S3 Guidelines for Colorectal Carcinoma

Results of an Evidence-Based Consensus Conference on February 6/7, 2004 and June 8/9, 2007 (for the Topics IV, VI and VII)

S3-Leitlinie „Kolorektales Karzinom“

Ergebnisse evidenzbasierter Konsensuskonferenzen am 6./7. Februar 2004 und am 8./9. Juni 2007 (für die Themenkomplexe IV, VI und VII)

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Bibliography

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- German Society of Pathology (DGP)
- German Society of Radio-oncology (DEGRO)
- Surgical Working Group for Oncology abdominal surgery (CAO-V)
- Germany Radiological Society (DRG)
- German Combined Society for Clinical Chemistry and Laboratory Medicine (DGKL)
- German Society of Coloproctology (DGK)
- Association for Stoma Patients and Persons with Colorectal Cancer (German ILCO)
- German Crohn's Disease and Ulcerative colitis Association (DCCV)
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Introduction

Colorectal carcinoma (CRC) is one of the most frequently-occurring malignant tumours in Germany with over 70000 newly-diagnosed illnesses and about 30000 deaths per year. For the first time in 1999, the DGVS, working together with the German Cancer Society, published S3 guidelines for CRC, which were intended to provide an exhaustive, standardised, high-value set of patient care guidelines based on evidence-based medicine [1]. In order to bring these recommendations to the most-current stage of scientific knowledge, the guidelines were updated in 2004 in close collaboration with the AWMF [2].
Due to the rapid progress in the area of medical tumour therapy (chapter "(Neo)adjuvant and palliative therapies for CRC") and due to new data on polyp surveillance, as well as the identification of serrated adenomas as a new entity associated with an increased carcinoma risk, (see chapter: "Endoscopy: Polyp Management"),

in 2008 a further update of the topics in IV, VI and VII was undertaken. These updated topics have now been incorporated into the original guidelines version of 2004. The full manuscript is presented in the following (2004 topics I, II, III, V and VIII; 2008 topics IV, VI and VII). The methodical procedure was performed according to Recommendations for the Creation of Guidelines by the AWMF (http://www.awmf-leitlinien.de).

Systematic review and critical appraisal of the evidence

A systematic search of the literature was performed in Bochum. The sources included Medline (PubMed) and the Cochrane Library. For the 2004 version of the guideline, literature was analysed from the time period after 1998. For the updated 2008 version of the guideline, the search strategies covered the literature published between 2004 and December 2007. Additionally, symposia contributions in the form of abstracts at the largest international symposia (ECCO, ASCO) were analysed for the updated guideline. Taking into account the preliminary character of such publications, citations of abstracts are specially marked with an asterisk.

Methods used for formulating the Recommendations, Grading of the strength of evidence, recommendations and consensus

For all topics/clinical questions of the guideline, structured questionnaires were developed and sent out to the authors/the members of the guideline group. Additionally, the literature providing the evidence to answer these questions was provided. The members of the guideline group/authors were asked to formulate preliminary recommendations on the basis of the evidence provided (Delphi method). On February 6 – 7, 2004 and June 8 – 9, 2007, these preliminary recommendations were discussed in consensus conferences held in Bochum.

Topic-specific working groups prepared recommendations in a nominal group process and presented these to the plenum of all members of the guideline development group for consideration and final voting. A methodologist and representative of the Association of the Scientific Medical Societies in Germany, AWMF, was available for all working groups to answer methodological questions and facilitated the consensus conference (Prof. Dr. I. Kopp).

The relevant literature was critically appraised and the strength of evidence was graded according to the recommendations of the Oxford Centre for Evidence based Medicine (http://www.cebm.net/), (**Table 1**). As a rule, the level of evidence determined the level of recommendation. Three modalities were used to grade the strength of recommendations: "We recommend" for strong recommendations (A), "We suggest" for weak recommendations (B), "can be considered" for options (0).

However, the grading of recommendations took into account not only the methodological quality of the evidence but also aspects of clinical judgment and is, therefore, a result of the formal consensus method (Nominal Group Process and Consensus Conference). Factors considered for considered judgment included the clinical relevance of study endpoints and effect sizes, the balance of possible benefits and harms, the economic burden and implementability in daily care, as well as patient preferences and ethical aspects. Therefore, in some cases, there were deviations between evidence and recommendation levels.

In cases of doubt, the AWMF offered an expert assessment. During the conferences, the percentage of the participants agreeing with the recommendations as well as the absolute number of votes in favour of the recommendation were counted and recorded in order to establish the strength of consensus.

If no consensus was reached, the reasons and/or different positions were presented in the text. The classification of the strength of consensus is presented in **Table 2**.

Table 1 Basis for the Evidence Levels: Centre of Evidence-Based Medicine Oxford.

level	studies for Therapy, Prevention, Etiology
1a	systematic overview of randomised, controlled studies (RCT)
1b	one RCT (with a narrow confidence interval)
1c	all-or-none principle
2a	systematic overview with well-planned cohort studies
2b	one well-planned cohort study or one RCT with a lower quality
2c	outcome studies, ecological studies
3a	systematic overview of case-controlled studies
3b	one case-controlled study
4	case series orcohort/case-control studies of lower quality
5	experimentation without explicit evaluation of the evidence or based on physiological models/laboratory research

Table 2 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

Propagation and Implementation of the Guidelines

The guidelines are aimed to help those who are active in screening and therapy of CRC in outpatient and inpatient set-

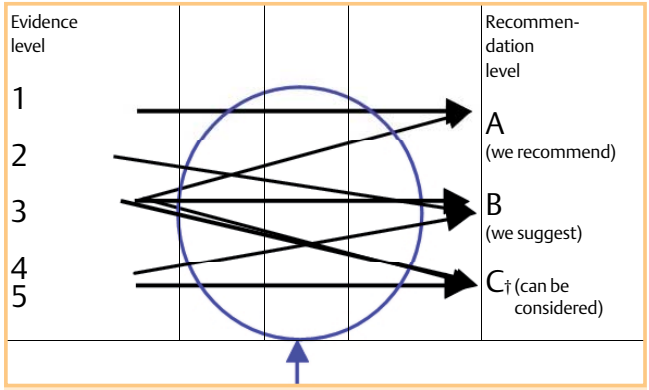

Fig. 1 Clinical Judgment – Classification of the Recommendation Levels (according to the recommendations of the European Council, 2001). ↑ = As a rule, the evidence specifies the recommendation level. Deviations are possible in cases with specific reasons: † Which were granted a recommendation level 0 in the topics IV, VI and VII, in adherence with the previously-used recommendation level C (see index text from 2004).

ting. The guidelines should support the process of decision making, but not taken as statutory. The treating physician is additionally obligated to assess the complete patient situation, and to find the appropriate procedures for the patient. It is nevertheless recommended to provide reasons for deviation from the recommendations in the guidelines.
A wide implementation of these modern, evidence-based therapy recommendations is decisive for improvement in the quality of patient care.
Despite broad agreement, this exhaustive implementation has not been achieved in recent years. A significant structural framework for the practical implementation of the S3 guidelines has been created at the DKG-certified centres for colorectal cancer, whose quality requirements were created according to the recommendations in the S3 guidelines.

Financing the Guidelines and Statements concerning Conflicts of Interest

The German Cancer Society e.V. supplied the financial means to accomplish this. These financial means were used for personnel costs (medical documentation specialist), office materials, literature acquisition and the consensus conferences (room charges, equipment, expenses, moderator honoraria, travel costs for the participants). The travel costs were reimbursed according to the German Travel Cost Law and/or according to the guidelines normally practiced in universities. The editorial updating of the guidelines was free of dependence on financing organisations. All members of the guidelines groups presented a written declaration of any potential conflicts of interest. We thank them for their strictly honorary work, without which the S3 guidelines could not have been produced.

Period of Validity and Update Processes

The S3 guidelines for CRC are continually updated. The period of validity for the now (2008) updated topics IV, VI and VII is estimated to be three to four years. They will be subject to a new revision by 2012 at the latest. Updating of the remaining topics I–III, V and VIII is planned for 2009.
The updating processes will be coordinated by the responsible guidelines secretary. The members of the guideline groups will observe newly-emerging scientific knowledge. From these, the individual topics will be updated if necessary.
All updates will be specially published (as an addendum to the internet version, scientific publications) and finally be worked into the full-text version of the guidelines. Commentaries and instructions for the updating process from clinical practice are encouraged, and can be addressed to the guidelines secretary.

Topic I: Primary Prevention (Asymptomatic Population) (2004)

▼

I.1. Life habits
I.2. Diet recommendations
I.3. Micro nutrients and drugs

I.1. Life habits

Recommendation

In order to reduce the risk of colorectal carcinoma, regular physical activity, as well as pursuing weight reduction for those who are overweight (BMI >25 kg/m2) is suggested.
Recommendation level: B, Evidence level: 2b, Strong consensus.
Patients should be advised to abstain from nicotine.
Recommendation level: A, Evidence level: 2b, Strong consensus.

Background

People with a high level of physical activity have been observed in cross-studies to have fewer colon polyps (adenomas) and a lower carcinoma risk. Two cohort studies showed that 30 to 60 minutes of moderate physical activity per day is associated with a lower carcinoma risk [3–8]. Colon polyps (adenomas) are found more frequently in patients with higher BMI's. For overweight subjects, the risk for a colon carcinoma was increased up to two times, but it is unclear whether the increased risk is caused by overweight, higher calorie consumption or a lack of physical activity [4, 9–11].
Smoking is associated with an increased risk for colon adenomas and carcinomas [6, 12–16]. Despite a level of evidence at 2b, the participants in the conference increased the recommendation level to A, in order to account for the proof of smoking-related increased extra-colonic morbidity and mortality.

I.2. Diet recommendations

Recommendation

In order to reduce the risk of colorectal carcinoma, the consumption of dietary fibre should be increased. Red and/or processed meats should not be consumed daily.
Recommendation level: B, Evidence level: 2a, Strong consensus.
Fruits and vegetables should be eaten more often (five portions per day). It is advised to limit the consumption of alcohol.
Recommendation level: B, Evidence level: 2b, Strong consensus.

Background

Despite the fact that there are contradictory studies, the evidence is sufficient in order to recommend a fibre-rich diet (30 g/day). The consumption of specific fibre-rich foods appears not to be sufficient in itself. In the EPIC study, in particular, in which a consumption of roughage between 12 and 35 g/day was examined, there was an inverse relationship between the amount of roughage consumed and the risk of carcinoma. The negative data from the Nurses' Health Study could be due to the fact that the amount of fibre was lower (range 9.8 to 24.9 g/day) [17–21].
A higher consumption of fruits and vegetables is associated with a reduced frequency of colon adenomas and carcinomas. The evidence for the consumption of vegetables is clearer than that of the consumption of fruit. It is unclear, however, which components (fibre, flavinoids, and anthocyanin) have a protective effect [17–19, 22–26]. It has been demonstrated in several studies that there is a moderate increase in the risk of carcinoma with the daily consumption of red and/or processed

meat [11, 25, 27–31]. Higher consumption of alcohol is associated with a higher risk for colon carcinoma, especially for those who have a reduced intake of folic acid. In addition, it appears that there is a negative synergistic effect between smoking and alcohol. The risk correlates with the amount of alcohol consumed and not with the type of alcoholic drink [11, 22, 32–35].

Recommendation

No recommendations can be given about fish consumption (strong consensus), the reduction of fat consumption (consensus) or the promotion of consumption of vitamin C-containing foods (strong consensus).

Background

Several studies have indeed shown an association between the consumption of fish and the reduced occurrence of colon polyps. The evidence is not sufficient, however, to give a recommendation [26, 27, 30]. Under the assumption that vitamin C-containing foods are for the most part fruits and vegetables, this can be recommended. There are no relevant studies available. An increased amount of fat in the diet is a possible risk factor for colorectal carcinoma. The effect of co-factors (meat consumption, overweight) cannot be separated [22, 25, 38].

Recommendation

In order to reduce the carcinoma risk, folic acid (recommendation level B) and calcium-rich foods (recommendation level C) should be consumed.

Level of evidence: 2b, Strong consensus.

Background

Folic acid-rich food was associated with a lower carcinoma risk. Whether this effect can be attributed to folic acid or to other elements in the folic acid-rich diet cannot be differentiated [39].

Calcium-rich nutrition was also associated with a lower carcinoma risk. It is not clear whether this effect can be attributed to calcium or other elements in a calcium-rich diet [40].

I.3. Micro nutrients and drug recommendations

Recommendation

At this time there is no verified data on the effective prevention of colorectal cancer by micronutrients and drugs. These data apply for calcium (recommendation level B, evidence strength 4), Magnesium (recommendation level C, evidence strength 5), β carotene (recommendation grade B, evidence strength 3b), Vitamin A (recommendation level C, evidence strength 3b), Vitamin C, Vitamin D, Vitamin E (recommendation level C, evidence strength 4), Folic Acid (recommendation level B, evidence strength 2b) and selenium (recommendation level C, evidence strength 4).

The intake of these substances in the context of primary prevention should therefore not be recommended at this time. There is no data on the use of Sulindac, Cox-2 inhibitors, 5-ASA, cholesterol synthesis inhibitors or ursodeoxycholic acid for the asymptomatic population so that these drugs should not be given for primary prevention purposes.

Strong consensus.

Background

There is evidence that the intake of folic acid in a multivitamin compound has a protective effect on the development of colorectal carcinoma. In any case, this effect has not been clearly shown for folic acid alone [41–43].

Several epidemiological studies on persons with increased intake of vitamin A could not prove a reduction of the risk for colorectal carcinoma [25, 44, 45].

For beta carotene, there was no effect found in several studies, however in two studies a reduction in colorectal carcinomas was observed among patients with increased alcohol consumption [25, 44, 45]. It cannot be clearly concluded that the intake of high doses of vitamin C reduces the risk for colorectal carcinoma [22, 44]. For vitamins D and E the data available is insufficient [25, 44–47].

Enriching diets with selenium was shown to reduce CRC in a prospective study. Because in this study the frequency of colorectal carcinoma was not the main criterion, these data are not sufficient to give a recommendation for the use of selenium for the reduction of the risk of colorectal carcinoma [48–50].

Recommendation

Aspirin should not be given for primary prophylaxis of colorectal neoplasia.

Recommendation level: A, Evidence level: 2a, Strong consensus.

