local Ablative Procedures for Liver Metastases

#### 9.13.1.1.    Thermal Ablation

Just like the surgical resection of colorectal metastases, thermal ablation (RFA, MWA) is a local therapeutic procedure. The significance of a comparison with surgical resection based on current data is strongly limited owing to the differences in patient selection. Local ablative procedures can be used when unresectable metastases are present, when the patient's overall health precludes a resection, after prior liver resection or in combination with a resection ([1186-1188]). Gillams et al. were able to demonstrate a mean survival of 28 months following percutaneous RFA of unresectable hepatic colorectal metastases in 309 patients with prior systemic therapy in the subgroup of patients with <5 metastases each measuring <5 cm in diameter ([1190]). In the subgroup of patients with >5 metastases and with metastases measuring >5 cm, on the other hand, the median survival was 14 months. In addition to the number and diameter of the hepatic metastases, the presence of extrahepatic metastases had a significant impact on median survival (28 months for exclusively hepatic metastases vs. 14 months for extrahepatic metastases). In summary, the long-term survival of patients up to 10 years following thermal ablation of hepatic oligometastases is well documented in the meantime ([1191], [1192]).

In addition to this, cohort studies and retrospective analyses are available which showed no difference in survival when comparing resection and thermal ablation of metastases measuring up to 3-4 cm in diameter ([1193], [1194]), so that thermal ablation can be offered as an alternative to resection in patients presenting this clinical constellation. A current meta-analysis of an international expert group ([1195]) reports similar results for RFA and surgery for colorectal metastases measuring up to 3 cm and in selected cases even up to a tumour size of 5 cm, with a mean 5-year survival of 31% despite a negative selection of patients who are generally unsuitable for surgery. A retrospective analysis of two prospectively randomised EORTC studies of the local recurrence rate after ablation + chemotherapy (6%) or after resection +/- chemotherapy (5.5%) of colorectal liver metastases yielded a similar result for resection and thermal ablation of metastases measuring up to 4 cm ([1196]). In any case, a safety margin of 5 mm between the metastasis and induced coagulation should be observed ([1197]).

Data of larger patient populations and/or with longer follow-ups have become increasingly available in recent years. These studies highlight, among other things, the advantages of ablation with the option of repeating the intervention. In a long-term study in 99 patients with colorectal liver metastases with a follow-up of more than 10 years, no statistically significant difference in survival was observed between the group without tumour recurrence and the group with ablatable tumour recurrence ([1198]). At present, a recommendation can only be made for radiofrequency or microwave ablation (MWA). Initial results show a lower local recurrence rate for the treatment of colorectal liver metastases in the proximity of large vessels for MWA versus RFA ([1199]). It is worth pointing out the long-term results of a prospectively randomised study comparing resection combined with thermal ablation and chemotherapy versus chemotherapy alone. After 8 years, there was a significant survival benefit of the combination therapy resection + RFA + chemotherapy versus chemotherapy alone (HR 0.58, 95% CI: 0.38-0.88, p=0.01). The 3-, 5- and 8-year survival rates were 57%, 43% and 36% for the combination SR + RFA + chemotherapy versus 55%, 30% and 9% for chemotherapy alone. The median survival was 45.6 months (95% CI: 30.3–67.8) for the combination therapy versus 40.5 months (95% CI: 27.5-47.7) for the chemotherapy group ([1200]. In view of

the continued lack of prospectively controlled studies, LITT or electroporation cannot be recommended for the treatment of liver metastases in CRC outside of clinical studies.

### 9.13.1.2. Other Locally Effective Interventional Procedures

Other local procedures for the treatment of liver metastases with little (SBRT, brachytherapy, cryotherapy) or lacking evidence (irreversible electroporation) are stereotactic body radiation therapy (SBRT), brachytherapy, cryotherapy and irreversible electroporation (IRE).

#### 9.13.1.2.1. SBRT

*SBRT* is a procedure that requires state-of-the art techniques for administering and planning radiotherapy, known as intensity modulated radiotherapy ([1201]). In the literature, the reported 2-year survival ranges between 32% and 83% ([1202], [1203]). The current literature covers approximately 250 patients with colorectal liver metastases. Studies with a 5-year survival with larger patient cohorts or randomised studies comparing SBRT with resection or thermal ablation in colorectal liver metastases are not available.

#### 9.13.1.2.2. Brachytherapy

In *brachytherapy* (interstitial high-dose-rate (HDR) brachytherapy), an iridium-192 source is administered quasi punctiform into the tumour tissue through an applicator previously placed under CT or MRI guidance by remote afterloading ([1191]). In a study with 73 enrolled patients with a total of 199 colorectal liver metastases who had previously undergone extensive systemic and surgical therapy, a median survival of up to 23.4 months was achieved with HDR brachytherapy. Local recurrences can be effectively prevented by a single-stage administration of ≥20 Gray (Gy) ([1204]). Long-term results for irreversible electroporation, SBRT and brachytherapy are not yet available.

### 9.13.2. Treatment of Lung Metastases

The resectability of lung metastases and local therapy with the possibility of ablation (RFA, MWA) or radiotherapy (SBRT) should be decided by a multidisciplinary tumour board, in which an experienced organ surgeon (thoracic surgery), an experienced interventional oncologist and a radio-oncologist are represented. According to the literature published by De Baere et al. or Vogl TJ et al., thermal ablation procedures are an appropriate therapeutic option for lung metastases measuring up to 3 cm and up to 3 metastases per lung. Depending on the technique used, local control is achieved in 69.2% to 88.3% of patients ([1205]; [1206]). Randomised studies are not available. Stereotactic body radiation therapy (SBRT) can be used alternatively; however, in this case, technical requirements must be observed, such as intensity modulated radiotherapy (IMRT) or an enhancement of IMRT with volumetric modulated arc therapy (VMAT). There are no randomised studies available for SBRT of lung metastases, and the number of published cases with risks of radiation-induced pneumonitis and a decrease in functional volume is still low.

## 9.14. Locoregional Procedures

Locoregional procedures include selective intra-arterial radiotherapy (SIRT) or intra-arterial chemotherapy of the liver (HAI, TACE).

## 9.14.1.     Selective Internal Radioembolisation (SIRT)

| 9.39. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | SIRT can be used to treat disseminated liver metastases of CRC in patients who have no other equivalent therapeutic option. | |
| Level of Evidence<br><br>**2b** | Sources: [1207] | |
| | Strong consensus | |

**Background**

In comparably small randomised studies, the combination of SIRT (selective intra-arterial radioembolisation with Yttrium-90 resin microspheres) with 5-FU was found to be more effective than chemotherapy alone. In patients refractory to chemotherapy who had undergone multiple prior therapies (n=44), the addition of SIRT to 5-FU monotherapy led to an improvement in the response rate (10% vs. 0%) and TTP (4.5 vs. 2.1 months, P<0.03) compared to 5-FU monotherapy [1207].

In the randomised comparison of SIRT plus 5-FU versus 5-FU, a significant increase in TTP (18.6 vs. 3.6 months, p<0.0005) and OS (29.4 vs. 12.8 months, p=0.025) was achieved in 21 patients in first-line therapy ([1208]). Based on the data of a phase I study, the combination of SIRT with FOLFOX chemotherapy was assessed in three randomised multicentre studies (SIRFLOX, FOXFIRE and FOXFIRE global) [1209].