Background

In some cohorts and case-controlled studies, a lower incidence of colorectal carcinoma was seen with the intake of aspirin [41, 52]. These findings were, however, not confirmed in other studies. Due to the unsure nature of the current data and the lack of evaluation of the benefit/risk correlation, aspirin should not be used as a primary preventative measure against colorectal carcinoma. In consideration of the strong consensus from the plenum meeting, a recommendation level A was decided upon.

Recommendation

Hormone replacement therapy should not be given to women for the purpose of reducing the risk of CRC.

Recommendation level: A, Evidence level: 2a, Strong consensus.

Background

Although there is evidence for a reduction of colorectal carcinoma by hormone replacement therapy [53–55], the overall effect (breast carcinoma risk, risk of thrombosis) at this time seems to be negative [56]. For this reason, there was a strong consensus for a classification for the recommendation level at A.

Topic II: Screening (Asymptomatic Population) (2004) ▼

II.1. Summary

- CRC-screening should begin at age 50 for the average risk group (absence of family history for CRC and/or polyps/adenomas)
- A physician consultation about available screening methods is essential
- Standard screening method is a colonoscopy. It is superior to sigmoidoscopy
- In order to ensure the safety of the screened individual, quality guidelines are of great importance.
- For those taking part in colonoscopy screening no additional FOBT screening is required.
- For those who refuse colonoscopy screening, a sigmoidoscopy should be performed every five years, as well as an annual FOBT (Guaiac test).
- For those who refuse any endoscopic screening procedure an a FOBT should performed once a year.
- A positive FOBT should not be repeated, but should result in performing a colonoscopy in every case.
- Other screening methods apart from colonoscopy, sigmoidoscopy and FOBT cannot be recommended at this time.
- High acceptance of screening programmes is a major requirement for a reduction in the incidence and mortality of colorectal cancer and an increase in cost effectiveness.

Asymptomatic Population – Definition

Persons who belong to no group with an increased risk for colorectal carcinoma.

II.2. Screening Age

Recommendation

Colorectal cancer screening for asymptomatic persons should begin at the age of 50. Due to the increased life expectancy no upper age limit for screening can be given. An individual decision should be made considering comorbidities.

Recommendation level: B, Evidence level: 4, Strong consensus.

Background

The incidence of CRC increases significantly after age 50 [57, 58]. In a prospective colonoscopy study it was observed that there was a lower rate of advanced adenomas among 40 to 49 year old subjects (3.5%) [59], so that beginning screening before the age of 50 appears to make less sense for the general population. Of great importance is the identification of persons with an increased risk of CRC, for whom special recommendations apply (see topic area III).

There are no prospective studies concerning an age limit for colorectal cancer screening. The incidence of advancing neoplasias increases with age [60]. Performing endoscopic procedures seems to be safe in older patients [61]. In a study the relative five-year survival rate after curative operations of colorectal carcinoma for patients over 74 years of age were comparable with patients aged between 50 and 74 [62]. The establishment of an age limit should therefore be made individually, depending upon the "biological age," as well as comorbidities. There is no sufficient data on the benefit/risk ratio for colorectal cancer screening in different age groups.

II.3. Testing procedures for colorectal cancer screening

FOBT

- Immunological stool test procedures
- Sigmoidoscopy
- Sigmoidoscopy + FOBT
- Colonoscopy
- CT-colonography
- MRI-colonography
- Molecular Screening

II.3.1. FOBT (Guaiac test)

Recommendation

For persons with an average CRC-risk who do not want a colonoscopy, an FOBT, which consists of three test cards (with 2 testing fields each) for three consecutive stools, should be conducted annually. The mortality rate from colorectal cancer can be significantly reduced with this screening test. A positive test result requires endoscopic testing of the entire colon.

Annual FOBT is better than testing once every two years. For those who take part in colonoscopy screening, there is no need for any additonal FOBT or other screening tests.

Recommendation level: A, Evidence level: 1a, Strong consensus.

Background

The basic principle of stool testing for occult blood (FOBT) is the fact that colorectal carcinomas bleed more often than normal colorectal mucosa. Traditional FOBT tests use filter paper impregnated with guaiac rosin which turns blue in the presence of haemoglobin in the stool after the addition of hydrogen peroxide.

Because many carcinomas bleed intermittently [63], repeated testing is required in order to improve detection of CRC [64, 65]. Accordingly in large studies three consecutive stools were tested using test cards with two fields each (ie. 6 fields total) [66].

The results of three large, randomised studies prove the effectiveness of FOBT as a screening method for colorectal carcinoma. A 15 – 33% reduction of CRC-related mortality was demonstrated in these studies [67 – 69]. A meta-analysis demonstrated an average reduction of CRC-related mortality by 23% [70]. This reduction in mortality was confirmed by data from a longer follow-up of the studies [71 – 73]. The annual testing was more effective in reducing mortality than testing every two years [69].

The sensitivity of the test is 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% [69, 74]) and is therefore not recommended. There is evidence that instructing patients before conducting the test in regards to nutrition and interfering drugs can reduce the number of false positive tests and therefore the number of necessary colonoscopies [75 – 77]. It therefore appears to be helpful to explain to patients the factors which can influence test results. The influence of plant peroxidises can alternatively be prevented by waiting for three days before test development [78]. The necessity of dietary restrictions for FOBT was questioned in a meta-analysis [79]. Any positive test result has to result in performing a complete colonoscopy. A colon contrast enema should only be used in case of a technically incomplete colonoscopy.

The effect of FOBT's on CRC-mortality results from the diagnosis of colorectal carcinomas at an earlier stage wie a more favourable prognosis. Advantages of FOBT include an easy test performance as well as low costs. A disadvantage is the moderate sensitivity for carcinomas and a low sensitivity for adenomas. In one randomised study, a reduction in the incidence

of colorectal carcinomas was shown; it must be considered however that in the context of this study over 30% of the participants underwent a colonoscopy [80].

II.3.2. Immunological Stool Test Procedures

Recommendation

Immunological tests currently do not present an alternative to the Guaiac procedure for screening.

Recommendation level: A, Evidence level: 3a, consensus.

Background

Immunological tests for haemoglobin or haemoglobin/haptoglobin in the stool have been shown to have a higher sensitivity than the guiac tests. Available data on specificity is nonuniform [81–85]. There is less data of immunological FOBT's available than for the Guaiac test. The tests are more costly and some are more complex to carry out. No change in diet is necessary with these tests. Immunological stool tests for albumin or calprotectin are not appropriate for screening [86]. The available data for M2-PK stool levels is not sufficient in order to justify use of the tests outside of clinical studies [87].

II.3.3. Molecular Screening Tests

Recommendation

Stool tests measuring DNA changes cannot be recommended for CRC screening outside of studies at this time.

Recommendation level: A, Evidence level: 4, Strong consensus.

Background

The development of colorectal carcinomas through the intermediate step of the adenoma takes place in many cases with characteristic genetic changes. Isolation and testing of DNA from colon epithelial cells in the stool has become possible. In one study, the stools of 46 patients with known carcinomas or adenomas were tested for APC mutations. The sensitivity for carcinoma was 61% and for adenoma 50% [88]. In further studies with even smaller numbers of cases on patients with known neoplasias, several markers were tested in stool samples. In these tests sensitivity for carcinoma ranged from 63 to 91%, for advanced adenoma from 57 to 82% [89–91]. Due to the lack of data for the asymptomatic population as well as the high costs, these procedures should only be evaluated in the context of clinical studies.

II.3.4. Endoscopic Procedures

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 carcinomas and adenomas with high sensitivity. By removing adenomas, the development of carcinomas can be effectively prevented (interruption of the adenoma-carcinoma sequence) [92, 93].

II.3.4.1. Sigmoidoscopy

Recommendation

The effectiveness of sigmoidoscopy as a screening method for CRC has been shown. It should however be considered that not all parts of the colon can be visualized, therefore a complete colonoscopy is considered to be superior to a sigmoidoscopy. Sigmoidoscopy is to be offered to those who refuse a colonoscopy, and should be repeated every five years.

For the possible detection of proximal carcinomas, an annual FOBT test should be performed in addition to a sigmoidoscopy. The effectiveness of the combination has not, however, been conclusively proven.

Recommendation level: A, Evidence level: 3b, Strong consensus.

Background

In case-control studies, a reduction of mortality from carcinomas of the rectosigmoid has been shown to be 60 to 80% after sigmoidoscopy [94–96]. Prospective, randomised studies are currently under way in the US, in the UK and Italy [97–99]. Mortality data will be available in a few years. In a prospective Norwegian study consisting of sigmoidoscopy followed by a colonoscopy for patients with evidence of polyps in the sigmoidoscopy, a reduction in CRC incidence was shown [100].

Compared with occult faecal blood tests, sigmoidoscopy has a higher sensitivity for colorectal neoplasias. In three randomised studies in which the combination of one-time FOBT and sigmoidoscopy was compared to FOBT alone, significantly more neoplasias were found with the combination [101–103]. The protective effect of a sigmoidoscopy for distal neoplasias appears to last for 6 to 10 years [96, 104], in one study as much as 16 years [105]. In a recently published study on 9,417 subjects, who underwent a sigmoidoscopy three years after a negative sigmoidoscopy, an advanced adenoma or carcinoma was found in the distal colon in 0.8% of the cases [106]. Despite this, due to the above-mentioned data, at this time a repeat sigmoidoscopy after a negative examination is recommended after five years. Because proximal tumours cannot be detected with a sigmoidoscopy, an additional annual FOBT makes sense. This should be performed before sigmoidoscopy, because a positive test requires a colonoscopy and thus an additonal sigmoidoscopy can be avoided. However, a reduction on CRC-related mortality by the combination of sigmoidoscopy and FOBT has not been proven yet. A prospective non-randomised 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 [107]. In several studies however a combination of sigmoidoscopy and one-time FOBT was not significantly better than the sigmoidoscopy alone [108, 109]. Possibly a FOBT which is repeated annually can result in a superior effect of the combination compared to a sigmoidoscopy alone.

II.3.4.2. Colonoscopy

Recommendation

The complete colonoscopy has the highest sensitivity and specificity for the detection of CRC and adenomas, and should therefore be recommended as the standard CRC screening test.

After a negative examination, colonoscopy should be repeated every 10 years. Colonoscopy should be performed according to the German Prevention Guidelines[1], including a digital rectal examination. For those taking part in screening additional FOBT screening is not necessary.

Recommendation level: A, Evidence level: 3b, Strong consensus.

Background

Although no randomised studies concerning effect on CRC-mortality exist, nearly all consensus participants consider colo-

[1] Early cancer detection guidelines from the Federal Committee of Physicians and Health Insurers in their current version, and in connection with the quality assurance standards in adherence to paragraph 135, sub-paragraph 2 (published in the German Physician's Gazette 2002).

noscopy that is performed according to the Guidelines to be the preferred screening method for colorectal carcinoma. In two case-controlled studies it was shown that the incidence of colorectal cancer through polypectomy in the context of a colonoscopy was reduced by 66 – 90% [92, 93] thus enabling the prevention of colorectal carcinoma. Unlike sigmoidoscopy colonoscopy has a proven high sensitivity for carcinoma and adenoma of the entire colon and allows, in particular, a detection of proximal neoplasias. In studies 46 to 52% of patients with proximal neoplasias showed no additional distal adenomas [110, 111]. A diagnosis of neoplasias using sigmoidoscopy would have been impossible in these patients.
The results of the case-control studies of sigmoidoscopy showing a protective effect should be transferrable to colonoscopy [94 – 96]. The protective effect shown in FOBT studies is also due to performing colonoscopy in patients with a positive test. In addition, in one case-controlled study, a protective effect of the colonoscopy was shown [112]. The complication rate for colonoscopy in one study from Germany was shown to be very low [113]. Tandem examinations showed that larger adenomas were seldom missed (0 – 6%) [114].
It seems reasonable to repeat a negative colonoscopy after 10 years. 5 years after a negative colonoscopy a colonoscopy found no carcinoma and less than 1% advanced neoplasias [115]. In a case-control study the protective effect of a colonoscopy lasted for at least 10 years [73].

II.3.5. Radiological Tests

Recommendation

Neither CT colonography nor MRI colonography can currently be recommended for screening outside of studies.
Recommendation level: A, Evidence level: 2b, Strong consensus.

Background

For the use of MRI colonography there are no large randomized studies (area or field studies) in the asymptomatic population. Only a few studies have looked at CT colonography as a screening tool for asymptomatic subjects. The available data showed a low sensitivity for small (< 10 mm) polyps. Flat polyps cannot be detected. Both methods (MRI- and CT-colonography have not been standardised, and the data for sensitivity is contradictory, so that their use as screening methods – other than in the context of studies – cannot be recommended at this time [116 – 124].
Their use after incomplete colonoscopies can be considered, but there are no studies.

II.4. Cost effectiveness

Recommendation

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).
Level of evidence: 4.

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 [125 – 133].

Topic III: Risk Groups (2004)

▼

III.1. Sporadic colorectal carcinoma
- III.1.1. Risk Groups
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People who, for reason of a special predisposition, have a higher risk for the development of colorectal carcinoma in comparison to the normal population, as a rule belong to one of three defined risk groups:
- People with a familial increased risk (genetic reasons not yet known) for a colorectal carcinoma
- Proven or possible carriers for a hereditary colorectal carcinoma
- Persons at risk due to inflammatory bowel disease

III.1. Sporadic colorectal carcinoma

III.1.1. Risk Groups

Relatives of patients with colorectal carcinoma

First degree relatives of patients with a colorectal carcinoma have an increased risk of developing colorectal carcinoma.
Level of evidence: 2a.
Second degree relatives have a slightly increased risk of developing colorectal carcinoma.
Level of evidence: 2b.

Background

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 carcinoma before age 45 and/or more than one first degree relative had a CRC [134 – 136]. In the age group under 50 years, there are also cases of undiscovered hereditary colon carcinomas (e.g. HNPCC; see below). The risk is higher for colon carcinomas than for rectal carcinomas (relative risk 2.4 vs. 1.9). For first-degree relatives of affected patients, the CRC risk can be divided further. If one parent is affected the risk is 2.3-fold increased compared to the average population, if a sibling is affected the risk is 2.6-fold increased. If the index patient devolops a colorectal cancer after age 60, the CRC risk for first degree relatives is only slightly increased [135]. Second degree relatives (grandparents, siblings of the parents, grandchildren) of patients with colorectal carcinomas have a slightly increased carcinoma risk (RR 1.5); this has not been adequately studied and verified in clinical practice [134, 137, 138, 147, 148]. Third degree relatives of patients with colorectal carcinoma do not seem to be at an increased carcinoma risk.

Relatives of patients with colorectal adenomas

Recommendation

First degree relatives of patients with a colorectal adenoma before age 50 have an increased colorectal cancer risk.
Level of evidence: 2b.

Background
The risk of these relatives to develop colorectal cancer is on average about two fold higher compared to the general population [135, 138, 149–152]; there is an 80% higher risk for parents and siblings of adenoma patients in comparison to their spouses [149]. 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 [150]. If the index patient is older than 60, the colorectal cancer risk 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 carcinoma. An exception is the rare hyperplastic polyposis syndrome (see hamartomatose polyposis syndrome).

Patients with colorectal adenomas
Each histologically verified adenoma poses an increased risk for a colorectal carcinoma (evidence 2b). This is especially true for
- multiple (≥ 3) adenomas
- large (> 1 cm) adenomas

Background
In general, the removal of small, singular adenomas results in a reduced risk of up to 90% to devolop a metachronous colorectal carcinoma [34, 106, 582, 585]. This reflects the preventive value of colonoscopy in the context of the adenoma-carcinoma sequence. The purpose of control examinations is particularly to discover overlooked or metachronous adenomas.
Adenomas larger than 1 cm are associated with a four-fold increase in carcinoma risk [138, 154–161]. In addition multiple adenomas are also asscociated with an increased risk (4–6fold) of developing a metachronous carcinoma [138, 154, 156, 157, 159, 160]. This increased risk is likely due to a higher individual disposition on the one side, on the other side an increased rate of missed polyps during the initial colonoscopy. In case of detection of ≥ 3 polyps during colonoscopy there is a significantly higher probability of missed polyps [114, 162].
It is currently unknown whether hyperplastic polyps should be regarded as precancerous lesions [163].

III.1.2. Primary prevention
Recommendation
No different recommendations other than for the average risk population can be given for primary prevention (dietetic measures, chemoprevention) due to contradictory data available for the mentioned risk groups.
Level of evidence: 1b, Strong consensus.

Background
In general, the recommendations for the average risk population (see topic I) also apply for members of risk groups; there is no data for special measures [164–166].

III.1.3. Screening Tests
First-degree relatives of patients with colorectal carcinoma
Recommendation
First-degree relatives of patients with colorectal carcinoma should undergo a complete colonoscopy starting at an age 10 years before the age at which the index patient was diagnosed with a colorectal carcinoma, but at the latest at the age of 50.
Recommendation level: B, Evidence level: 4, Strong consensus.

Background
The risk of a first-degree relative of a patient with colorectal carcinoma to also develop a colorectal carcinoma is increased [138, 140, 148, 167–170] (see also Section III.1.1.), especially if the index patient's age at diagnosis is less than 50.
For young index patients, a diagnosis of an HNPCCS syndrome should be considered (see section III.2.3.) and a microsatellite analysis and/or immunohistochemical examination of the mismatch-repair proteins should be conducted. If this is not possible, the preventative care should be intensified.

Recommendation
Colonoscopy should be repeated at least once every 10 years.
Recommendation level: B, Evidence level: 4, Strong consensus.

Background
There is no data on the maximum examination interval for this group; at this time it appears probable that as a rule an interval of 10 years should be adequate. However the 10 year interval should not be exeeded.

Relatives of patients with colorectal adenomas
Recommendation
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. Colonoscopy should be repeated at least once every 10 years.
Recommendation level: C Evidence level: 5, Strong consensus.

Background
The recommendation is based on the higher risk in this population as demonstrated in section III.1.2 [58, 140, 148, 150].

III.2. Hereditary colorectal carcinoma
Monogenic-inherited colorectal carcinomas occur infrequently (less than 5% of all colorectal carcinomas). The diagnosis has significant consequences for patients and their relatives. In case of suspicion of an inherited colorectal cancer, an experienced centre 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 [171]. All patients and persons with higher risk in these groups have, in addition to an increased risk for colorectal cancer, an increased risk for extra colonic neoplasias. Due to the autosomal-dominant inheritance process, first-degree relatives of index patients have a 50% risk of having inherited this genetic predisposition. A predictive genetic test always has to be preceded by genetic counselling of the patient concerned and can only take place if a clear pathogenic germ cell mutation has been identified in an affected family member [171].

III.2.1. Risk Groups
Patients with familial adenomatous polyposis (FAP)
All patients with untreated FAP will – with rare exceptions – develop colorectal carcinoma.
Level of evidence: 2a.

Background

FAP is characterised by the presence of more than 100 colorectal adenomas. The formation of polyps generally begins in the second life decade.

Due to the large number of adenomas, the carcinoma risk is nearly 100%. Most patients develop, in addition to this, further extra colonic intestinal manifestations. The most important manifestations are duodenal and/or papillary adenomas, which occur in about 75% of all patients and are to be regarded as pre-cancerous (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 tumours, thyroid gland carcinomas, and malignant CNS tumours (mostly medulloblastomas), hepatoblastomas as well as harmless, but often diagnostically indicative osteomas, epidermoid cysts or pigment anomalies of the retina [172].

Patients with attenuated familial adenomatous polyposis (FAP)

Attenuated FAP (AAPC) has to be distinguished from typical familial adenomatous polyposis. Patients with AAPC are also at a very high risk for colorectal carcinoma, however polyps and carcinomas generally develop later, and more often in the proximal colon.

Background

Unlike FAP, with AAPC there are typically less than 100 colorectal adenomas. Extra-colonic manifestations (e.g. desmoids) can occur [172–176].

From the genetic point of view, AAPC is a heterogeneous group with evidence of APC mutations (5' and 3' end of the gene) and MYH mutations. In addition the differentation from HNPCC can be difficult in individual cases [177]. Therefore a molecular genetic diagnosis can be very helpful (microsatellite analysis, APC, MYH) in the differential diagnosis of some cases of attenuated FAP. With the majority of patients with the clinical diagnosis AAPC, no identification of a genetic mutation is possible, so it has to be assumed that addtional mutations in unidentified genes exist.

Patients with HNPCC (hereditary colorectal carcinoma without polyposis)

HNPCC syndrome is defined according to diagnostic criteria (Amsterdam I and II criteria; see appendix 1). In order to identify additional risk patients, the Bethesda criteria are used (Bethesda criteria, see appendices 2 and 3). Mutation carriers have a very high risk of developing colorectal carcinoma (up to 80%). This applies to a lesser extent also for extra-colonic neoplasias such as endometrial, ovarian, stomach and small bowel carcinomas, as well as urothelial carcinoma of the renal pelvis and ureter.

Level of evidence: 2a.

Persons who fulfill the Amsterdam criteria or one of the Bethesda criteria with evidence of a microsatellite instability (MSI), and their relatives are risk persons for HNPCC.

Level of evidence: 1c.

Background

In contrast to FAP, it is not easy to identify HNPCC clinically. This is due to the lack of conspicuous phenotypes. For this reason, criteria have been defined (see appendix 1) which appear to be useful to initiate a mutation search. A diagnosis of HNPCC can be made if, in the family of the patient, the so-called Amsterdam I criteria are fulfilled [178]. With HNPCC, in addition to CRC there is an increased rate of endometrial and urothelial carcinoma, as well as carcinoma of the small intestine. The Amsterdam II criteria include these extra-colonic manifestations [179].

These criteria present a pragmatic implementation from the clinical point of view. Because many families are small nowadays, there is often no possiblity of fulfilling these criteria. Therefore a lack of positive familiy history – particularly in small families – is no argument against HNPCC. The less specific Bethesda criteria allow formulating a suspicion of HNPCC in smaller families and individual cases (appendix 2)[180].

Microsatellite instability can be demonstrated in about 80 to 90% of the tumour tissue of patients who meet the Amsterdam I/II criteria. This phenomenon can be traced back to the underlying defect in a DNA repair enzyme which can no longer repair missing base matches during cell mitosis. Such missing matches occur relatively easily in repetitive short DNA fragments (so-called microsatellites). Accordingly in repair-deficient HNPCC tumours a different microsatellite pattern compared to normal cells is found, which has led to the term "microsatellite instability."

In patients whose families fulfil the less-stringent Bethesda criteria, microsatellite instability is found in about 30% of the patients. The classical Bethesda criteria were revised in 2004 (appendix 3) [181].

The general tumour 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. Colorectal cancers are rarely seen before age 25. The cumulative lifetime risk of an NHPCC carrier to develop a CRC is 60 to 80%.

Endometrial carcinoma is, after CRC, the second-most common tumour in HNPCC. The lifetime risk for female carriers to develp an endometrial carcinoma is 40 to 60% with a median age of diagnosis between 46 and 48 years. Carcinomas of the ovaries occur in 3 to 12% of all carriers. Stomach carcinomas occur in 2 to 13% of HNPCC patients, and are diagnosed on average between the ages of 51 and 56. Most such carcinomas are of the intestinal type. The cumulative lifetime risk for small bowel carcinoma in the context of an HNPCC is one to four percent. In about 35% of the cases, HNPCC-associated small bowel carcinomas are localised in the duodenum. The risk appears to be higher among carriers with a MLH1 mutation than for patients with a MSH2 mutation.

Carcinomas of the upper urinary tract (ureter/renal pelvis) often appear as second or third carcinomas. The average age for these tumours is given as 50 to 63. The lifetime risk is given as 1–12%, and appears to be higher among patients with an MSH2 mutation. Kidney and bladder carcinomas do not seem to occur at a significantly greater rate among patients with HNPCC [182–188].

The lifetime risk for biliary tumours is higher with HNPCC, but altogether relatively low. In contrast pancreatic carcinomas are not found significantly more frequently compared to the general population. For brain tumours there is a slightly increased risk with HNPCC, histologically these are primarily astrocytomas and glioblastomas. The median age of presentation is 40 to 54 [188–190]. Muir-Torre syndrome is a rare phenotypic

variant of HNPCC which on top of the typical HNPCC-associated tumours is associated with sebaceous gland adenomas or carcinomas [191].

Patients with hamartomatous polyposis syndromes

Peutz-Jeghers syndrome, juvenile polyposis coli and Cowden syndrome belong to hamartomatous polyposis syndromes. These diseases do not occur frequently (their percentage of all CRC's is less than 0.1 percent). Carriers have an increased risk for colorectal carcinoma as well as for other intestinal and extra intestinal tumours (stomach, breast, etc.).
Level of evidence: 2a.

Background

Differential diagnosis of hamartomatous polyposis syndromes can be very difficult in individual cases and requires interdisciplinary collaboration of gastroenterologists, surgeons, pathologists, radiologists and other clinical specialities. For the diagnosis and clinical care for these patients centers with experience with these syndromes should therefore be consulted. Peutz-Jeghers syndrome (PJS) is an autosomal-dominantly inherited disease, characteristized by the appearance of hamartomatous polyps in the gastrointestinal tract and mucocutaneous melanin pigmentation which primarily occur perioral-ly. The disease is caused by germ cell mutations of the STK11/LKB1 gene. With PJS, there is a significantly increased risk of devoloping a series of intestinal and extra intestinal tumours [192 – 198]. In addition to CRC, new meta-analyses in the published literature show an increased risk for carcinomas of the stomach, small intestine, pancreas, breast, ovary and uterus [199]. The cumulative lifetime risk for a malignant tumour can amount to about 90%, and CRC risk to 39%. The tumours are generally diagnosed between the ages of 30 and 50 [199].
The autosomal-dominantly inherited familial juvenile polyposis coli (FJP) is should be suspected in case of the diagnosis of five or more juvenile polyps in the colon, evidence of extra-colonic juvenile polyps or evidence of juvenile polyps with a relevant positive familiy history. The lifetime CRC-risk is 17 to 68%. Additionally to this, there is a possible risk for stomach and pancreatic carcinoma [200 – 204].
The Cowden syndrome (autosomal-dominant inheritance) is especially associated with an increased risk for breast and thyroid carcinomas, whereas the risk for gastrointestinal tumours does not seem to be increased. The Ruvalcaba-Myhre-Smith syndrome appears to be a variant of Cowden syndrome. Both syndromes are associated with germ cell mutations of the PTEN gene. Recently the hereditary mixed polyposis syndromes and the hyperplastic polyposis syndrome have been described in more detail and presumed to be associated with an increased CRC-risk [205 – 209]. Both diseases however are very rare so that the significance of the postulated tumour risks is not completey clear.

III.2.2. Surveillance

Recommendations for patients with familial adenomatous polyposis (FAP)

Recommendation

Relatives of a FAP patient who could be a mutation carrier due to the autosomal dominant inheritance are defined as persons at risk. For these persons at age 10 a predictive genetic testing should be performed after genetic counselling of the family.
Recommendation level: A, Level of evidence: 4, strong consensus.

Recommendation

If in a person at risk (children with at least one parent with FAP or siblings of FAP patients) the mutation has been excluded, a special surveillance is no longer necessary.
Level of Recommendation A, Level of evidence: 1c, strong consensus.

Recommendation

Persons at risk for whom the mutation is confirmed or cannot be excluded should have a rectosigmoidoscopy, starting at the latest at age 10. If there is evidence of adenomas, a complete colonoscopy must follow, and be repated annually until a proctocolectomy has been performed (see below).
Level of Recommendation A, Level of evidence: 4, strong consensus.

Background

For children the genetic consultation is done together with their legal guardians. Initiating a genetic diagnosis before the age of 10 is seldom necessary, because colorectal carcinomas are only rarely seen among children younger than 15 [210]. The molecular genetic testing can be carried out with direct (mutation testing in the APC gene) or indirect (testing of the inheritance of the causing mutation through coupling analysis) genotyping. Predictive testing can only be conducted in patients where the pathogenic germ cell mutations have been identified in an affected family member and must always be combined with human genetic counselling [171]. A mutation is detected in about 70% of such patients. With the presence of at least two affected members in the family, the inheritance of the gene defect responsible for FAP can be tested for the presence of neighbouring polymorphic markers (coupling analysis). Both molecular genetic methods taken together enable a mutation detection in over 90%. In many families another method that can be used for identification of gene carriers is an eye background check to identify the characteristic congenital hypertrophy of the retinal pigment pithel (CHRPE). However nowadays this method is used less often because of the possibility of DNA testing.
With classic FAP polyps in the rectum and sigma are always observed. If rectal polyps are identified, further proximal adenomas or carcinomas can be present. In these cases, a complete colonoscopy should be performed which, depending upon the findings, should be repeated at least once a year. In families where genetic testing has not been performed or did not provide definitive results, all persons at risk should undergo endoscopic surveillance from age 10 onwards [138, 210, 211]. With specific mutations, earlier carcinoma manifestation in the family or presence of symptoms, initiating screening at an even earlier age should be considered.