In the SIRFLOX study, PFS (primary endpoint) was not improved by adding SIRT to the FOLFOX chemotherapy regimen in first-line therapy [1210]. Overall survival was analysed as the primary endpoint in the joint evaluation of all three studies under the blanket of the FOXFIRE global study. The results of the FOXFIRE global study were presented for the first time during the 2017 ASCO Annual Meeting. In the intention-to-treat population (n=1103), the addition of SIRT to an oxaliplatin-/5-FU-based first-line chemotherapy showed no advantage in relation to PFS or overall survival. However, the treatment with SIRT caused additional side effects [1211]. The high proportion of synchronous hepatic (87%) and extrahepatic metastases (35%), of 50-55% primary tumours in situ, and of 36% ECOG 1 patients in this study population is remarkable. These results should at least partly explain the modest effect of an isolated liver-associated therapy such as SIRT on overall survival. The addition of SIRT to 5-FU/oxaliplatin-based (+ bevacizumab) chemotherapy led to a significant improvement in the response rate (odds ratio 1.52, p=0.001) in the ITT population of the FOXFIRE global study. Even though a significant benefit of the SIRT therapy was also observed in the hepatic response, the resection rate in both treatment arms was almost identical (16% vs. 17%, p=0.669). Moreover, the secondary resectability was evaluated by a panel of hepatobiliary surgeons in the SIRFLOX study. In this blinded analysis of imaging at the time of the best response, a significantly higher potential resectability was found in the SIRT arm than in the control arm (Garlipp et al. ASCO 2017) [1212].

### 9.14.2.     Hepatic Intra-Arterial Chemotherapy

#### 9.14.2.1.     Hepatic Arterial Infusion Chemotherapy (HAI)

Hepatic arterial infusion (HAI) chemotherapy is a locoregional treatment method which has been performed successfully in specialised centres [1213], [1214]. A currently on-going European multicentre phase II study (OPTILIV study; [1215]) shows that resectability can be restored in the second line of therapy by means of dose-intensive, intra-arterial chemotherapy (HAI, irinotecan, oxaliplatin, 5-FU), with a 4-year survival rate of 37.4% taking into account R0 and R1 resections. A consensus regarding a recommendation for HAI for the treatment of liver-dominant metastases in specialised centres was not achieved.

#### 9.14.2.2.     Use of Irinotecan-Loaded Microbeads

Even if the amount of available data on this topic is limited, a prospectively randomised study in palliative patients progressing after second- and third-line chemotherapy showed an improvement in survival with a better quality of life following the intra-arterial administration of irinotecan-loaded particles ([1216]). A further prospective, randomised study reports higher response rates with an improvement in progression-free survival for the combination of FOLFOX +/- bevacizumab with irinotecan-loaded particles versus FOLFOX +/- bevacizumab ([1217]).

### 9.14.3.     Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

| 9.40. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | For patients with isolated and limited peritoneal carcinosis, a cytoreductive operation with subsequent hyperthermal intraperitoneal chemotherapy (HIPEC) can be performed if the following criteria are fulfilled:<br><br>- PCI (peritoneal cancer index) < 20<br>- No extraabdominal metastases<br>- Possibility of macroscopic complete removal or destruction of all tumour manifestations<br>- Therapy in a specialised centre<br><br>HIPEC should be performed as part of a study. | |
| Level of Evidence<br><br>**4** | Sources: [785, 786, 1218-1220] | |
| | Consensus | |

**Background**

Owing to the associated morbidity, the performance of HIPEC therapy is bound to certified high-volume centres [1218]. The effectiveness of the cytoreductive surgery depends especially on the extent of the peritoneal cancer. As a result, only patients with limited peritoneal metastatic spread are considered for this procedure. The PCI (peritoneal cancer index) can be used as an aid in decision making [1219]. Recurrences after cytoreductive therapy and intraperitoneal chemotherapy are common and are considered unfavourable prognostic factors [1220].

The specific efficacy of HIPEC therapy has only been studied in a smaller randomised study in 2003 [785], [786]. This study enrolled 105 patients and compared a treatment with 5-FU/leucovorin +/- surgical resection with surgical cytoreduction plus hyperthermic chemotherapy. The median survival was markedly longer in the experimental treatment arm (22.3 vs. 12.6 months, p=0.032) than in the standard arm, but morbidity was high and mortality was 8% ([785]). In addition, it must be noted that neither oxaliplatin nor irinotecan nor molecular biological substances (anti-EGFR or anti-VEGF) were used in this study.

In view of the limited evidence obtained in prospective, controlled studies, the relevance of HIPEC in the current therapeutic landscape remains unclear. At the same time, the significance of the various components of HIPEC therapy (cytoreduction, hyperthermia, intraperitoneal chemotherapy, choice of chemotherapeutic agents) must also be clearly defined. As a result, the performance of HIPEC outside of studies cannot be generally supported.

## 9.15.    Interprofessional Management of Symptoms, Side Effects and Toxicities of the Therapy

| 9.41. | Consensus-based Recommendation | 2017 |
|---|---|---|
| EC | Under chemotherapy for metastases and in the palliative situation, assessment of disease- and therapy-induced side effects as well as targeted treatment of symptoms should be performed regularly in all patients. The primary objective is to prolong progression-free and overall survival with otherwise low toxicity and a good quality of life.<br><br>Patients should receive regular instructions on effective self-management of the symptoms. | |
| | Consensus | |

**Background**

Up to 30% of all mCRC patients suffer from disease- and therapy-related toxicities (grade III-IV CTC), particularly diarrhoea, nausea and vomiting, mucositis/stomatitis, constipation and neuropathies ([1221], [1222]). To prevent unintended de-escalation and treatment discontinuations, the occurrence and aggravation of therapy- and disease-related symptoms should be recorded regularly. This can be done with the help of validated assessment instruments, such as the National Cancer Institute Common Toxicity Criteria Scale (NCI-CTC 4.0).

Without systematic monitoring, there is a high risk of final treatment discontinuations of up to 30% due to a persistently high rate of side effects associated with a reduced overall survival, especially in patients aged over 65 years [1223].

Studies confirm the improvement in health-related quality of life [1224], the reduction in symptomatic burden [1225] and the prevention of therapy discontinuations [1226] with a regular assessment of toxicities, side effects and adverse events.

Regarding the management of these aspects, please refer to the guideline „Supportive Therapy in Oncological Patients", AWMF registration number: 032/054OL (http://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/).       The symptomatic therapy should be chosen by taking into account individual patient characteristics (age, gender, comorbidity, symptomatic burden) and the informed patient decision [1052].

Furthermore, there is evidence supporting the efficacy of effective self-assessment, self-management and adequate communication to reduce and prevent symptoms and discomforts [1225], [1227]. For this reason, patients should be given the possibility of receiving regular instruction and training in self-management.

# 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 [1228-1237]. The risk is increased in case of a genetic predisposition [1232] and with advancing tumor stages [1238, 1239]. 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 [1240].

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 [1241]. Data from 267 articles relating to this topic were evaluated in a meta-analysis [1242]. 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 [1242].

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 |
|---|---|---|
| **EC** | 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%) [1243]. 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 1. The pT1N0M0 (UICC Ia) tumors demonstrated 2.9% recurrences and pT2 cancer (UICC Ib) 5.6% recurrences [1244]. In stage Dukes A, recurrences were only seen in patients with rectal cancer (11%, n=6/55), not in colon cancer [1245].

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 periocolonic veins [1246, 1247], angiolymphatic invasion [1248,

1249], G3/G4 tumors or pT2 tumors) (see Chapter 8). Here the sole assessment of CEA was sufficient [1244].

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

Tab. 19

| 10.2. | Recommendation/ Consensus-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**1a** | [1241, 1242, 1250-1259] | |
| | Strong consensus | |

| 10.3. | Consensus-based Recommendation | 2008 |
|---|---|---|
| **EC** | 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 [1228-1239]. There are 6 randomized controlled studies [1254-1259] 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" [1257, 1259]. 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) [1241, 1242, 1250-1253] 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 [1252]. An active follow-up led only to a slight survival benefit of 0.5 to 2% after five years [1237.

A recent Cochrane publication [1260] included 3 other studies in this meta-analysis [1259, 1261, 1262]. 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 [1263]. 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 [1264].

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 [1265].

Definite recommendations on type and frequency of follow-up tests cannot be given, because good studies are missing [1266-1268]. 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 |
|---|---|---|
| **EC** | 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 [1267, 1269]. All participants of the consensus conference agreed on this.

## 10.3.2.   CEA Testing

| 10.5. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**4** | [1257, 1270, 1271] | |
| | Strong consensus | |

**Background**

CEA was shown to be superior to colonoscopy, computer tomography, and ultrasound for the early detection of liver metastases [1257, 1270, 1271]. A meta-analysis of 7 non-randomized studies showed a survival benefit of 9% for patients for whom the follow-up program included CEA [1250]. Other studies showed no or only minimal benefit [1255, 1272]. CEA was not recommended for follow-up in a literature review [1268]. However, American (ASCO) and European (EGTM, European Group on Tumor Markers) follow-up guidelines include the use of CEA [1267, 1269, 1271]. 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 [1273]. 30% of all colorectal tumors do not release CEA [1273, 1274], while 44% of the patients with normal preoperative values show an increase postoperatively [1275]. The further clarification of increased CEA values requires diagnostic imaging and if necessary, 18-fluorodeoxyglucose positron emission tomography [1276, 1277].

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. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | The routine testing of laboratory values in the context of follow-up is not advisable. | |
| Level of Evidence<br><br>**3b** | : [1266, 1269] | |
| | 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 [1266]. For these reasons, a routine testing of these serum parameters is not advised. The same applies for complete blood count [1269].

## 10.3.4.    FOBT

| 10.7. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | The testing for occult blood in the stool is not appropriate for follow-up. | |
| Level of Evidence<br><br>**3b** | [1274, 1278] | |
| | 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 [1274]. 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 [1278].

## 10.3.5.    Ultrasound

| 10.8. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**5** | [1252, 1254, 1268] | |
| | Strong consensus | |

**Background**

The sensitivity of abdominal ultrasound for the detection of liver metastases varies widely between 53% and 82% [1268]. In most studies it was not as accurate as computer tomography. In a controlled, randomized study [1254] 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 [1252]. If the calculation of these results was done as a risk difference and not as an odds ratio, this advantage was no longer detectable [1252]. 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. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**3b** | [1279] | |
| | 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 [1279].. 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 [1279]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**0** | A chest x-ray can be performed annually for patients with stage II and III rectal cancer for five years. | |
| Level of Evidence<br><br>**3b** | de Novo: [1280] | |
| | Consensus | |

**Background**

In a French cohort study 5.8 % of patients developed lung metastases within 5 years after curative resection of CRC [[1280]. 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 metachronic 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**1b** | Evidence from update literature search: [1257, 1258, 1260, 1281-1283] | |
| | 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 [1258]. 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 [1257, 1258, 1283].

An update of the ASCO guideline from 2005 led to the recommendation of annual abdominal CT examinations over 3 years [1281]. The committee justified their decision to recommend the use of abdominal CTs in follow-up exams with the work of Chau et al. [1282]. 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 [1260]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation <br><br> **B** | 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. <br><br> If neoplasia is detected during colonoscopy after 6 or 12 months, further follow-up should be performed according to Chapter 6.5. | |
| Level of Evidence <br><br> **2b** | de Novo: [1253, 1284-1287] | |
| | Strong consensus | |

### 10.3.9.2. Sigmoidoscopy

| 10.13. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation <br><br> **B** | 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. | |
| Level of Evidence <br><br> **4** | Strong consensus | |

### 10.3.9.3. Rectoscopy

| 10.14. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | 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. | |
| Level of Evidence<br><br>**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 [1253]. 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) [1284].. 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 [1285]. 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 [1282. 2-7% of patients had at least one metachronic tumor. It cannot be concluded whether these were real metachronic lesions or whether they were synchronic 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% [1229].. Since the risk of metachronic tumors persists, a colonoscopic follow-up analogous to the screening of colon cancer is indicated [1287].

## 10.3.10.        Colon Contrast Enema, Virtual Colonography, and PET

| 10.15. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**B** | Colon contrast enema, virtual colonography, PET, PET-CT, and PET-MRI should not be part of a follow-up program. | |
| Level of Evidence<br><br>**4** | de Novo: [193, 1288, 1289] | |
| | 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 [1288] 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 [193] 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 wre 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 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 [1289] 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 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 |
|---|---|---|
| **EC** | 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 [1290]. This also applies to rectal cancer, although with this tumor entity a few locoregional recurrences were observed after this period [1235]. 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 [1250, 1251, 1253, 1254. A 3-month interval was found to be superior to a 6-month interval in one study with otherwise similar examination methods [1257]. However, the patients in the 3-month follow-up group received an additional annual CT, which in another study was not beneficial [1258]. 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 [1254-1259] 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. | Evidence-based Recommendation | 2017 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | After complete removal (R0) of low-risk (pT1, low-grade (G1, G2, L0)) cancer, endoscopic surveillance examinations of the local resection site shall be performed after six months.<br><br>A complete colonoscopy shall be performed after three years. | |
| Level of Evidence<br><br>**4** | Strong consensus | |


| 10.18. | Consensus-based Recommendation | 2008 |
|---|---|---|
| **EC** | After palliative tumor resection (R2 resection), programmed follow-up examinations are not necessary. | |
| | Strong consensus | |


| 10.19. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | After curative therapy of metastases, stage IV patients should undergo a programmed follow-up. | |
| | Strong consensus | |


| 10.20. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**2a** | Strong consensus | |

| 10.21. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | For cancer patients with FAP who have undergone proctocolectomy, a pouchoscopy should be performed annually (see also recommendation 5.35.). | |
| Level of Evidence<br><br>**2a** | Strong consensus | |

| 10.22. | Evidence-based Recommendation | 2008 |
|---|---|---|
| Grade of Recommendation<br><br>**A** | After iliorectostomy, a rectoscopy is necessary every 6 months (see also recommendation 5.35.). | |
| Level of Evidence<br><br>**2a** | Strong consensus | |

## 10.7.  Rehabilitation After Resection of Colorectal Cancer

| 10.23. | Consensus-based Recommendation | 2013 |
|---|---|---|
| **EC** | After completing primary therapy, rehabiliation should be offered to all eligible patients. If rehabiliation 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 [1264, 1291, 1292].

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 [1293, 1294]. 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 [1295, 1296]. Studies confirm the advantage for patients of case management by concomitant professional steering of the treatment and follow-up course [1297]. Current systematic reviews show that health care continuity can be optimized especially by care interventions [1298, 1299]. 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 [1297-1300].

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 [1293].

### 10.8.1.2. Continuation of Health Promoting Activities

Patients should be encouraged to continue lifestyle activities 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 [1301, 1302]. 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) [1297, 1299, 1300, 1303]. 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. | Evidence-based Recommendation | 2013 |
|---|---|---|
| Grade of Recommendation<br><br>**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<br><br>**2b** | Evidence from update literature search: [1304-1306] | |
| | Consensus | |

**Background**

Three cohort studies [1304-1306] 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 [1304]. Weight reduction in overweight patients does not reduce the relapse rate [1304]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 [1307]. 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 [1308, 1309]. 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 [1310]. 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 [1311, 1312]. 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 [1312] 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 [1313, 1314]. 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 [1295, 1311. A Cochrane-analysis [1315]  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 v.

### 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 20: 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 |

\*        if a complete colonoscopy was not done pre-operatively

\*\*        if result is negative (no adenoma, no cancer), next colonoscopy after 5 years

\*\*\*        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.

\*\*\*\*        only for rectal cancer without neoadjuvant or adjuvant radiochemotherapy

\*\*\*\*\*        only for rectal cancer an annual chest x-ray may be done

x        only for rectal cancer 3 months after tumor-specific therapy has been completed (operation or adjuvant radiotherapy/chemotherapy) as initial finding

# 11.        Quality Indicators

Quality indicators (QI) are measured variables that serve to evaluate the quality of structures, processes or results they are based on [1316][1312][1282]. Quality-indicators are an important part of quality management. Their aim is to continuously improve the level of care by presenting, critically reflecting on and (where necessary) correcting the results of that care. The quality indicators used in this guideline were selected according to the methodology of the Guideline Program in Oncology [1317]. A working group under the name "WG Quality Indicators" was formed for this purpose. The working group created the final set of quality indicators based on the existing quality indicators of the 2013 guideline, the new strong recommendations (grade of recommendation A, "must/has to") of the updated guideline, the results of the existing quality indicators from the certified colorectal cancer centres of the German Cancer Society[9] and the results from reviews of existing national and international QIs. The exact procedure and the composition of the working group are explained in the Guideline Report. Following a face-to-face meeting and a telephone conference of the working group, 4 new indicators were accepted (QI 1-4). These were added to the 7 existing indicators (QI 5–11), resulting in a final set of 11 quality indicators.