Recommendation

Patients with classical FAP should undergo a prophylactic proctocolectomy if possible no earlier than the end of puberty.
Level of Recommendation A, Level of evidence: 1c, strong consensus.

Recommendation

After a proctocolectomy a pouchoscopy should be performed annually. Patients with a retained rectum should receive a rectoscopy every 4 months.

Level of Recommendation A, Level of evidence: 2a, strong consensus.

Background

The timely proctocolectomy is decisive for preventing colorectal carcinoma formation [212–216]. The operation should generally be performed between the end of puberty and age 20. The exact time point should however be decided on an individual basis according to age, diagnosis and endoscopic/histological findings (number of polyps and level of dysplasia) [215–217]. In the natural course of FAP, carcinomas appear at a median age of 36 [218]. 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 carcinoma is 13% after 25 years [219], the long-term prognosis for IPAA (ileo-pouch anal anastamosis) concerning the CRC-rate is better [220–223]. For this reason, a proctocolectomy is recommended for patients with classical FAP. The operation should be conducted in an experienced centre. Carrying out a proctocolectomy with a final, permanent ileostoma can in most cases now be avoided. The use and risk of a laparoscopic proctocolectomy cannot be conclusively evaluated at this time. Because some patients develop polyps in the area of the pouch next to the ileoanal anastamosis, that can progress to carcinoma an annual postoperative pouchoscopy is recommended. In case of an IRA an inspection of the remaining rectum should be performed every 4–6 months including removal of new polyps. The available data on the effectiveness of influencing the growth of polyps with the non-steroidal atiphlogistic Sulindac is contradictory [224–229]. It is uncertain whether the selective COX2 inhibitor Celcoxib that was shown to lead to a reduction of rectal adenomas [230], will also reduce the risk of CRC in these patients.

Recommendation

An EGD with inspection of the papilla region should be carried out every three years starting atage 30. The interval should be shortened to as much as one year depending on the degree of severity of the adenoma burden.

Level of Recommendation B, Level of evidence: 4, strong consensus.

Recommendation

Further extra colonic manifestations must be observed. There should therefore be an annual ultrasound of the abdomen and the thyroid gland from age 10.

Level of Recommendation C, Level of evidence: 4, strong consensus.

Background

The lifetime risk of developing duodenal polyps is between 80 and 90% for FAP patients [231, 232]. Fewer than 10% of the patents show stomach adenomas, about 30% show fundic gland polyps of the stomach. In regards to the expression of duodenal polyposis, the Spigelman classification (**Table III.1**) should be used [231]. The average age of patients with serious adenomatosis of the duodenum is about 43 (range 24–65)

Table III.1 Classification of the Characteristics of Duodenal Polyposis (according to [231]).[1].

	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
dysplasias	low-grade	middle-grade	high-grade

[1] Stage 0: 0 points, Stage I: 1–4 points, Stage II: 5–6 points, Stage III: 7–8 points, Stage IV: 9–12 points.

[233]. Altogether it appears that the growth behaviour of the duodenal adenoma is slower than that of the colorectal adenomas [234, 235], and depends more on increasing age (increases at age >40) than the initial stage [236]. The mutation location (Codon 279–1390) is correlated with the severity of the polyposis in the duodenum, but not with the possibility that a high-grade dysplasia develops [237, 238]. The lifetime risk for a duodenal carcinoma for patients with FAP is between 3 and 4% [239] and is therefore up to 300 times more common than in the normal population [240]. The risk that an invasive carcinoma is present depends on the severity of the duodenal polyposis. Thus the risk for an invasive carcinoma with Spigelman II and III is 2%, versus 36% for Spigelman IV [241].

The aim of an endoscopic surveillance cannot be the removal of all polyps, but must be directed at the detection of neoplasias. If endoscopic control of the duodenal polyps is possible with biopsy and/or polypectomy, this is of course encouraged [242]. For the majority of FAP patients it appears that a screening interval of three years is sufficient [234]. Due to the higher risk of carcinoma in Spigelman stage IV, a surgical procedure is recommended.

The pancreas-containing duodenectomy is the preferred procedure partly due to a lower morbidity rate than with a pancreatic duodenectomy. An operative duodenotomy with polypectomy cannot be recommended due to a high rate of recurrence [233, 244]. In principal, even after extensive surgical treatment the appearance of new adenomas cannot be prevented [233]. At this time it is also not clear whether regular surveillance of the duodenum is life-extending [239].

In summary, it appears that the following monitoring program makes sense, whereby one must certainly adjust the approach to the individual situation: Spigelman I: examination every three years; if necessary a polypectomy should be performed; Spigelman II ≤40 years of age: examination every three years; if necessary a polypectomy should be performed; Spigelman II >40 years of age and Spigelman III: annual examination and, if necessary, polypectomy, Spigelman IV: surgery.

About 1 to 2% of all patients with an FAP develop a thyroid carcinoma. The risk is higher for female mutation carriers. The diagnosis is generally made between the ages of 15 and 30 [245–248]. For this reason, from the age of 10 an anual thyroid ultrasound is recommended. Desmoid tumours appear in up to 30% of all patients with FAP. Therefore an anual abdominal ultrasound is recommended. Next to a clear genophenotype correlation (APC mutation codon >1300) [249, 250], surgical trauma can act as a trigger factor. About 50% of the desmoids appear intra-abdominally and above all mesenterially and due to their local infiltrative growth 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. From the age of 10 an anual abdominal ultrasound is recommended.

Hepatoblastomas are very rarely observed as a manifestation of FAP. Fewer than 0.5% of all children of FAP patients develop a hepatoblastoma nearly exclusively before the age of 10 [251]. It seems however that the risk for boys is higher than for girls. In a portion of the cases there was a positive family history [252]. Due to the rareness of occurence and the unclear data on whether the prognosis for hepatoblastoma patients can be improved, screening is not recommended.

Recommendation

A general recommendation for treatment of adenomas in the upper gastrointestinal tract cannot be given at this time. This also applies for the administration of COX-2 inhibitors.

Evidence strength: 4, strong consensus.

Patients with attenuated familial adenotemous polyposis

Recommendation

A patient with an attenuated FAP treatment should depend on age, the number of polyps and histological findings. With endoscopically uncontrollable polyposis a colectomy is indicated. Patients who do not undergo a colectomy must have a colonoscopy once a year for the rest of their lives.

Level of Recommendation B, Level of evidence: 4, strong consensus.

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 undergo an annual colonoscopy starting at age 20.

Level of Recommendation C, Level of evidence: 4, strong consensus.

Background

With patients who have an attenuated FAP, polyps occur later and with fewer numbers than with classic FAP. The diagnosis of a CRC in adolescence has casuistically been described [253]. The polyps are often found on the right side of the colon. Hence a complete colonoscopy must be conducted for surveillance [173, 174, 176, 254].

Because the clinical characteristics can significantly vary, 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 leaving a rectal remainder is reasonable. Because extra colonic manifestations can appear exactly like with classical FAP [255–257], the recommendations for classical 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 conducted.

Patients with hereditary non-polyposis coli colon carcinomas (HNPCC)

Recommendation

Persons at risk at age 18 or older should be offered genetic counselling. As soon as the mutation which causes the disease has been identified in the affected family, persons at risk should be tested for this mutation.

Level of Recommendation A, Level of evidence: 1c, strong consensus

Recommendation

If the mutation causing the disease has been excluded in a person at risk, the general cancer preventative measures apply.

Level of Recommendation A, Level of evidence: 1c, strong consensus.

Background

Carriers of HNPCC have mutations in so-called mismatch repair genes. Up to now, germ cell mutations have be demonstrated in four different genes: MSH2, MLH1, MSH6 and PMS2. The significance of mutations in the PMS1 and MLH3 genes has not been clarified in a conclusive manner yet. Almost 90% of the mutations identified up to now exist in the genes MSH2 and MLH1 [28], about 10% in the MSH6 gene. A predictive genetic examination must only be conducted after a genetic consultation [171]. A predictive test is only possible if a definite pathogenic mutation has been identified in a member of the family with a clear manifestion of HNPCC. The identification of polymorphisms or mutations with unclear pathogenic significance is not suitable for predictive genetic testing.

Recommendation

Persons at risk for HNPCC should undergo a complete colonoscopy annually starting at age 25.

Level of Recommendation A, Level of evidence: 2a, consensus.

In any case, five years before the youngest age that the illness occurred in the family.

Level of Recommendation C, Level of evidence: 5, consensus.

Background

Colorectal carcinomas occur in HNPCC patients at a median age of 44. More than 50% of these carcinomas are found on the right side of the colon [189]. For these reasons, a rectoscopy and/or rectosigmoidoscopy are not sufficient as a surveillance test. A prospective study showed a significant reduction in mortality as well as the incidence of CRC by more than 60% respectively with three-year testing intervals [259]. Due to an accelerated tumour progression with interval carcinomas in about 4% of all patients with three-year testing intervals, an annual interval is recommended [259, 260]. The stage distribution and therefore the prognosis of HNPCC-associated colorectal carcinoma that have been discovered in the context of a surveillance program is significantly more favourable than compared to a diagnosis due to symptoms [261]. Data on medical chemoprevention of CRC with HNPCC does not yet exist. For this reason medical chemoprevention outside of studies cannot be recommended.

Recommendation

For female patients at risk and mutation carriers, from the age of 25, in addition to the annual gynaecological exam a transvaginal ultrasound should be conducted because of the risk of endometrial and ovarian carcinomas.

Level of Recommendation C, Level of evidence: 4, strong consensus.

If a stomach carcinoma has occurred in the family, starting at age 25 an EGD should be undertaken.

Level of Recommendation C, Level of evidence: 4, strong consensus.

Recommendation

With all persons at risk and mutation carriers from the age of 25, an annual abdominal ultrasound should be performed.

Level of Recommendation C, Level of evidence: 5, strong consensus.

Background

These recommendations arise from the natural progression of HNPCC (see above). For female carriers, the risk of developing an endometrial carcinoma up to the age of 70 is 40 to 60%, and for an ovarian carcinoma 3 to 12% [187, 188]. Up to now there has been only one prospective study for HNPCC on the efficiency of gynaecological preventative care in regards to endometrial carcinomas [262]. In this study, no benefit due to the use of screening was found. However, the study demonstrated significant methodical weaknesses, especially in regards to the post-observation time and the age distribution of the patients and can therefore not be used as a counterargument for screening.

Some groups have discussed and recommended aspiration cytology or a hysteroscopy for the early recognition of HNPCC-associated endometrial carcinomas [263–266]. Data on the early detection of ovarian carcinomas with screening and control testing in HNPCC do not exist in either prospective or retrospective form. Due to the relatively good prognosis of HNPCC-associated endometrial carcinomas, a prophylactic hysterectomy is not generally recommended [267]. A prophylactic adenectomy can also not be recommended, as there is a lifetime risk of 2 to 13%. Both interventions could however be indicated in individual cases. These options are especially worthy of discussion with postmenopausal mutation carriers (or for those who have decided to have no more children). Data on medical chemoprevention with HNPCC is currently not available. For this reason medical chemoprevention outside of studies cannot be recommended.

The effectiveness of an early diagnostic gastroscopy has not been sufficiently investigated as yet. In the only prospective study on the effectiveness of esophageal-gastric-duodenoscopy (EGD) for HNPCC-patients no benefit was found [268]. The study showed significant methodolgical weaknesses, especially in regards to the number of patients, age distribution and post-observation times. In view of the fact that 35% of all carcinomas of the small intestine in HNPCC cases are localised in the duodenum [185], an EGD should always try to reach up to the Treitz band.

Due to the increased risk for urothelial carcinoma and hepatobiliary carcinoma, an abdominal ultrasound should be performed annually. The use of a urine cytological examination is not supported and is generally no longer recommended. However it may make sense to perform a urine cytology, if there is a positive family history and for carriers with a MSH2 mutation, because the risk is significantly higher in this case [188].

Recommendation

Colonoscopic surveillance of patients after oncological resection must be continued as prior to the resection.

Level of Recommendation A, Level of evidence: 2a, strong consensus.

Recommendation

A prophylactic colonectomy and/or proctocolectomy cannot be recommended at this time.

Level of Recommendation C, Level of evidence: 5, strong consensus.

Background

Because regular surveillance is able to detect pre-malignant adenomas and nearly all surveillance detected carcinomas are UICC stage I or II [259, 260] and the penetrance of the disease is not complete a prophylactic colectomy and/or proctocolectomy cannot be recommended at this time.

When a carcinoma has been detected the patient should be operated upon according to oncological surgical standard criteria (see also topic area V). The risk of colorectal carcinoma in the remaining lower intestine and the risk of extra colonic neoplasias remains clearly increased, so that these patients must undergo intensive postoperative care. In these cases, the tumour postoperative surveillance for sporadic CRC should be combined with the HNPCC-specific screening program for CRC and extra colonic tumours. Whether a prophylactic extended tumour resection for the prophylaxis of metachronous CRC is superior to a surveillance at short intervals is currently unknown and subject of a prospective randomized clinical trial.

Hamartomatous Polyposis Syndromes

Recommendation

General surveillance recommendations cannot be given due to the limited availability of data. Monitoring of patients and persons at risk should be carried out in cooperation with an experienced centre.

Level of Recommendation C, Level of evidence: 5, strong consensus.

Background

Due to the relatively low incidence of these diseases, at this time no general surveillance recommendations can be given. Most studies are retrospective and include small case numbers. According to these studies, the relative risk for a patient with Peutz-Jeghers syndrome to develop a colorectal carcinoma is clearly higher than the general population (see above). In addition, the risk for a number of further tumours is also significantly higher. Due to the low incidence of this disease, these patients should be handled in close collaboration with experienced centres. Next to intestinal and extra intestinal screening, however, there is in particular a need for the prevention and early recognition of benign colorectal complications such as bleeding, anaemia, obstruction and invagination of polyps that can occur even in younger patients. For this reason, an overall diagnostic evaluation of the entire gastrointestinal tract should be performed from about the age of 10.

An overall diagnostic evaluation of the entire gastrointestinal tract should also be undertaken for patients with a juvenile polyposis due to the higher risk for CRC and stomach carcinoma and in order to prevent and recognize early benign complications.

III.3. Chronic inflammatory bowel disease

III.3.1. Risk Groups

Patients with ulcerative colitis

Patients with ulcerative colitis also show an increased risk for colorectal carcinoma. The risk depends upon the extent, age at manifestation and duration of the illness, as well as the existence of a primary sclerosing cholangitis [269 – 274].
Evidence strength: 2a.

Background

The majority of studies show an increased risk for the development of CRC [269, 270]. In a meta-analysis the cumulative risk of carcinoma for pancolitis was 2% after 10 years, 9% after 20 years and 18% after 30 years [275]. In an entirely Danish study with a high colectomy rate no higher incidence of CRC was observed [276]. A meta-analysis confirmed primary sclerosing cholangitis to be a risk factor for the development of a colorectal carcinoma in ulcerative colitis patients [277]. Two case-controll studies showed an increased CRC-risk for ulcerative colitis patients with a positive family history for CRC [278, 279].
Ulcerative colitis-associated intraepithelial neoplasias (especially DALM) should be differentiated from sporadic adenomas with intraepithelial neoplasias by means of macroscopic and microscopic criteria [280].
According to the WHO definition DALM (dysplasia-associated lesion or mass), is a high-grade lesion in which a CRC is already present in 40% of the cases [281].

Patients with Crohn's Disease

With Crohn's disease one can also assume an increased risk of colorectal carcinoma. This is however insufficiently characterized in comparison to ulcerative colitis, but is possibly lower. There is an increased risk of small intestine carcinoma.
Evidence strength: 2a.

Background

Data for Crohn's disease is scarce and in some cases non-uniform [282 – 286]. The data vary between no increased risk and a 3.5 – 7fold increased risk. The validity of most studies related to colorectal carcinoma risk with Crohn's disease is limited due to low case numbers. For the studies which observed no increased risk of colorectal carcinoma and Crohn's disease [283, 287], one can critically remark that the validity is relatively low due to methodological weaknesses. Thus the proportion of Crohn patients with a colon manifestation was too low and/or those with an extensive colon resection too high, and/or the period of observation was too short.

Patients with other inflammatory large bowel illnesses

An increased colorectal carcinoma risk on the basis of other inflammatory large bowel illnesses is not established.
Evidence strength: 5.

Background

The evidence for an approximately 1.8-times increased risk of left-sided carcinoma as well as a Wnt 2-gene overexpression for patients with diverticulitis [288, 289] is not robust. With collagenic colitis there is only casuistic evidence of an increased risk [290].

III.3.2. Primary prevention

Recommendation

Aminosalicylates can be used for colorectal cancer prophylaxis in ulcerative colitis.
Level of Recommendation B, Level of evidence: 2b, consensus.

Background

Prospective studies for the use of aminosalicylates for carcinoma prophylaxis are not available. In several case-controll studies there was a reduction in carcinomas with the use of 5-ASA medication [279, 291, 292]. In one cohort study the risk of a CRC was significantly reduced for patients who had taken aminosalicylates over a period of years [293]. Long-term use of aminosalicylates therefore appears to reduce CRC risk. The provider should discuss continuing aminosalicylate therapy for carcinoma prophylaxis with the individual patient in consideration of the risk factors present. It does not replace the necessity of regular endoscopic monitoring.
In patients with ulcerative colitis in combination with PSC ursodeoxycholic acid (UDCA) therapy appears to show a protective effect on the development of colorectal neoplasias [294].
Folic acid may have a protective effect for patients with ulcerative colitis [295], but further studies are necessary.

III.3.3. Surveillance for patients with ulcerative colitis

Recommendation

For patients with ulcerative pancolitis which has been present for more than 8 years, or left-sided colitis which has persisted for at least 15 years, a complete colonoscopy with biopsies (a minimum of 4 biopsies every 10 cm*) should take place annually.*
Level of Recommendation B, Level of evidence: 2b, consensus.

Background

Apparently the mortality from colorectal carcinoma in ulercative colitis patients can be significantly reduced with regular colonoscopic surveillance [296 – 298]. A series of biopsies should be taken – if possible during disease remission because the histomorphological differentiation of inflammatory versus low-grade intraepithelial neoplastic changes can be difficult. At least four biopsies every 10 – 12 cm, altogether 40 – 50 biopsies should be taken. The biopsies should be taken from all macroscopically suspicious areas, but also from mucosal areas with no macroscopic abnormalities. From one study it can be concluded that taking 33 biopsies per colonoscopy is associated with a 90% chance of detecting a present intraepithelial neoplasias; taking 56 biopsies increases the chance of detection to 95% [299].

Recommendation

With clear and, through an independent second pathological examination, confirmed high-grade intraepithelial neoplasias in flat, non-inflamed mucosa it is recommended that the patient should undergo elective, continence-retaining proctocolectomy.
Level of Recommendation B, Level of evidence: 2b, strong consensus.

Background

With the evidence of a high-grade intraepithelial neoplasia and its confirmation by an independent pathologist, due to

the clearly increased risk of carcinoma among such patients a proctocolectomy is recommended [300]. Proceeding on the basis of the finding of low-grade intraepithelial neoplasias is not clear based on the current data available.
While some studies showed frequent progression to advanced neoplastic lesions [301, 302] in other studies this high progression rate was not observed [303]. An existing problem for the assessment of the meaning of low-grade intraepithelial neoplasias is the low degree of diagnostic agreement even among specialized pathologists [304, 305]. Due to the recent data it was decided that a general recommendation for proctocolectomy in case of detection of low-grade intraepithelial neoplasias can – in contrast to the previous guidelines – no longer be recommended. Instead it is recommended to intensify anti-inflammatory therapy as well as performing a control colonoscopy after 3 – 6 months and discussing the further management options with the patient. In the presence of a singular dysplasia in an adenomatous area without proof of synchronous dysplasia in the surrounding mucosa, endoscopic removal and follow-up examinations at short intervals are sufficient [306, 307].
The development of intraepithelial neoplasias up to carcinomas has been described in some cases after a proctocolectomy [308]. This is the basis for the recommendation of regular pouchoscopies with biopsies taken. However the risk of developing a dysplasia in the pouch after proctocolectomy seems to be very low [308 – 310], so that the value of a regular pouchoscopy to detect dysplasia appears unclear at this time.
Performing a prophylactic proctocolectomy in patients with long standing ulcerative colitis without having performed regular surveillance colonoscopies before as is being done especially in Scandinavia cannot be recommended [311].
First data on the use of chromoendoscopy for surveillance in ulcerative colitis patients appear promising, but further studies are necessary [312].

Patients with Crohn's Disease

Recommendation

For patients with Crohn's disease, at this time no general recommendation for endoscopic surveillance can be given.
Evidence strength: 5

Background

Because endoscopic examinations for patients with Crohn's disease should be planned on an individual basis and depend on the progression and extend of the disease, and there is no conclusive data on the benefit of an endoscopic surveillance, no general recommendations for surveillance can be given at this point in time although the CRC-risk for these patients seems to be elevated. The indications for colonoscopy (apart from the screening recommendations for the normal population) depend on specific questions in the context of the underlying disease.

Topic IV: Endoscopy: Performance and Polyp Management

▼

IV.1. Endoscopy for the detection of Polyps and Colorectal Carcinomas
  IV.1.1. Sigmoidoscopy versus Colonoscopy
  IV.1.2. Chromoendoscopy
  IV.1.3. Zoom Endoscopy
IV.2. Polypectomy
  IV.2.1. Snare versus biopsy forceps
IV.3. Histological Examination
IV.4. pT1 Carcinomas
IV.5. Polyp Surveillance
IV.6. Medical Secondary Prevention of Adenomas

IV.1. Detection of Polyps and Colorectal Carcinomas

Recommendation

The complete colonoscopy is the standard procedure for the detection of colorectal polyps and carcinomas. It has the highest sensitivity and specificity for the detection of colorectal cancer and polyps. The effectiveness of colonoscopy is influenced decisively by the examination quality. The examination quality is influenced by technical factors and the endoscopist.
Evidence strength: 1b, strong consensus.

Recommendation

With an incomplete colonoscopy due to a stenosing tumour, an additional preoperative CT or MRI colonography can be performed. A complete colonoscopy should be conducted postoperatively.
Level of Recommendation A, Level of evidence: 4, strong consensus.

Recommendation

With incomplete colonoscopy due to another cause (e.g. adhesions), a CT or MRI colonography should be performed.
Level of Recommendation B, Level of evidence: 4, strong consensus.

Background

Colonoscopy is the most-reliable procedure for the detection of colorectal carcinomas and polyps if performed with high quality. Important quality features include a complete examination up to the coecum, optimal preparation with little or no remaining stool remains as well as the careful inspection of the colorectal mucosa during withdrawal. It was shown that the polyp detection rate correlates with withdrawal time after reaching the coecum. The withdrawal time should be at least six minutes [313 – 315]. Further quality features include the primary detection of polyps in 20 – 50% of examinations (polyp detection rate) [316], as well as missing polyps in less than 10% of patients (polyp miss rate) [123, 317].
However colonoscopy also has limitations: 4 – 6% of carcinomas are missed during the initial exam [318 – 320]. Also within a time period of three years after a colonoscopy with polypectomy of adenomas, interval carcinomas appear in up to 1% [321]. These can partly be attributed to missed lesions (see also the section on polyp management, chapter IV.5).
Sensitivity and specificity of CT colonography has improved in the past few years since the presentation of the last guidelines. In one study, colonoscopy and CT-colonography performed equally in the detection of polyps > 5 mm [123]. However in other studies this particularly good result could not be achieved [322, 323]. Here CT-colonography was clearly inferior to colonoscopy, [324, 325], but was better than double contrast enema [323, 326]. Nowadays double contrast barium enema of the colon does not play any role in sceening. For the evaluation of MR colonography for screening, there are too few study results available [327 – 329].

Diagnostic problems with CT colonography can include remaining stool and poor unfolding of the colorectal lumen. The detection of flat, sunken and small polyps is more difficult than prominent polyps. Due to missing standardization, the results at this time are strongly dependent on the centre performing them. In addition the high price and the radiation exposure associated with CT colonography have to be considered.
For this reason, for the work-up of a positive faecal occult blood test (FOBT) or in case of a suspected tumour, a complete colonoscopy is regarded as the gold standard. Colonoscopy also allows the posibillity of taking biopsies for histological diagnosis, as well as performing polypectomy. In case of pathological findings during colonoscopy, a location classification according to endoscopic-anatomical structures or diphanoscopy are insufficient; a statement of distance from the anus in cm should only be used for lesions in the rectum and lower sigmoid colon. With findings that are unclear or have a clear surgical indication labelling using a clip (only at a time close to surgery) or India ink should be performed in order to enable reidentifying the lesion later on.
For patients with stenotic tumours additional or incomplete colonoscopies for other reasons, in case series additional proximal tumours or polyps were detected using CT or MR colonography [330 – 333].

IV.1.1. Sigmoidoscopy versus Colonoscopy

Recommendation

In case of a positive FOBT, suspicion of a tumour or sigmoidoscopic evidence of neoplastic polyps a full colonoscopy has to be performed.

Level of Recommendation A, Level of evidence: 2b, strong consensus.

Background

Work-up of a positive FOBT test and/or suspicion of tumour requires a complete colonoscopy, because this method is able to detect adenomas and carcinomas in the right hemicolon. Relevant neoplastic lesions proximal to the sigma are found in 25 – 55% of cases. In screening studies it could be shown that in 30 to 46% of cases with proximal advanced neoplasias in the right hemicolon the rectosigmoid is free of adenomas [108, 110].
A sigmoidoscopy should only be performed as an exception when a complete bowel preparation is not possible. A complete colonoscopy is possible in a high percentage of cases and can also be conducted among older patients with a low rate of side-effects [324, 325]. Sigmoidoscopy plays no significant role in Germany as a screening test.

IV.1.2. Chromoendoscopy

Recommendation

Chromoendoscopy can be performed in patients with inflammatory bowel disease and HNPCC for improved detection of neoplastic lesions. It can in addition be used for a better demarcation of flat and sunken lesions before endoscopic therapy.

Level of Recommendation 0, Level of evidence: 1b, strong consensus.

Background

Among patients with IBD or HNPCC, an increased detection rate of neoplastic lesions using chromoendoscopy has been shown [312, 336, 337]. In studies on patients without hereditary tumour diseases or IBD, a higher detection rate of mostly small adenomas was found [338 – 340], this however was not confirmed in another study [341].
It is currently unclear whether the recognition of an increased rate of primarily smaller lesions is useful for the patient and justifies the greater amount of time required for the examination.
Employing chromoendoscopy with indigo carmine or methylene blue enables a better delimitation of flat and sunken lesions from the surrounding healthy mucosal tissue [342 – 347]. Chromoendoscopy can therefore be used before the endoscopic removal of flat adenomas.

IV.1.3. Magnifying Endoscopy

Recommendation

The use of magnifying endoscopy with evaluation of lesions according to the "pit pattern" classification is not a standard procedure at this time.

Level of Recommendation 0, Level of evidence: 2b, strong consensus.

Background

The goal of magnifying endoscopy is to differentiate between hyperplastic and neoplastic lesions without histology using the "pit-pattern" classification, and to decide which lesions have to be removed. In some studies this was possible with high sensitivity [339, 348, 349]. In other studies however the specificity was not sufficient with 75% [344, 346, 350, 351]. Magnifying endoscopy does not replace histology at this time. Magnifying endoscopy is helpful in the evaluation of polypoidal and flat lesions before polypectomy, but cannot at this time be recommended as a standard procedure.
Procedures such as narrow-band imaging (NBI) or Fuji intelligent chromoendoscopy (FICE) represent further methods for the evaluation of neoplastic lesions. In uncontrolled studies NBI was helpful in the detection of flat adenomas, the detection of intraepithelial neoplasias in patients with ulcerative colitis as well as differentiating benign and malignant lesions [352 – 354]. For FICE there are currently no comparable data available. Confocal laser microscopy is a diagnostic procedure that should be further evaluated in clinical trials [355].

IV.2. Polypectomy

IV.2.1 Removal of polyps by snare versus forceps

Recommendation

Polyps should 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 Recommendation A, Level of evidence: 1c, strong consensus.