**Table 21: Quality Indicators 2017**

| Quality indicator (The numerator is always a subset of the denominator) | Reference Recommendation | Evidence base/ further information |
|---|---|---|

**QI 1: Recording of family history (new in 2017)**

| **Numerator:** No. of patients who completed the patient questionnaire  **Denominator:** All patients with the initial diagnosis CRC | None  Rationale for this QI:  The analysis of the internationally applied QIs (here in particular ASCO) showed that international QIs for obtaining the family history are described. The guideline group believes this area to be relevant; therefore, this QI is included in the guideline without a strong consensus recommendation. | **Quality objective:**  As often as possible: completed patient questionnaires to record the family history. |

Comment: Patient questionnaire:

https://www.krebsgesellschaft.de/zertdokumente.html?file=files/dkg/deutsche-krebsgesellschaft/content/pdf/Zertifizierung/Erhebungs-

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[9] Available from the German Cancer Society (DKG). Annual report published by the certified colorectal cancer centres. URL: https://www.krebsgesellschaft.de/jahresberichte.html?file=files/dkg/deutsche-krebsgesellschaft/content/pdf/Zertifizierung/Jahresberichte%20mit%20DOI%20und%20ISBN/dz_jahresbericht-2017-A1_170616.pdf

| Quality indicator (The numerator is always a subset of the denominator) | Reference Recommendation | Evidence base/ further information |
|---|---|---|
| %20und%20Kennzahlenboegen/PatientenFragebogen%20familiaerer%20Darmkrebs%20%2803032017%29.pdf | | |

**QI 2: Complete report after tumour resection in CRC (new in 2017)**

| | | |
|---|---|---|
| **Numerator:** Number of patients with a report containing details of: <br>• Tumour type according to WHO classification <br>• Tumour invasion depth (pT classification) <br>• Regional lymph node status (pN classification) <br>• Number of lymph nodes examined <br>• Grading <br>• Distance from the resection margins (for rectal cancer, also circumferential) <br>• R-classification <br><br>**Denominator:** All patients with CRC and surgical resection | 7.58. <br><br>The following data are obligatory components of the pathology report: <br>• Tumour type according to WHO classification (level of evidence 1c) <br>• Tumour invasion depth (pT classification) (level of evidence 1c) <br>• Regional lymph node status (pN classification) (level of evidence 1c) <br>• Number of lymph nodes examined (level of evidence 2a) <br>• Grading (level of evidence 2a) <br>• Distance from the resection margins (for rectal cancer, also circumferential) (level of evidence 2a) <br>• R-classification (level of evidence 1c) | GoR A <br><br>**Quality objective:** <br>As often as possible: Complete reports following tumour resection for CRC. |

**QI 3: Mutation determination in mCRC (new in 2017)**

| | | |
|---|---|---|
| **Numerator:** Number of patients in whom the RAS (= KRAS and NRAS mutations) and BRAF mutation was determined at the start of first-line therapy <br><br>**Denominator:** All patients with mCRC and first-line therapy | 9.4. <br><br>Where possible, (All) RAS and BRAF mutations should be determined prior to initiating first-line therapy. | GoR A, LoE 1 <br><br>**Quality objective:** <br>As often as possible: Mutation determination prior to first-line therapy in mCRC. |

| Quality indicator (The numerator is always a subset of the denominator) | Reference Recommendation | Evidence base/ further information |
|---|---|---|

| Comment: |
|---|
| Determination "at baseline" = date of mutation determination max. +15d from the start date of first-line therapy |

### QI 4: Combination chemotherapy in mCRC (new in 2017)

| **Numerator:** Number of patients with combination chemotherapy

**Denominator:** All patients with mCRC, ECOG 0-1 and systemic first-line therapy. | 9.24. In first-line chemotherapy, and under the condition of good overall health and high motivation, a fluoropyrimidine-based combination regimen with infusions of 5-fluorouracil, such as FOLFIRI, FOLFOX or FOLFOXIRI, or with the oral fluoropyrimidine capecitabine (mainly with oxaliplatin, CAPOX) should primarily be used. | **GoR A, LoE 1a**

**Quality objective:** As often as possible: Combination therapy in the first-line therapy of patients with mCRC, ECOG 0-1. |
|---|---|---|

### QI 5: Report on distance to the mesorectal fascia (since 2013, formerly: CRC 1)

| **Numerator:** All patients with documented distance to the mesorectal fascia in the report.

**Denominator:** All patients with rectal cancer and MRI or thin-layer CT of the pelvis. | 7.17. The report should include information on the distance to the mesorectal fascia. | EC (Expert Consensus)

**Quality objective:** As often as possible: Details of the distance to the mesorectal fascia if MRI/CT was carried out in rectal cancer. |
|---|---|---|

### QI 6: Quality of TME (since 2013, formerly: CRC 3)

| **Numerator:** Number of all patients with good or moderate quality (grade 1: mesorectal fascia intact or | 7.66. Since the quality of the surgical resection according to the above-mentioned categories allows conclusions on the prognosis concerning the development of local recurrence, this shall be | EC (Expert Consensus)

**Quality objective:** |
|---|---|---|

| Quality indicator (The numerator is always a subset of the denominator) | Reference Recommendation | Evidence base/ further information |
|---|---|---|
| grade 2: intramesorectal tears) TME.<br><br>**Denominator:**<br>All patients with radically operated rectal cancer. | described in the pathohistological report as follows<br><br>The quality of the resection specimen is assessed by the integrity of the mesorectal fascia in the three categories<br><br>• mesorectal fascia is intact<br>• intramesorectal tears<br>• tears down to the muscularis propria or the tumour.<br><br>In case of rectal extirpation, preparation tears and tumour positive circumferential safety margins are not as frequent with a complete resection of the<br><br>levator musculature.<br><br>Therefore, the pathohistological report shall describe the radicality in the levator musculature region. The following categories have to be used:<br><br>Parts of the muscularis propria are missing or opening of the intestine or tumour<br><br>Muscularis propria intact, no opening of the intestine or tumour<br><br>Levator musculature included in resection, no opening of the intestine or tumour<br><br>The analysis shall be performed by a pathologist. | As often as possible: Good or moderate quality of TME in rectal cancer. |

| Quality indicator (The numerator is always a subset of the denominator) | Reference Recommendation | Evidence base/ further information |
|---|---|---|

**QI 7: Presentation in tumour conference (since 2013, formerly: CRC 5)**

| | | |
|---|---|---|
| **Numerator:** Number of patients who were presented in an interdisciplinary tumour conference before therapy. **Denominator:** All patients with rectal cancer and all patients with stage IV colon cancer. | 7.1. All CRC patients should be presented in an interdisciplinary tumour conference after they have completed their primary therapy (e.g. operation, chemotherapy). Patients with the following constellations should already be presented before therapy: Denominator - every rectal cancer - every stage IV colon cancer - metachronous distant metastases - local recurrence - before every local ablative procedure, e.g. RFA/LITT/SIRT | EC (Expert Consensus) **Quality objective:** As often as possible: Presentation of patients with rectal cancer and of patients with stage IV colon cancer in the pretherapeutic tumour conference. |

**QI 8: Adjuvant chemotherapy (since 2013, formerly: CRC 6)**

| | | |
|---|---|---|
| **Numerator:** Number of patients who have undergone adjuvant chemotherapy. **Denominator:** All patients with colon cancer UICC stage III who have had an R0 resection of the primary tumour. | 8.4 For patients with R0 resected stage III colon cancer, adjuvant therapy is indicated. | Recommendation LoE 1a, strong consensus **Quality objective:** Adequate performance of adjuvant chemotherapy after R0 resection in stage III colon cancer. |