Background

In order to allow an exact classification, polyps should be individually retrieved for histological processing and their localization be recorded. With several polyps in one segment, combined retrieval of these polyps is justified. With this, however, the oncological resection borders must be respected; marking the colon segment where the polypectomy has been performed can be useful.
The following endoscopic procedures are available:

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

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

A requirement and limitation for an endoscopic removal of larger polyps are the realistic chance of a complete removal of the polyp with low bleeding and perforation risks. The experience of the endoscopist and the localization of the polyp can also be limiting factors. Other factors that should be considered include the increasing rate of carcinoma with increasing size of neoplastic polyps (up to 15%), the polyp characteristics (sessile or flat vs. pedunculated), the general status of the patient as well as the increased risk of perforation in the proximal colon [356–360]. Flat lesions can be removed using an endoscopic mucosectomy (EMR) [360–362]. Exclusively depressed, flat lesions (IIc) should as a rule be treated surgically and not endoscopically, because most of these lesions do not present so-called 'early invasive T1 carcinoma' and complete endoscopic removal (R0) is seldom possible. Evidence of this is a non-lifting sign. Independent factors in relation to the risk of perforation are polyp size over 1 cm as well as localisation in the right colon, for the risk of bleeding only a polyp size of > 1 cm [363]. The risk of severe bleeding (requirering transfusion, surgical intervention, recurrent bleeding) is 0.9%, risk of perforation in the right colon 1.2%, in the left colon 0.4%. A prophylactic injection of NaCl or adrenalin into the base or the shaft of the polyp or the use of an endoloop reduces early-onset bleeding with the removal of larger polyps > 1 cm [364–367]. The rate of late-onset bleeding is not reduced, however [368].

A polypectomy can also be carried out in patients who are taking a platelet-aggregation inhibitor [369–371], the combination of aspirin and clopidogrel, however, increases the risk of bleeding and should be avoided [372]. The complete removal of a polyp is always required, because the remaining rest of an incompletely removed polyp can still contain a high-grade intraepithelial neoplasia or a carcinoma. The size of the removed polyp, the histological type of adenoma and the degree of severity of the intraepithelial neoplasias specifies the degree of risk for local recurrence and metachronous polyps. With polyps > 2 cm the local recurrence rate is 8–20% [373]. The recurring polyp can as a rule also be removed endoscopically.

With possible or expected need for a surgical treatment of a polyp, preoperative marking of the polyp area with clip or ink has to be performed to aid localizing the lesion (exception: coecum and distal rectum).

An alternative is performing an intraoperative colonoscopy to localise the polyp or the site of removal. Marking a polypectomy area should be also carried out after endoscopic interventions in cases of difficult localisation (with a decreased ability to find the area again during repeat or surveillance examinations).

Recommendation

In order 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.*

In general diagnostic colonoscopies should only be performed if the possibility of performing a polypectomy using a snare is given.

Level of Recommendation A, Level of evidence: 3b, strong consensus.

Background

In order to prevent double examinations, a colonoscopy should only be performed if the possibility of performing interventions is given. If the removal as a lesion is not possible or does not make sense (risk situation in an out-patient setting, inadequate expertise with larger polyps), the lesion should be marked and the patient should be referred to an expert centre. A biopsy of polyps does not make sense if removal is technically possible. In addition, the result of such a biopsy is unreliable [374]. Furthermore, extensive biopsies can cause scarring which can make it more difficult to perform a subsequent endoscopic removal. Biopsies are obligatory when clear malignancy criteria are met with a primary indication for surgery. For polyps ≤ 5 mm adenomas with invasive carcinomas are rarely seen, with polyps ≤ 1 cm the rate is < 1%. The goal of a colonoscopy must be to achieve a polyp-free colon (clean colon). For polyps ≤ 5 mm a complete removal using biopsy forceps is required in order to histologically classify the lesion. Small (≤ 5 mm) polyps in the rectum with typical macroscopic appearance of hyperplastic polyps do not have to be removed. In recent years evidence has accumulated that, in addition to the adenoma-carcinoma sequence, a further pathway to colorectal carcinoma the so-called "serrated pathway" exists (see below).

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

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

- at least 5 hyperplastic polyps proximal to the sigmoid colon, whereby two should be larger than 1 cm;
- the appearance of hyperplastic polyps proximal to the sigmoid colon, independent of the polyp number and size, if a first-degree relative (parents, children, siblings) have been diagnosed with a hyperplastic polyposis;
- if more than 30 hyperplastic polyps of any size appear proximal to the sigmoid colon [375–381].

IV.3. Histological Examination

Recommendation

The histological examination of each polyp is obligatory. The histological reporting of polyps should follow WHO criteria [281]*with a statement about the completeness of the removal. Conventional adenomas are classified according to histological type of growth (tubular, tubulo-villous and villous) and the level of intraepithelial neoplasia (low- and high-grade intraepithelial neoplasias); serrated lesions are sub classified under hyperplastic polyps, sessile serrated adenomas, mixed polyps (with IEN grade) and traditional, serrated adenomas (with IEN grade)* [382–383].

Level of Recommendation A, Level of evidence: 3b, strong consensus.

Background

About 8% of the polyps classified as hyperplastic are sessile serrated adenomas according to new findings (SSA). These adenomas possess a potential to progress to carcinoma, especially if their size is greater than 1 cm and they are located on the right side of the colon. In addition, mixed mucosal

polyps (mixed polyps) may occur. In addition, 2% of all colorectal polyps are traditional serrated adenomas (TSA). All of these variants demonstrate a similar molecular pathway on their progression to cancer.

Recommendation

In case of a carcinoma, the histology report has to contain the following characterizations [384]*:*

- *A measure of the depth of infiltration (pT category), with sessile polyps the invasion measurement in µm,*
- *the histological differentiation grade (grading),*
- *Presence or absence of lymph vessel invasion (L classification), and*
- *the judgment of the resection borders (R classification in regards to the local removal in healthy tissue (for depth and on the sides).*

Level of Recommendation A, Level of evidence: 2b, strong consensus.

Recommendation

Because of the therapeutic consequences for completely removed pT1 carcinomas, a classification into "low-risk" (G1, G2 and no lymph vessel invasion (L0) or "high-risk" (G3, G4 and/or lymph vessel invasion (L1) should be performed.

Level of Recommendation A, Level of evidence: 2b, strong consensus.

Background

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

IV.4. Approach for pT1 Carcinomas

Recommendation

In the context of an endoscopically R0-removed polyp with a pT1 carcinoma, no additional oncological resection should be performed, if there is a low-risk situation with a carcinoma-free polyp base (R0) [385–388]. *In the high-risk situation, radical surgical therapy is required, even if the lesion has been completely removed.*

Level of Recommendation A, Level of evidence: 3a, consensus.

Recommendation

With incompletely removed low-risk pT1 carcinoma, a complete endoscopic or local surgical removal has to follow [389]. *If an R0 situation cannot be achieved or it is doubtful that a pT1 situation exists, an oncological-surgical resection is necessary.*

Level of Recommendation A, Level of evidence: 3a, strong consensus.

Background

The prognosis of pT1 carcinomas can vary widely.

The major determinant of a risk stratification is the probability of lymph node metastases. Overall the group of T1 carcinomas shows a lymph node metastasis rate (N+) of 0–20% [386, 390–392]. For the estimation of the rate of lymph node metastases, there are qualitative and quantitative prognostic criteria [392, 393].

Qualitative criteria are: Grading (G1 – well differentiated, G2 – moderately differentiated, G3 – poorly differentiated, G4 – undifferentiated) and the invasion of lymph vessels (L classification) of the polyps. Quantitatively, the submucosal invasion of the surgical and endoscopically removed specimen can be measured. A proven method involves deviding the submucosa into three layers. In case of endoscopic removal of a sessile polyp the measurement of the submucosal invasion depth in µm makes more sense, because the submucosa is not available as a total layer and/or no muskularis propria is present. The so-called early invasion forms (sm1, sm2 and/or submucosa invasion ≤1000 µm) have a low N+ risk of 0–6% [393, 394]. On the other hand, with sm3 carcinomas the risk of lymph node metastasis is about 20% [394, 395]. Cave: The measurement of submucosal thickness for stalked polyps in µm is not helpful and/or can lead to false conclusions, because the sub mucosal thickness depends upon the length of the stalk; this means that the stalk is always level sm1. The presence of vein invasion (V classification) should be mentioned, but the value for local therapy is currently unknown.

Additional comments

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

Warning signs are: presence of ulcerations, depressed lesions, contact bleeding and the lack of a lifting sign when injecting under the lesion. Proof of having achieved a R0 situation is mandatory; the necessity of a safety margin of 1 mm from the base is controversial [393]. An endoscopic removal as an en-bloc resection is optimal. Removal using a piecemeal technique appears adequate. With this, evaluation of lateral R0-margins is done macroscopically during endoscopy, evaluation of vertical infiltration and complete removal is performed histologically (basal R0). In any case, an early (2–6 months) endoscopic reexamination of the resection site is necessary. According to available data in a low-risk situation [386, 388, 392–394, 396], the post-interventional rate of metastases and/or local recurrence is 0–5%, whereby the concept of early invading sub mucosal carcinomas is only adressed in the newer studies. Local endoscopic therapy of early colorectal malignant neoplasias is a safe and effective therapy in specialized centres, and is considered to be the standard procedure if all low-risk criteria are present. In this situation a radical surgical resection according to oncological criteria is not necessary.

Recommendation

After complete removal (R0) of low-risk (pT1, low-grade (G1, G2, L0) carcinomas endoscopic surveillance examinations of the local resection location should be performed after six months and after two years.

Level of Recommendation A, Level of evidence: 4, strong consensus.

Background

The recommendations are made to enable the recognition of local recurrences and consist of inspection of the former lesion site. A colonoscopy of the whole colon for the early detection and treatment of recurrences should be performed according to the recommendations for adenoma surveillance.

IV.5. Polyp Surveillance

Recommendation

After removal of small single, non-neoplastic polyps, there is no necessity for endoscopic surveillance [397 – 399].

Level of Recommendation A, Level of evidence: 3b, strong consensus.

Reasoning: unnecessary use of endoscopic resources

Background

Patients with small (< 1 cm) hyperplastic polyps and negative family history, do not seem to haven an increased colorectal cancer risk. Here the general recommendations for CRC screening apply, i.e. a screening colonoscopy every 10 years. Exceptions are non-neoplastic polyposis syndromes (hyperplastic, juvenile, Peutz-Jeghers) with an increased CRC-risk [400].

Recommendation

After complete removal of neoplastic polyps (adenomas) a surveillance endoscopy is necessary. The time point of the surveillance endoscopy should be dependent upon the number, size and histology of the removed adenomas. With patients with 1 or 2 adenomas < 1 cm *without high-grade intraepithelial neoplasia a surveillance colonoscopy after five years is sufficient.*

Evidence strength: 2b, strong consensus.

With patients who have 3 – 10 adenomas, or at least one adenoma that is 1 cm or larger, or an adenoma with villous histology, the first control colonoscopy should follow after 3 years.

Evidence strength: 1b, strong consensus.

For patients with adenomas with high-grade intraepithelial neoplasia and histologically-confirmed complete removal, a surveillance colonoscopy after three years is sufficient.

Evidence strength: 1b, strong consensus.

With histologically non-confirmed complete removal, even if macroscopically the removal was complete, an early (2 – 6 months later) control should be performed.

Evidence strength: 3b, strong consensus.

In the case of over 10 adenomas, the control interval should be shorter than 3 years.

Evidence strength: 3b, strong consensus.

After removal of large, flat or sessile adenomas in piecemeal technique, a short-term control of the removal area should follow after 2 – 6 months.

Level of evidence: 3b, strong consensus.

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 carcinoma and independent of an IEN grade, a control surveillance should follow after three years.

Evidence strength: 4, strong consensus.

Background

The recommendations for post-polypectomy management should be influenced by the individual risk of the respective patients (family history, comorbidities, diverticulosis [401]), and the cleanliness of the colon in the last colonoscopy. The recommendations made above rely upon a high-quality base line colonoscopy (see above). After diagnosis and removal of adenomas interval carcinomas are diagnosed in 0.7 to 0.9 % of patients within 3 years [321]. This is caused by missed lesions (miss rate), incomplete polypectomies as well as the occurence of tumours with a faster progression rate [123, 317, 319, 402].

An underlying principle for the establishment of surveillance recomendations after polypectomy is a patient risk stratification according to the low-/high-risk adenoma concept. The classification of patients into these risk groups follows according to the number, size and histology of the removed adenomas during the base-line colonoscopy.

According to this classification, a low-risk adenoma situation is defined as follows: 1 – 2 tubular adenomas, each < 1 cm, only LGIEN, exclusion of HGIEN and villous components. A high-risk adenoma situation (so-called advanced adenomas) is defined as follows: ≥ 3 tubular adenomas, ≥ 1 adenoma with ≥ 1 cm, adenoma with tubulo-villous or villous structure, ≥ 1 adenoma with HGIEN, ≥ 10 adenomas independent of size or histology [403].

Also in piecemeal technique removed flat or sessile adenomas belong to this high-risk group.

A surveillance interval of five years for the so-called low-risk adenoma group seems reasonable. If no adenomas are detected during the surveillance colonoscopy the colonoscopy should be repeated after 5 years. For the so-called high-risk adenoma groups, the control interval should be three years provided that there is histological proof of complete removal of the lesion. If the surveillance colonoscopy is without adenom detection the next colonoscopy can follow after 5 years.

After removal of flat or sessile adenomas in piecemeal technique, the recurrence rate is significantly increased, especially with larger adenomas (9 – 28 %) [373, 404 – 407]. The use of argon plasma coagulation to remove remaining tissue to ensure a complete removal can be helpful [405, 407]. In this case, however, a complete histological examination cannot be done. The special group of patients with removal of flat or sessile adenomas using the piecemeal technique should undergo surveillance colonoscopy after a short period of time (2 – 6 months), due to the higher rate of metachronous lesions, then after three years, then after five years; in some cases, if necessary, sooner than that. In cases of larger ≥ 1 cm and especially right-sided sessile serrated adenomas (earlier classified as hyperplastic polyps), a potential accelerated progression risk for carcinoma appears to be established (via the serrated pathway), so that in these cases a complete removal and a short control interval are recommended (according to the current level of understanding, after three years).

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

For recommendations for surveillance with HNPCC, FAP and IBD patients (see guideline manuscript from 2004, section VIII.6.).

IV.6. Medical Secondary Prevention with Adenomas

Recommendation

Medical secondary prophylaxis should not be given after polypectomy, except in the context of clinical studies.

Level of Recommendation B, Level of evidence: 1b, strong consensus.

Background

Even though a small preventative effect has been demonstrated for aspirin in several prospective randomized studies with high levels of evidence (1b) [408, 409], this cannot be recommended due to the small effect (reduction of the recurrence rate by a maximum of 35 %) and the known side-effects [410].

The same is true for COX-2 inhibitors, for which a reduction in the adenoma recurrence rate of 24 to 45% has been shown [411–413], associated however with a significantly increased rate of cardiovascular side-effects [414, 415], which outweigh their potential benefit [416]. The reduction of the adenoma recurrence rate of 12% with calcium appears to be too low in order to recommend long-term administration for this indication [417].

Topic V: Pre-operative Diagnosis and Surgery (2004)

▼

V.1. Introduction
V.2. Definition of colon and rectal carcinoma
V.3. Preoperative Evaluation
V.4. Surgical Therapy with curative Intention
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V.6. Special situations
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V.1. Introduction

In the following the general principles of diagnosis and therapy, as long as they apply to both colon and rectal carcinoma, will be shown in a summary fashion for both entities. Unique diagnostic and therapeutic aspects will be listed separately.
The therapy of colorectal carcinomas should be planned primarily on the basis of a histopathological examination. A colorectal carcinoma is defined by atypical epithelial formations infiltrating into the submucosa (pT1 or more). Not included are the so-called mucosal carcinomas or intraepithelial carcinomas (pTis) who have no metastatic potential, and can be treated by local excision alone.

V.2. Definition of colon and rectal carcinoma

The border between the colon and rectum has been defined differently. The intraoperative assessment in regards to the end of the taeniae or the peritoneal fold is different for each individual and depends upon age, sex and other factors. The preoperative determination of the distal tumour 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 [418, 419], rectal carcinomas have aboral borders 16 cm or less from the anocutaneous line as measured by a rigid rectoscopy. According to UICC 2003, rectal carcinomas are furhther subdivided by the distance from the anocutaneous line in carcinomas of the upper rectal third (12–16 cm), the middle rectal third (6–<12 cm) and the lower rectal third (<6 cm) [420]. In the US, colon carcinomas by definition have a distal magin more than 12 cm and rectal carcinomas a distal margin less than 12 cm from the anlcutaneous line. This is based on the significantly higher local recurrence rate with tumours with less than 12 cm distance from the anocutanoeus line [423].

V.3. Preoperative evaluation

Recommendation

The following examinations should be obligatory components of a preoperative evaluation of patients with with colorectal carcinomas:

- *digital rectal examination*
  Evidence strength: 5, Recommendation level: A, strong consensus.
- *complete colonoscopy with biopsy*
  Evidence strength: 4, Recommendation level: A, strong consensus.
- *In the case of an endoscopically impassable stenosis, complete colonoscopy 3–6 months postoperatively,*
  Level of evidence: 3b, Recommendation level: A, strong consensus.
- *Abdominal ultrasound*
  Evidence strength: 5, Recommendation level: A, strong consensus.
- *Chest X-ray (2 planes)*
  Evidence strength: 4, recommendation level: A, strong consensus.
- *CEA test*
  Evidence strength: 1a, Recommendation level: B, strong consensus.

Background

Before therapy of a patient with a colorectal carcinoma a colonoscopy with biopsy has to be performed. Because in up to 5% of colorectal carcinomas there are synchronous tumours which can be missed on intraporative evaluation, a colonoscopy of the entire colon should be undertaken [424–426]. If for technical reasons a complete colonoscopy is not possible, an alternative radiological procedure should be used. The virtual colonography presents a promising alternative to the colon contrast procedure with higher sensitivity in a case series [332]. If a complete colonoscopy is not possible due to a stenotic process, a colonoscopy should be undertaken 3 to 6 months after resection. A preoperative colon contrast enema is of little value and in the case of stenoses has the danger of creating an ileus and is therefore not recommended. The establishment of virtual colonography for these indication cannot be answered due to a lack of data.
The digital-rectal examination allows an initial judgment of the sphincter function as well as the depth of infiltration with deep-seated rectal carcinomas and allows an estimation of the possibility of sphincter preservation.
Percutaneous ultrasound of the abdomen is generally conducted as a screening examination of the abdomen (liver, ascites, and gallstones). In addition, possible infiltration of adjacent organs can be assessed. Suspicious findings in the liver must be evaluated by additional imaging tests (see below). A chest x-ray in two planes serves as a proof or exclusion of lung metastases. Suspicious findings are also to be evaluated with additional imaging tests (see below).
The preoperative CEA value is an independent prognostic parameter and should therefore be established preoperatively [427–429].

Recommendation

The following examinations can be useful in individual cases:

- *Spiral computed tomography or MRI of the abdomen*
- *Spiral computed tomography of the thorax*

Recommendation level: A, strong consensus.

Background

A spiral or multi-slice CT is routinely indicated only for ambiguous or pathological findings on abdominal ultrasound. In studies of routine use of preoperative abdominal computed tomography in patients with colorectal cancer, there was a change of the further management in only a few cases [430, 431]. It can be useful to have a CT or MRI of the abdomen in patients who have a clinical or sonographic suspicion of a tumour extension beyond the colon/rectum and with sigmoid carcinomas with regard to the question of infiltration of neighbouring organs (bladder, uterus/adrenals).

Spiral computer tomography of the thorax serves to clarify a suspicion of lung metastases.

PET is not useful in the primary diagnosis of colorectal carcinomas. A micrometastatic diagnosis is at this time without therapeutic consequence and is not an independent prognostic parameter.

Special diagnostic procedures in rectal carcinoma (see also topic area VI)

Recommendation

The following examinations should be obligatory components of preoperative evaluation of patients with rectal carcinomas:

- *Rigid rectoscopy*
  Evidence strength: 1c, Recommendation level: A, strong consensus.
- *Endoscopic ultrasound*
  Evidence strength: 2b, Recommendation level: A, strong consensus.

The following examinations can be useful in individual cases:

- *Pelvic CT or MRI*
  Evidence strength: 2a, Recommendation level: B, strong consensus.
- *Anal sphincter manometry*
  Evidence strength: 4, Recommendation level: B, strong consensus.
- *Gynaecological examination*
  Evidence strength: 5, Recommendation level: B, strong consensus.
- *Cystoscopy*
  Evidence strength: 5, Recommendation level: B, strong consensus.

Background

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

In addition, imaging of local tumour extension is useful in order to determine the necessity of a neoadjuvant therapy. Transrectal endoscopic ultrasound has the highest accuracy to determine depth of infiltration and is therefore essential before treatment by local excision. However the quality of the examination depends significantly on the experience of the examiner [432–439]. With high-grade stenoses or tumours in the proximal rectum, an endoscopic ultrasound is frequently impossible for technical reasons.

Except for unambigouos uT1/2, uN0 tumours, local staging by computed tomography or MRI is desirable [440]. CT has the advantage of widespread availability. The sensitivity for the assessment of local tumour infiltration was 66–88% in studies; the sensitivity regarding lymph node status is lower with about 60% [441]. The first results for the use of multiple-detector spiral CT for the delineation of the mesorectal fascia and the possibility of secondary reconstructions are quite promising [442]. Thin-layer MRI allows a higher accuracy of delineation of the mesorectal fascia and a tumour's relationship to them [443–446]. In the most recent studies MRI using special techniques was better than CT with regard to the assessment of infiltration of the mesorectal fascia [447].

Anal sphincter manometry generally has no influence on the decision regarding sphincter preservation, compared to the digital rectal examination and a detailed history. In ambigous cases, it can aid in the decision regarding sphincter preservation.

In case of a suspected infiltration of the bladder, a cytoscopy can be helpful. In the question of infiltration of the vagina, uterus or ovaries, a gynaecological examination should be performed. Contrary to earlier guidelines, a urine sediment test is not recommended for patients with rectal or sigmoid carcinomas, because the examination is too unspecific.

V.4. Surgical Therapy with curative Intention

V.4.1. Intraoperative Staging

Recommendation

An intra-operative inspection and palpation of the liver should be performed in any case, i.e. also with inconspicious preoperative evaluation.

Level of Recommendation A, Level of evidence: 5, strong consensus.

An intraoperative sonography of the liver is desirable in case of ambigous preoperative staging; in the case of inconspicious staging it is not necessary.

Level of Recommendation C, Level of evidence: 5, strong consensus.

Background

In particular, subserous liver metastases can remain undetected by any preoperative imaging method. So an intraoperative inspection and palpation of the liver is always required.

Intraoperative ultrasound combined with palpation has the highest sensitivity for liver metastases [448, 449] and therefore is a useful additional staging method for ambigous liver results in the context of preoperative staging. With clear-cut negative preoperative evaluation, the diagnostic gains do not justify the effort.

V.4.2. Intraoperative pathological examination

In general, rapid sections should be used restrictively. The most frequent indication is in the evaluation of metastatic spread, e.g. on the peritoneum, in the liver or in non-regional (e.g. periaortal) lymph nodes.

With local surgical excision (full wall excision), the important question is posed whether a carcinoma proven by previous biopsy was excised with tumour-free margins. In the case of a deep-seated rectal carcinoma, rapid section examination of the aboral resection margin can be helpful for the decision of performing a total rectal extirpation.

With segmental resections of large colon polyps, especially of villous histology, in which preoperative 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!). It therefore is recommended to use the standard oncological resection in these cases.

In case of adherence of a tumour to neighbouring organs it is not feasible to determine macroscopically whether an infiltration of the neighbouring organs or only a peritumourous inflammatory reaction is present. In such cases, biopsies with rapid sections should be strictly avoided, because of possible local tumour cell dissemination, which can be associated with reduced survival [450]. This is the reason for the en-bloc resection in all cases of tumour adherence to neighbouring organs or other structures (see section on therapy and multivisceral resection).

V.4.3. Radical surgical therapy of colon carcinomas

Colorectal carcinomas grow primarily in a circular manner and metastasize for the most part constantly into the regional lymph nodes. Under the viewpoint of the intramural tumour spread, a safety margin of 2 cm is sufficient. The regional lymph drainage area extends beyond this margin. Lymph node metastases usually extend centrally along the concomitant vessels, primarily along the pericolonic vessel arcades up to 10 cm from the primary tumour [451].

The extent of resection is determined by the area supplied by the resected vessels and the area of lymphatic drainage defined by them. If the primary tumour lies between two central vessels, both are resected with it (at least 10 cm on both sides of the tumour.) In the case of a right-sided colon resection, a resection of 10 cm of terminal ileum is deemed sufficient from an oncological point of view.

Oncological Principles

In contrast to this, in the treatment of rectal carcinoma the necessity of a radical surgical procedure has not been demonstrated through randomized, prospective studies. Two randomized studies could not find a benefit of the "no-touch technique" [452] or a complete hemicolectomy [453]. Still, adherence to oncological principles is recommended on the basis of pathological-anatomical findings, prospective observer studies and theoretical considerations.

Resection of carcinoma of the coecum and the ascending colon

Standard procedure is a right hemicolectomy with radical dissection of the A. colica dextra and the A. ileocolica.

The A. colica arises primarily from the A. colica media and in less than 15% of all cases from the A. mesenterica superior [454]. The proximal part of the A. colica media is retained; the right-turning branches of the A. colica media are divided centrally. The major omentum in the area of the tumour (e.g. right colonic flexure) is also removed.

Resection of carcinomas of the right colonic flexure and proximal transverse colon

Standard procedure is an extended right hemicolectomy. In addition to a right hemicolectomy the A. colica media is ligated centrally at the beginning of the A. mesenterica superior. The distal resection margin lies next to the left colonic flexure. The major omentum is resected together with the gastrocolic ligament and the branches of the A. and V. gastroepiploica dextra corresponding to the position of the carcinoma in the transverse colon. With carcinomas of the right colonic flexure the lymph nodes cranial of the head of the pancreas are dissected; with carcinomas of the left flexure the lymph nodes at the caudal margin of the pancreas.

Resection of carcinomas of the middle transverse colon

With tumours in the middle of the transversum, the transverse colon is resected followed by the central ligature of the A. colica media and, depending on the situation, additional resection of the flexures. In case of doubt, an extended left hemicolectomy is preferred. The major omentum is resected together with the ligamentum gastrocolicum and the gastroepiploic branches (see above).

Resection of carcinomas of the distal transverse colon and the left colonic flexure

Standard procedure is an extended left hemicolectomy with the removal of the lymph drainage area of the A. colica media and the A. mesenterica inferior. Of similar value is the central ligature of the A. colica sinistra with retention of the proximal part of the A. mesenterica inferior. With this, the A. rectalis superior is retained, whereby the distal sigma can be left. Depending on the tumour location and the amount of bleeding, the right colonic flexure can be retained. The lymph nodes accompanying the proximal part of the A. mesenterica superior should be dissected up to the aorta for diagnostic reasons.

Resection of carcinomas of the colon descendens and proximal sigmoid colon

Standard procedure is a left hemicolectomy performed with ligature of the A. mesenterica inferior. The distal resection margins are in the upper third of the rectum. The left colonic flexure is resected along with it (transversorectostomy). For technical reasons it can be necessary to cut through the A. colica media, in order to assure a tension-free anastamosis.

Resection of carcinomas of the middle and distal sigmoid colon

Standard procedure is the (radical) sigmoid resection. The A. mesenterica inferior is ligated proximal or distal to the origin of the A. colica sinistra. An advantage of a proximal resection of the A. mesenterica inferior (near the origin) has not been demonstrated. The resection margins lie in the area of the descending colon and in the top third of the rectum.

V.4.4. Radical surgical therapy of rectal carcinoma

As a general rule the curative therapy of rectal carcinoma requires, in addition to the complete resection of the primary tumour, the partial or total removal of the mesorectum and with this the regional lymph drainage area (so-called radical resection according to the international documentation system for colorectal carcinoma [418, 419]). Only in strictly selected cases a curative resection is possible with only local measures. The following operative procedures are considered as equivalent in compliance with the criteria of oncological surgery, whereby the differential indication depends on tumour localisation, especially the relation to the dentate line and the levator muscle, the depth of infiltration and the anal sphincter function.

- The (deep) anterior rectal resection
- The abdominoperineal rectal extirpation

- The intersphincteric rectal resection (also described as an abdominal-perianal rectal resection). This operation requires special experience.

If at all possible, a continence-preserving procedure should be preferred with regard to the future quality of life. With poor sphincter function, a deep resection with rectal extirpation with permanent colostomy should be preferred.