**QI 9: Anastomotic leakage in rectal cancer (since 2013, formerly: CRC 8)**

| | | |
|---|---|---|
| **Numerator:** Number of patients with anastomotic leakage grade B (with | None Rationale for this QI: **Comment:** | No evidence basis to support a strong recommendation, since this indicator was not derived from a recommendation. |

| Quality indicator (The numerator is always a subset of the denominator) | Reference Recommendation | Evidence base/ further information |
|---|---|---|
| administration of antibiotics or interventional drainage or transanal lavage/drainage) or C ((re-)-laparotomy) after elective interventions.<br><br>**Denominator:**<br><br>All patients with rectal cancer with creation of an anastomosis during elective primary tumour resection. | 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 quality indicator is included in the guideline without strong consensus recommendation. | **Quality objective:**<br><br>As seldom as possible: Grade B or C anastomotic leakage following the creation of an anastomosis during surgery to treat rectal cancer. |

**QI 10: Anastomotic leakage in colon cancer (since 2013, formerly: CRC 9)**

| | | |
|---|---|---|
| **Numerator:**<br><br>Number of patients with anastomotic leakage requiring re-intervention after elective interventions.<br><br><br>**Denominator:**<br><br>All patients with colon cancer with creation of an anastomosis during elective tumour resection. | None<br><br>Rationale for this QI:<br><br>**Comment:**<br><br>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 quality indicator is included in the guideline with strong consensus recommendation. | No evidence basis to support a strong recommendation, since this indicator was not derived from a recommendation.<br><br><br>**Quality objective:**<br><br>As seldom as possible: Grade D anastomotic leakage requiring re-intervention following the creation of an anastomosis during surgery to treat colon cancer. |

**QI 11: Marking of stoma position (since 2013, formerly: CRC 10)**

| | | |
|---|---|---|
| **Numerator:**<br><br>Number of patients with preoperatively marked stoma position<br><br><br>**Denominator:**<br><br>All patients with rectal cancer who have had surgery with stoma construction | 7.42.<br><br> The stoma position has to be marked preoperatively. | EC<br><br>(Expert Consensus)<br><br><br>**Quality objective:**<br><br>As often as possible: Preoperatively marked stoma position. |

# 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 22: 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 [236, 1318]** |

| | |
| :--- | :--- |
| 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). |

## 12.4. Changes to the Recommendations Due to the 2017 and 2019 Updates

| Version 2.0 (2017) | Version 2.1 (2019) |
|---|---|
| | A) In the adjuvant setting the accumulating (neuro-)toxicity shall be weighed against the therapeutic benefit.<br><br>B) In case of a low risk of recurrence (T1-3 N1) therefore a combination of oxaliplatin and capecitabine (CAPOX/XELOX) should be given for three months. |
| | Patients with a high risk of recurrence (T4 or N2) should continue to receive an oxaliplatin-based therapy (FOLFOX or CAPOX/XELOX) for 6 months. |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| **Chapter 6.1. Role of Endoscopy in the Diagnostics of Polyps and Colorectal Cancer** | |
| 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.<br><br>(2008: Recommendation 6.2.) | If a colonoscopy was incomplete due to a stenosing tumour, an additional preoperative CT colonography can be performed.<br><br>A complete colonoscopy should be conducted postoperatively.<br><br>(2017: Recommendation 6.2.) |
| If a colonoscopy was incomplete due to other causes (e. g. adhesions), a CT or MR colonography should be performed.<br><br>(2008: Recommendation 6.3.) | If a colonoscopy was incomplete due to other causes (e. g. adhesions), a CT colonography should be performed.<br><br>(2017: Recommendation 6.3.) |
| In case of a positive FOBT, suspicion of a tumor, or sigmoidoscopic evidence of neoplastic polyps a full colonoscopy has to be performed.<br><br>(2008: Recommendation 6.4.) | In case of a positive FOBT/<u>FIT test</u>, suspicion of a tumour, or sigmoidoscopic evidence of neoplastic polyps, a full colonoscopy has to be performed.<br><br>(2017: Recommendation 6.4.) |
| 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. | Chromoendoscopy can be performed in patients with chronic inflammatory bowel disease and HNPCC for improved detection of neoplastic lesions.<br><br>(2017: Recommendation 6.5.) |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| (2008: Recommendation 6.5.) | |
| The use of magnifying endoscopy with evaluation of lesions according to the "pit pattern" classification is not a standard procedure at this time.<br><br>(2008: Recommendation 6.6.) | deleted |
| **Section 6.2. Polypectomy** | |
| 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.<br><br>In general, diagnostic colonoscopies should only be performed if the possibility of performing a polypectomy using a snare is given.<br><br>(2008: Recommendation 6.8.) | To obtain a representative histological specimen and achieve a definitive therapy, polyps >5 mm should be completely removed using a snare.<br><br>In general, diagnostic colonoscopies should only be performed if the possibility of performing a polypectomy using a snare is given in the same session.<br><br>(2017: Recommendation 6.7.) |
| **Section 6.3. Histological Examination** | |
| The histological examination of each polyp is obligatory. The histological reporting of polyps should follow WHO criteria [568] 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) [569, 570].<br><br>(2008: Recommendation 6.9.) | The histological examination of each polyp is mandatory. The histological reporting of polyps <u>shall</u> follow WHO criteria [568 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 intraepithelial neoplasia (low- and high-grade intraepithelial neoplasia); serrated lesions are subclassified as hyperplastic polyps, sessile serrated adenomas, <u>mixed</u> polyps (with IEN grade) and traditional, serrated adenomas (with IEN grade) [569, 570].<br><br> (2017: Recommendation 6.8.) |
| | The extent of tumour budding can be rated as an additional parameter.<br><br>(2017: Recommendation 6.10.) |
| | Tumour cell budding greater than 1 can also be rated as "high-risk".<br><br>(2017: Recommendation 6.12.) |
| **Section 6.4. Approach for pT1 Cancer** | |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| 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) [589, 1319-1321]. In the high-risk situation, radical surgical therapy is required, even if the lesion has been completely removed.<br><br>(2008: Recommendation 6.12.) | 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). In the high-risk situation, radical surgical therapy shall be performed, even if the lesion has been completely removed.<br><br>(2017: Recommendation 6.13.) |
| With incompletely removed low-risk pT1 cancer, a complete endoscopic or local surgical removal has to follow [589, 1319-1321]. If an R0 situation cannot be achieved or it is doubtful that a pT1 situation exists, an oncological-surgical resection is necessary.<br><br>(2008: Recommendation 6.13.) | With incompletely removed low-risk pT1 cancer, a complete endoscopic or local surgical removal has to follow. If an R0 situation cannot be achieved or it is doubtful that a pT1 situation exists, an oncological-surgical resection shall be performed.<br><br>(2017: Recommendation 6.14.) |
| 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.<br><br>(2008: Recommendation 6.14.) | 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.<br><br>Complete colonoscopy should be performed after three years.<br><br>(2017: Recommendation 6.15.) |
| **Section 6.5. Polyp Management (Follow-Up)** | |
| After removal of small single, non-neoplastic polyps, there is no necessity for endoscopic surveillance.<br><br>(2008: recommendation 6.15.)) | After removal of small single, non-neoplastic polyps, no endoscopic surveillance should be performed.<br><br>(2017: Recommendation 6.16.) |
| 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.<br><br>(2008: Recommendation 6.16.) | The timing of the surveillance colonoscopy after complete removal of neoplastic polyps (adenomas) shall depend on the number, size and histology of the removed adenomas.<br><br>(2017: Recommendation 6.17.) |
| | For patients who have 1 or 2 adenomas <1 cm without higher-grade intraepithelial neoplasia, a |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| | surveillance colonoscopy should follow after 5-10 years.<br><br>(2017: Recommendation 6.18.) |
| | If, however, no or only 1-2 adenomas <10 mm without a mostly villous histology or HGIEN are discovered during this surveillance colonoscopy, the next surveillance colonoscopy should follow after 10 years.<br><br>(2017: Recommendation 6.19.) |
| 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.<br><br>(2008: Recommendation 6.17.) | For patients who have 3-4 adenomas, or one adenoma that is ≥1 cm, or an adenoma with a mostly villous histology or HGIEN, the first surveillance colonoscopy should follow after 3 years.<br><br>(2017: Recommendation 6.20.) |
| For patients with adenomas with high-grade intra-epithelial neoplasia and histologically-confirmed complete removal, a surveillance colonoscopy after three years is sufficient.<br><br>(2008: Recommendation 6.18.) | For patients with adenomas with high-grade intraepithelial neoplasia and histologically confirmed complete removal, a surveillance colonoscopy should be performed after three years.<br><br>(2017: Recommendation 6.21.) |
| With histologically non-confirmed complete removal, even if macroscopically the removal was complete, an early (2-6 months later) control should be performed.<br><br>(2008: Recommendation 6.19.) | With histologically non-confirmed complete removal of adenomas >5 mm, even if macroscopically the removal was complete, a control should be performed after 6 months.<br><br>(2017: Recommendation 6.22.) |
| 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).<br><br>(2008: Recommendation 6.20.) | In case of ≥5 adenomas of any size, the control interval should be <3 years.<br><br>(2017: Recommendation 6.23.) |
| 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.<br><br>(2008: Recommendation 6.21.) | After removal of large adenomas in piecemeal technique, a short-term control of the removal area shall follow after 2-6 months.<br><br>(2017: Recommendation 6.24.) |
| | After complete removal of a traditional serrated adenoma or sessile serrated adenoma, the |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| | follow-up should follow that of classic adenomas.<br><br>(2017: Recommendation 6.25.) |
| 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.<br><br>(2008: Recommendation 6.22.) | deleted |
| **Section 8.1. Adjuvant Therapy of Colorectal Cancer** | |
| There is no age limitation for performing adjuvant chemotherapy; general contraindications (see above) should be considered.<br><br>(2008: Recommendation 8.1.) | Adjuvant therapy should not be omitted solely for reasons of age. However, there is insufficient evidence to support the performance of adjuvant chemotherapy in patients aged over 75 years.<br><br>(2017: Recommendation 8.1.) |
| | Adjuvant chemotherapy should be initiated as soon as possible postoperatively.<br><br>(2017: Recommendation 8.2.) |
| | In the randomised studies, adjuvant chemotherapy was initiated within 8 weeks.<br><br>(2017: Recommendation 8.3.) |
| For patients with R0 resected stage III colon cancer, adjuvant therapy is indicated.<br><br>(2008: Recommendation 8.2.) | For patients with R0 resected stage III colon cancer, adjuvant chemotherapy shall be carried out.<br><br>(2017: Recommendation 8.4.) |
| 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.<br><br>(2008: Recommendation 8.5.) | For patients with stage II, the microsatellite status has to be determined prior to establishing an indication for adjuvant chemotherapy. Further parameters (e.g. level of CEA protein, level of differentiation of the tumour, 18q loss, isolated tumour cells in lymph nodes or in bone marrow, DNA ploidy and TS/p53 expression, lymph and blood vessel invasion, molecular genetic analyses) shall not be used as an indication for adjuvant chemotherapy.<br><br>(2017: Recommendation 8.7.) |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| | If microsatellite instability (MSI-H) is present, adjuvant chemotherapy should not be performed in stage II.<br><br>(2017: Recommendation 8.8.) |
| | Oxaliplatin-based therapy should not be performed in patients aged over 70 years.<br><br>(2017: Recommendation 8.10.) |
| | Monoclonal antibodies or irinotecan shall not be used in the adjuvant therapy of colon cancer.<br><br>(2017: Recommendation 8.12.) |
| If patients with stage II tumors have adjuvant chemotherapy, fluoropyrimidines can be administered as monotherapy.<br><br>(2008: Recommendation 8.8.) | If patients with stage II tumours have adjuvant chemotherapy, fluoropyrimidines should be administered as monotherapy.<br><br>(2017: Recommendation 8.13.) |
| **Section 8.2. Perioperative Therapy of Rectal Cancer** | |
| Perioperative therapy is not indicated for stage I tumors.<br><br>(2008: Recommendation 8.9.) | Preoperative therapy should not be performed in UICC stage I (cT1-2N0).<br><br>(2017: Recommendation 8.14.) |
| 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.<br><br>(2008: Recommendation 8.10.) | For UICC stages II and III (cT3/4 and/or cN+) neoadjuvant radiochemotherapy or short-term radiotherapy should be performed for tumours in the lower and middle third of the rectum.<br><br>(2017: Recommendation 8.15.) |
| | Primary resection can be performed in patients with rectal cancer in UICC stage II/III in the following exceptions:<br><br>cT1/2 tumours in the lower and middle third with potential lymph node involvement in imaging procedures<br><br>cT3a/b tumours in the middle third with only limited infiltration into perirectal adipose tissue on the MRI (cT3a: <1 mm, cT3b: 1-5 mm) and without suspected lymph node metastases or extramural vascular invasion (EMVI) in imaging procedures with adequate quality assurance of the MRI diagnostics and TME surgery.<br><br>(2017: Recommendation 8.16.) |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| | The radial distance of the primary tumour measured in the thin-layer MRI (or lymph node involvement in imaging procedures) from the mesorectal fascia (mrCRM) shall not be used as a deciding factor for primary surgery outside of studies.<br><br>(2017: Recommendation 8.17.) |
| 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.<br><br>(2008: Recommendation 8.11.) | Rectal cancer in the upper third without a risk constellation for a local relapse for a local relapse shall be treated by primary surgery and receive adjuvant therapy as for colon cancer.<br><br>(2017: Recommendation 8.18.) |
| | In case of a risk constellation in the upper third of the rectum (e.g. T4, mrCRM+, definite and extensive lymph node involvement in imaging procedures) preoperative radio(chemo)therapy can be performed.<br><br>(2017: Recommendation 8.19.) |
| | Neoadjuvant radiotherapy can be performed either as short-term radiation with 5x5 Gy followed by immediate surgery or as conventional fractionated radiochemotherapy (1.8-2.0 Gy to 45-50.4 Gy) at intervals of 6-8 weeks until surgery is performed.<br><br>(2017: Recommendation 8.20.) |
| 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), preoperative 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.<br><br>(2008: Recommendation 8.12.) | For T4 tumours, proximity of the tumour to the mesorectal fascia (<1-2 mm) or deep tumours with intended sphincter retention, preoperative radiochemotherapy should be performed.<br><br>(2017: Recommendation 8.21.) |
| | For patients in whom downsizing of the tumour is attempted, short-term radiotherapy with a longer interval of up to 12 weeks to surgery (with and without neoadjuvant chemotherapy) can be performed.<br><br>(2017: Recommendation 8.22.) |
| Neoadjuvant radiochemotherapy should include 5-Fluorouracil monochemotherapy with or without folinic acid.<br><br>(2008: Recommendation 8.13.) | Neoadjuvant radiochemotherapy should include oral capecitabine or infusional 5-fluorouracil.<br><br>(2017: Recommendation 8.23.) |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| | Surgery should be performed 6-8 weeks after neoadjuvant radiochemotherapy.<br><br>(2017: Recommendation 8.24.) |
| | After short-term radiotherapy (5x5 Gy), surgery should be performed either within 10 days after starting radiotherapy or after 4-8 weeks.<br><br>(2017: Recommendation 8.25.) |
| | Neoadjuvant chemotherapy before or after radiochemotherapy (or as neoadjuvant therapy alone without radio(chemo)therapy) should not be performed outside of studies.<br><br>(2017: Recommendation 8.26.) |
| | Short-term RT with 5x5 Gy followed by neoadjuvant chemotherapy and surgery within a reasonable period can be performed for synchronous metastases.<br><br>(2017: Recommendation 8.27.) |
| **Section 8.2.2. Adjuvant Therapy** | |
| In stage I, adjuvant therapy is not indicated after a R0-resection.<br><br>(2008: Recommendation 8.14.) | In UICC stage I (pT1/2N0) R0 resection should not be followed by adjuvant therapy.<br><br>(2017: Recommendation 8.28.) |
| After a R1-resection or intraoperative tumor tears, a postoperative radiochemotherapy should be conducted unless neoadjuvant radio(chemo)therapy has been performed previously.<br><br>(2008: Recommendation 8.16.) | In case of histopathologically confirmed risk factors for a locoregional relapse (e.g. R1 resection, intraoperative tumour tears, pCRM+, insufficient TME quality, pT4, pT3c/d, pN2, extranodal tumour growth in the mesorectum, pT3 in the lower third of the rectum) adjuvant radiochemotherapy should be performed.<br><br>(2017: Recommendation 8.29.) |
| Patients with UICC stage II and III, who have not undergone neoadjuvant radiochemotherapy or short-term radiotherapy, should receive adjuvant radiochemotherapy.<br><br>(2008: Recommendation 8.15.) | If no adjuvant radiochemotherapy is performed after primary R0 resection in stage II/III, adjuvant chemotherapy should be performed as per the indication criteria and regimens for colon cancer.<br><br>(2017: Recommendation 8.30.) |
| | A recommendation for or against adjuvant chemotherapy following neoadjuvant |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
|  | radiochemotherapy cannot be given on the basis of the available data for rectal cancer.<br><br>(2017: Recommendation 8.31.) |
| Adjuvant therapy should begin 4-6 weeks after the operation.<br><br>(2008: Recommendation 8.17.) | deleted |
| Radiation therapy can take place at the same time as the first and second chemotherapy cycle or as the third and fourth cycle.<br><br>(2008: Recommendation 8.18.) | deleted |
| Radiation therapy should be combined with 5-FU monochemotherapy.<br><br>(2008: Recommendation 8.19.) | deleted |
| 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.<br><br>(2008: Recommendation 8.20.) | deleted |
| 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).<br><br>(2008: Recommendation 8.21.) | deleted |
| Adjuvant chemotherapy should either be conducted as a 5-FU monotherapy or as a combination with 5-FU/folinic acid.<br><br>(2008: Recommendation 8.22.) | deleted |
| **Section 9.1. Treatment Strategy (2017 version)** | |
|  | In principle, patients should have access to all treatment modalities, preferably at certified sites, during the course of their disease.<br><br>(2017: Recommendation 9.1.) |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
|  | If an indication for tumour 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. |
|  | To enable the choice of the optimal first-line therapy, a decision algorithm can be applied to assign the patients to defined treatment groups. Three decision-making levels can be distinguished:<br><br>Overall health (tolerability of intensive therapy)<br><br>Disease spread including localisation (therapeutic options are governed by the possibility of resectability or locoregional intervention)<br><br>Molecular biology of the tumour (definition of the optimal targeted therapy) |
| **Section 9.2. Initial Molecular Biological Diagnostics Prior to Commencing Therapy (2017 version)** | |
|  | Where possible, (ALL) RAS and BRAF mutations should be determined prior to initiating first-line therapy.<br><br>(2017: Recommendation 9.4.) |
|  | The RAS mutation status can be determined either in primary tumour tissue or in metastases. If the RAS mutation status cannot be determined in the tissue, consideration can be given to determining the RAS mutation status in the blood of circulating tumour DNA.<br><br>(2017: Recommendation 9.5.) |
| **Section 9.3. Pharmacogenetic Diagnostics Prior to First-Line Therapy (2017 version)** | |
|  | The regular determination of **UGT1A1** prior to palliative CTX with irinotecan is not recommended. It can, however, be determined, especially in Gilbert syndrome or other bilirubin conjugation disorders.<br><br>(2017: Recommendation 9.6.) |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| | Determining the DPD deficiency is a diagnostic option prior to fluoropyrimidine therapy. The regular evaluation of DPYD*2A polymorphism can be performed.<br><br>(2008: Recommendation 9.7.) |
| **Section 9.6. Treatment of Patients Without an Indication for Intensified Therapy (2017 version)** | |
| | For primarily resectable metastases, the patient's ability to undergo surgery should be determined. If primary surgery is not an option, the practicability of surgery / resectability should be verified in regular follow-ups (e.g. every 8 weeks).<br><br>(2017: Recommendation 9.8.) |
| | Primarily palliative, symptomatic therapy has priority in patients with a reduced overall condition that precludes intensive chemotherapy.<br><br>Initial therapy with fluoropyrimidine + bevacizumab or dose-reduced doublet chemotherapy (+/- bevacizumab) can be performed. In case of RAS-WT tumours in the left hemicolon (from the left flexure) or in the rectum, anti-EGFR monotherapy can be additionally performed.<br><br>(2017: Recommendation 9.9.) |
| | If the poor overall condition is caused mainly by the cancer, intensification therapy can also be performed primarily in patients with a poor performance status (ECOG >1) after assessing all risks.<br><br>(2017: Recommendation 9.10.) |
| **Section 9.7. Treatment of Patients with an Indication for Intensified Systemic Therapy (2017 version)** | |
| In general, patients should have access to all available drugs during the course of their therapy.<br><br>(2008: Recommendation 9.11.) | In general, patients should have access to the most effective and still tolerable therapy. If there is a curative objective and no restrictions regarding the (potential) choice of therapy, the following parameters should in principle be considered in the decision-making process to determine the optimal multimodal approach: |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
|  | surgical criteria (practicability of surgery, resectability including local ablative procedures) prognostic criteria (2017: Recommendation 9.11.) |
| Resectable pulmonary metastases should be resected. (2008: Recommendation 9.1.) R0-resectable metastases limited to the liver should be resected. (2008: Recommendation 9.2.) | Primary resection of metastases should be performed for resectable tumour manifestations and favourable prognostic criteria. (2017: Recommendation 9.12.) |
| The resectability of metastases should be evaluated by a surgeon with considerable experience in the surgery of liver metastases. (2008: Recommendation 9.3.) | The evaluation should be performed by a tumour board with the involvement of a surgeon with considerable experience in the surgery of metastases. (2017: Recommendation 9.13.) |
|  | Primary systemic therapy can be performed for primarily resectable tumours and unfavourable prognostic criteria (e.g. brief disease-free interval or synchronous metastases). (2017: Recommendation 9.14.) |
|  | If disease stabilisation can be achieved by systemic therapy, resection should be performed promptly (i.e. after 2-3 months). (2017: Recommendation 9.15.) |
|  | Small metastases (≤1 cm) can be removed primarily, as they may possible otherwise during initial chemotherapy and would no longer be identifiable by the surgeon intraoperatively. (2017: Recommendation 9.16.) |
| Neoadjuvant systemic therapy of resectable liver metastases can be considered in founded exceptional cases. (2008: Recommendation 9.6.) | Neoadjuvant therapy of primarily resectable liver metastases should not be performed. (2017: Recommendation 9.17.) |
|  | Owing to insufficient evidence, the question of whether the segments in which metastases are no longer detectable also have to be resected in liver resection following chemotherapy can currently not be answered definitively. |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
|  | (2017: Recommendation 9.18.) |
| After R0 resection of synchronous or metachronous liver metastases, adjuvant chemotherapy can be considered.<br><br>(2008: Recommendation 9.7.) | Adjuvant/additive chemotherapy should not be performed after resection of metastases.<br><br>(2017: Recommendation 9.19.) |
| For primarily irresectable pulmonary metastases, systemic chemotherapy should be conducted.<br><br>(2008: Recommendation 9.12.) | For primarily unresectable tumours, systemic tumour therapy should be performed first. Depending on the tumour and patient characteristics, the most effective available therapy should be used at the start of treatment.<br><br>(2017: Recommendation 9.20.) |
| Active systemic tumor therapy is generally indicated, because a survival benefit has been proven.<br><br>(2008: Recommendation 9.8.) | deleted |
| 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.<br><br>(2008: Recommendation 9.9.) | deleted |
| 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.<br><br>(2008: Recommendation 9.10.) | deleted |
| 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).<br><br>(2008: Recommendation 9.13.) |  |

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| 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.<br><br>(2008: Recommendation 9.14.) | |
| 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.<br><br>(2008: Recommendation 9.15.) | |
| 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.<br><br>(2008: Recommendation 9.16.) | Deleted in section 9.1, but retained in section 7.5.2.3 |
| 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.<br><br>(2008: Recommendation 9.17.) | Deleted in section 9.1, but retained in section 7.5.2.3 |
| A LITT for the treatment of CRC liver metastases should only be performed as part of a clinical trial.<br><br>(2008: Recommendation 9.18.) | Deleted in section 9.1, but retained in section 7.5.2.3 |
| **Section 9.8. Selection of Systemic Therapy Depending on the Molecular Biological Subgroup and the Tumour Localisation (2017 version)** | |
| | Patients found to have a RAS wild type (RAS-wt) in an extended RAS analysis (KRAS and NRAS, exons 2-4) and with a left-sided primary tumour (colon cancer) should preferably be treated with doublet chemotherapy plus anti-EGFR therapy in the first-line therapy of the metastatic disease.<br><br>(2017: Recommendation 9.21.) |
| | Doublet chemotherapy should be used primarily in patients with a RAS mutation. Whether triplet therapy is better than doublet therapy or |

| Version 1 (2013) | Version 2 (2017) |
|---|---|
| | whether bevacizumab should be used has not been confirmed.<br><br>(2017: Recommendation 9.22.) |
| | Patients with a BRAF mutation should primarily receive the most effective chemotherapy, e.g. triplet therapy, or be enrolled in a clinical study.<br><br>(2017: Recommendation 9.23.) |
| **Section 9.9. Performance of First-Line Chemotherapy (2017 version)** | |
| 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).<br><br>(2008: Recommendation 9.19.) | |
| 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.<br><br>(2008: Recommendation 9.20.) | |
| 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.<br><br>(2008: Recommendation 9.21.) | |
| | In first-line chemotherapy, and under the condition of good overall health and high motivation, a fluoropyrimidine-based combination regimen with infusions of 5-fluorouracil, such as FOLFIRI, FOLFOX or FOLFOXIRI, or with the oral fluoropyrimidine capecitabine (mainly with oxaliplatin, CAPOX) should be used primarily.<br><br>(2017: Recommendation 9.24.) |
| | The combination with an effective substance (anti-EGFR or anti-VEGF) should be based |

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|---|---|
| | primarily on the main therapeutic goals, the molecular biological tumour characteristics and the tumour localisation. Therapeutic decisions should be based first and foremost on the treatment that can achieve the longest overall survival with acceptable tolerability.<br><br>(2017: Recommendation 9.25.) |
| | In patients with a reduced overall condition, chemotherapy with fluoropyrimidine monotherapies (5-fluorouracil/folinic acid or capecitabine) can usually be used in combination with bevacizumab.<br><br>(2017: Recommendation 9.26.) |
| | FOLFOXIRI ranks among the most effective chemotherapy regimens, but should only be used in patients with a good overall condition (ECOG performance status 0-1) owing to its increased risk of side effects.<br><br>(2017: Recommendation 9.27.) |
| | The addition of anti-EGFR antibodies (cetuximab or panitumumab) to chemotherapy significantly increases the effectiveness in relation to ORR, PFS and OS. Anti-EGFR antibodies should only be given if an all-RAS wild type in the tumour is confirmed.<br><br>(2017: Recommendation 9.28.) |
| | According to a meta-analysis of the study data, the addition of bevacizumab to an infusional combination chemotherapy significantly increases the effectiveness in relation to PFS, but not to ORR and OS. On the other hand, the addition of bevacizumab to monochemotherapy with a fluoropyrimidine significantly increases the effectiveness in relation to ORR, PFS and OS.<br><br>(2017: Recommendation 9.29.) |
| | Combination therapy with an anti-EGFR antibody plus a VEGF signalling pathways inhibitor should not be used.<br><br>(2017: Recommendation 9.30.) |
| | Where possible, oxaliplatin-based induction therapy (FOLFOX, CAPOX, FOLFOXIRI) should be |

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| | performed over a period of 4-6 months before de-escalating to oxaliplatin-free therapy.<br><br>Not only allergic reactions, but also the development of peripheral polyneuropathy, the incidence and severity of which increases with the cumulative dose of oxaliplatin, is a limiting factor for the use of oxaliplatin.<br><br>(2017: Recommendation 9.31.) |
| There is not sufficient evidence to justify stopping an initiated systemic chemotherapy before disease progression has occurred.<br><br>(2008: Recommendation 9.22.) | After induction chemotherapy, the treatment can be paused or de-escalated to maintenance therapy.<br><br>(2017: Recommendation 9.32.) |
| **Section 9.10. Second-Line Therapy (2017 version)** | |
| | Second-line therapy is usually markedly less effective than first-line therapy. Within the scope of the sequential use of active substances, the choice of second-line therapy should be based primarily on the effectiveness and side effects of the prior therapy.<br><br>(2017: Recommendation 9.33.) |
| **Section 9.11. Therapy Sequence (2017 version)** | |
| | In patients with RAS wild type tumours, the localisation of the primary tumour is an important determinant in the evaluation of the optimal therapy sequence. In patients with left-sided mCRC and RAS wild type, first-line therapy should include the use of an anti-EGFR antibody in combination with chemotherapy. In this constellation, anti-VEGF therapy is only considered in the context of second-line therapy.<br><br>(2017: Recommendation 9.34) |
| | In patients with right-sided mCRC and RAS wild type, no anti-EGFR antibodies should be used in combination with chemotherapy in first-line therapy. |

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| | (2017: Recommendation 9.35.) |
| **Section 9.12. Chemotherapy in Later Lines of Therapy (2017 version)** | |
| | Trifluridine/tipiracil should be used in patients who have received all available chemotherapies/ antibodies or in whom these are not indicated.<br><br>(2017: Recommendation 9.36.) |
| | Regorafenib can be used in patients previously treated with all available chemotherapies/ antibodies.<br><br>(2017: Recommendation 9.37.) |
| **Section 9.13. Local Ablative Procedures (2017 version)** | |
| | Local ablative procedures can be performed if non-resectable metastases are present or if the patient's overall condition does not allow resection, especially following prior resection of liver metastases.<br><br>(2017: Recommendation 9.38.) |
| **Section 9.14. Locoregional Procedures (Version 2017)** | |
| | SIRT can be used to treat disseminated liver metastases of CRC in patients who have no other equivalent therapeutic option.<br><br>(2017: Recommendation 9.39.) |
| 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:<br><br>• PCI (peritoneal cancer index) < 20<br>• No extraabdominal metastases<br>• Possibility of macroscopic complete removal or destruction of all tumor manifestations<br>• Therapy at a specialised centre<br><br>These procedures should preferably be performed as part of a trial. | For patients with isolated and limited peritoneal carcinosis, a cytoreductive operation with subsequent hyperthermal intraperitoneal chemotherapy (HIPEC) can be performed if the following criteria are fulfilled:<br><br>• PCI (peritoneal cancer index) <20<br>• No extraabdominal metastases<br>• Possibility of macroscopic complete removal or destruction of all tumour manifestations<br>• Therapy at a specialised centre<br><br>HIPEC should be performed as part of a study. (2017: Recommendation 9.40.) |
| **Section 9.15. Interprofessional Management of Symptoms, Side Effects and Toxicities of the Therapy** | |

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| | Under chemotherapy for metastases and in the palliative situation, assessment of disease- and therapy-induced side effects as well as targeted treatment of symptoms should be performed regularly in all patients. The primary objective is to prolong progression-free and overall survival with otherwise low toxicity and a good quality of life.<br><br>Patients should receive regular instruction on effective self-management of the symptoms.<br>(2017: Recommendation 9.41.) |
| **Old section 9.1: Primarily Resectable Pulmonary Metastases (2013 version)** | |
| A PET-CT can be performed in patients with resectable CRC liver metastases.<br>(2008: Recommendation 9.4.) | Deleted in section 9.1, but retained in section 7.4.2.3 |
| A PET-CT shall not be performed within 4 weeks after systemic chemotherapy or antibody therapy, because this significantly reduces its sensitivity.<br>(2008: Recommendation 9.5.) | Deleted in section 9.1, but retained in section 7.4.2.3 |
| 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.<br>(2008: Recommendation 9.23.) | For background text see section 9.12.4 Reinduction / Rechallenge |

# 13.      List of Figures

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# 15.        References

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