Oncological Principles

Surgical therapy should adhere to the following principles:

- Removal of the regional lymph drainage areas with resection of the A. mesenterica inferior at least distal to the origin of the A. colica sinistra. The central dissection of the A. mesenterica inferior close to its origin has no prognostic significance; however this is often necessary due to technical reasons for the mobilization of the left hemicolon used for reconstruction [455]. A benefit of a lymph node dissection at the origin of the A. mesenterica inferior proximal to the exit of the A. colica sinistra has not been shown (strength of evidence: 2b) [456 – 458].
- The complete removal of the mesorectum with carcinomas of the middle and lower part of the rectum and the partial mesorectal excision with carcinoma of the upper third of the rectum through sharp dissection along the anatomical structures between the fascia pelvis visceralis and parietalis (total mesorectal excision TME) [459, 460].
- The observance of an appropriate safety distance (see below).
- As a rule, the en-bloc resection of tumour-adhering organs (multivisceral resection) to prevent local tumour cell dissemination [461].
- The preservation of the autonomic pelvic nerves (Nn hypogastrici, plexus hypogastrici inferiores and superior) [462, 463].

Approach to tumours of the upper third of the rectum

Recommendation

With tumours of the upper third of the rectum, resection of the rectum with partial mesorectal excision 5 cm *distal to the macroscopic tumour border, measured in-vivo should be performed. The mesorectum should be cut horizontally without a proximally-oriented thinning (no coning).*

Level of Recommendation A, Level of evidence: 3b, strong consensus.

Background

The reason for this procedure [464, 465] is that with T3 and T4 tumours, in a few cases satellite nodes or lymph node metastases can occur up to 4 cm distal to the macroscopic tumour margin, measured from the histological cut after fixation of the non-stretched preparation, Level of evidence: 3b [459, 466 – 468].

Approach to tumours of the middle and lower third of the rectum

Recommendation

With tumours of the middle and lower third of the rectum, a total mesorectal excision (TME) should be performed up to the pelvic floor, preserving the plexus hypogastricus superior, the Nn hypogastrici and the plexus hypogastrici inferiores [462, 469 – 478].

Level of Recommendation A, Level of evidence: 1b, strong consensus.

Recommendation

With low-grade tumours with high or moderate differentiation of the lower third of the rectum, a safety margin of 2 cm in-situ is sufficient. As a minimum a 1 cm *margin on fresh, non-stretched preparation can be sufficient in order to enable a continence-preserving resection. With high-grade tumours (G3/4), a larger safety margin must be attempted* [460, 479 – 482].

Level of Recommendation B, Level of evidence: 2b, strong consensus.

With carcinomas of the lower third as an alternative to the otherwise recommended rectal extirpation, the intersphincteric rectal resection has been conducted (also called the abdominal-perianal rectal resection), if – under observance of the above-named safety margins – the puborectal loop is not infiltrated. This operation requires special experience.

After a total mesorectal resection with an anastomosis near the anal sphincter, significant functional disturbances can occur. These are most often encountered after straight anastomoses. These consequences can be partially reduced through different alternative reconstruction procedures.

Some possibilities available include:

- the colon J-pouch
- the transverse coloplasty
- the side-to-end anastomosis

The available evidence is in favour of the colon J-pouch.

Recommendation

In the case of a length of pouch loop of more than 6 cm, *evacuation problems can be expected.*

Apart from this with a very fatty mesocolon technical problems may make this procedure impossible. Alternatives include the side-to-end anastomosis and the transverse coloplasty, whose final significance cannot be determined due to low number of reported cases and/or contradictory results [483 – 492].

Level of Recommendation A, Level of evidence: 1b to 3b.

After a total mesorectal excision creation of a protective stoma is recommended. With this, the rate of insufficiency will not be reduced, but postoperative morbidity associated with it will decline. Ileostoma and colostomy are of equal value [493 – 496].

Level of Recommendation A, Level of evidence: 2b.

Local excision of rectal carcinomas

Recommendation

Local surgical excision of rectal carcinoma (full wall excision) as the only treatment is only recommended for pT1 carcinomas with a diameter up to 3 cm, good or moderate differentiation, without lymph vessel invasion (low-risk histology), with complete resection (R0) being a prerequisite. [497 – 500].

Level of Recommendation A, Level of evidence: 1b, strong consensus.

Recommendation

With T1 high-risk carcinomas (G3/4 and/or lymph vessel invasion) and with T2 carcinomas, the probability of lymphatic spread is around 10 – 20%, so that in general local excision alone cannot be recommended.

Level of Recommendation B, Level of evidence: 3b, strong consensus.

(see also section IV.4)

V.5. Laparoscopic surgery

Recommendation

The results of laparoscopic surgery in colorectal cancer cannot be conclusively evaluated due to the lack of data on long-term follow-up. At the moment, laparoscopic surgery should only take place in the setting of prospective studies with long-term follow-up [501 – 505].

Level of Recommendation A, Level of evidence: 2a, majority agreement.

Also, with regard to quality of life after laparoscopic surgery for colorectal cancer, so far there are no convincing data confirming a benefit [506].

Level of Recommendation A, Level of evidence: 1b, majority agreement.

Background

Concerning the treatment of rectal carcinoma there is only one randomized study of postoperative functional impairment in comparison to open surgery with an increased rate of urogenital functional impairment with laparoscopic treatment. Data regarding long-term follow-up are limited to observational studies and do not allow a final conclusion [507].

V.6. Special situations

Multivisceral resection

In the case of adherence of a tumour to neighbouring organs it is not feasible to determine macroscopically whether an infiltration of the neighbouring organs or only a peritumourous inflammatory reaction is present. In such cases, biopsies and immediate sectioning should be strictly avoided, because of the possibility of local tumour cell dissemination, which can be associated with a reduced survival [450]. *This is the basis for performing an en-bloc resection in all cases of tumour adherence to neighbouring organs or other structures (multivisceral resection). In the case of rectal carcinoma total pelvic exenteration can be necessary.*

Level of Recommendation Level of evidence: 4, strong consensus.

Multiple carcinomas of the colon and rectum

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

Synchronous distant metastases

The resection of distant metastases can be synchronous or metachronous.

Level of Recommendation B, Level of evidence: 3b.

Emergency surgery

In the setting of ileus, tumour perforation or colorectal perforation with a stenotic tumour the procedure performed depends on the individual situation. The preferred surgical option is a radical resection according to the standard oncological procedures, if feasible. In appropriately selected cases of ileus due to a colorectal carcinoma, the placement of an endoluminal stent can be discussed 508]. An ileus usually accompanies a rectal carcinoma only in far-advanced cases, so that a neoadjuvant radio/chemotherapy should be undertaken (see VI.2.2). For this reason, a colostoma of the right transverse colon is often constructed in this situation. Tumour-associated bleeding is only rarely relevant for further decisions regarding therapy.

Carcinomas in familial adenomatous polyposis

The procedure of choice for FAP patients is a proctocolectomy with ileoanal pouch including a lymph node dissection depending the localisation of the carcinoma, and the resulting consequences (e. g. radial vessel cutting, total mesorectal excision). Depending on anal sphincter function or an incurable tumour stage, a proctocolectomy or a limited resection can be carried out.

In attenuated FAP with only minimal involvement of the rectum, an ileorectostomy is recommended (see also III.2.2). [223].

Level of Recommendation B, Level of evidence: 3b, strong consensus.

Carcinoma in hereditary colorectal carcinoma without polyposis (HNPCC)

At this time two alternative management strategies are being discussed: Management according to the procedure in sporadic carcinoma, and conversely complete colectomy in the case of a colon carcinoma and/or the restorative procto-colonectomy in the case of rectal carcinoma. Data comparing the two strategies are lacking (see also III.2.3).

Carcinomas in ulcerative colitis

The preferred procedure is a proctocolectomy with an ileoanal pouch (IAAP), if applicable according to oncological or functional considerations.

Level of Recommendation Level of evidence: 3b, strong consensus.

V.7. Postoperative histopathological examination

The following data are obligatory components of the pathology report [281, 509 – 521]

- *Tumour type according to WHO classification*
  Level of evidence: 1c, Recommendation level: A
- *Tumour invasion depth (pT-classification)*
  Level of evidence: 1c, Recommendation level: A
- *Regional lymph node status (pN classification)*
  Level of evidence: 1c, Recommendation level: A
- *Number of lymph nodes examined*
  Level of evidence: 2a, Recommendation level: A
- *Minimum number of lymph nodes examined*
  Level of evidence: 2a, Recommendation level: A
- *Grading*
  Level of evidence: 2a, Recommendation level: A
- *Distance from the resection margins (with rectal carcinoma, circumferential)*
  Level of evidence: 2a, Recommendation level A
- *R classification*
  Level of evidence: 1c, Recommendation level: A

Background

Increasingly and especially after a neoadjuvant radio/chemotherapy the degree of remission achieved ascertainable by pathohistological examination is reported according to the Dworak classification [522].

Recommendation

Testing for microsatellite stability may be performed in case of suspected HNPCC

Level of Recommendation A

Background

The data mentioned above allow a reliable classification of tumour stage and are relevant for prognoses and decisions regarding future therapy.

Several case-control studies are available concerning the number of lymph nodes examined necessary for the correct establishment of the pN category. From these, different numbers are derived (n = 12 to n = 17) [512, 532 – 525].

In the case of rectal carcinoma, the minimal distance to the circumferential resection margins is to be measured on a macroscopic preparation or histological section. A margin of less than 1 mm should be documented in the pathology report due to its prognostic relevance, but should not be classified as R1. Lymph node metastases (< 2 mm) are to be documented, because they have to be included in the N category. They have to be differentiated from isolated tumour cells [526].

V.8. Supplement

At the time of the initiation of the consensus process, there were no generally accepted recommendations for the determination and documentation of the quality of the mesorectum excision. In the meantime, recommendations have been put forward [477], based on the grading used in the M.E.R.C.U.R.Y. study (magnetic resonance imaging and rectal cancer European equivalence study project [2002 study protocol]) [517]. This grading system has not yet been validated, but its use as an oncological quality assurance parameter seems useful.

Grading system according to the M.E.R.C.U.R.Y. study:

- Grade 1: Intact mesorectum with only small irregularities of the mesorectal surface, no defect greater than 5 mm. No coning.
- Grade 2: Moderate amount of mesorectum with irregularities on the mesorectal surface. Moderate coning. Muscularis propria not seen (except at the area of the levator muscle).
- Grade 3: Little mesorectum with defects up to the muscularis propria.

Topic VI: Adjuvant and neoadjuvant therapy

▼

VI.1. Adjuvant therapy of colon carcinoma
- VI.1.1. Indications for adjuvant therapy of colon carcinoma
- VI.1.2. Age limitations for conducting adjuvant chemotherapy
- VI.1.3. UICC-Stage III
- VI.1.4. UICC-Stage II
- VI.1.5. UICC stage II with risk factors
- VI.1.6. Chemotherapy protocols

VI.2. Perioperative therapy of rectal carcinoma
- VI.2.1. Obligatory diagnostics prior to therapy
- VI.2.2. Perioperative therapy – indications for perioperative radio- or radiochemotherapy
  - VI.2.2.1. Stage I
  - VI.2.2.2.. Stage II/III
  - VI.2.2.3. Stage IV
- VI.2.3. Adjuvant therapy
  - VI.2.3.1. Adjuvant therapy with primary surgery (without neoadjuvant therapy)
  - VI.2.3.2. Adjuvant therapy after neoadjuvant radiotherapy or radiochemotherapy

VI.1. Adjuvant therapy of colon carcinoma

VI.1.1. Indications for adjuvant therapy of colon carcinoma

A requirement for adjuvant therapy in colon carcinoma is a R0-resection of the primary tumour. Basis for the indication for adjuvant therapy after tumour resection is a histopathological stage determination, especially the determination of the pN status. In order to determine a pN0 status, at least 12 regional lymph nodes should be examined (UICC 2002). Immunocytological detection 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 indications for adjuvant therapy outside of clinical trials.

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

Contra-indications for adjuvant chemotherapy of colon carcinoma

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

VI.1.2. Age limitations for conducting adjuvant chemotherapy

Recommendation

There is no age limitation for performing adjuvant chemotherapy; general contraindications (see above) should be considered. Level of Recommendation A, Level of evidence: 1, strong consensus.

Background

Randomized studies concerning the effect of adjuvant chemotherapy on colon cancer outcome had an under representation of older patients. Among other reasons, this was due to an age limitation as part of the inclusion criteria in most of these studies. A prospective cohort study including patients with colon cancer who were at least 67 years old showed that at older age also, patients have a significant survival benefit from adjuvant chemotherapy in comparison to surgery alone [527]. Additionally, a retrospective study consisting of a smaller number of patients revealed that no significant differences in survival time were found depending upon age [528]. This result was confirmed by a pooled analysis of seven studies with a total of 500 patients 70 years or older [529]. In this study occurrence of gastrointestinal side-effects did not depend upon age, however leucopoenia was found more often among older patients. In another study, stomatitis was the only side-effect

being seen more often in the group with age over 70 years [530]. Hence, in most cases adjuvant chemotherapy seems to be tolerated well by older patients. Furthermore, a sub group analysis of the MOSAIC study revealed that the benefit of additional adjuvant therapy with oxaliplatin was not dependent on age [531]. The age of a patient therefore has no sole predictive value [532].

VI.1.3. UICC stage III

Recommendation

For patients with R0 resected stage III colon carcinoma, adjuvant therapy is indicated.

Level of Recommendation A, Level of evidence: 1a, strong consensus.

Background

Various randomized studies have demonstrated a significant survival benefit for patients with stage III colon carcinoma due to adjuvant chemotherapy [533, 534]. Meta-analyses and pooled analyses (e.g. Gill et al) including 3303 patients with stage II and III colon carcinoma unequivocally showed that, compared to surgery alone, adjuvant chemotherapy is associated with a significant improvement of prognosis for patients with lymph node positive disease (stage III) [529, 535 – 537].

VI.1.4. UICC stage II

Recommendation

For patients with curatively resected stage II colon carcinoma, adjuvant therapy can be performed.

Level of Recommendation 0, Level of evidence: 1b, strong consensus.

Background

The absolute benefit of adjuvant therapy in UICC stage II without risk factors is between 2 and 5%. Studies and pooled analyses of studies of patients with stage II colon carcinoma did not show a significant survival benefit from postoperative adjuvant chemotherapy. A pooled analysis of 7 randomized studies which compared adjuvant chemotherapy to sole operation with regards to stage II colon carcinoma, merely demonstrated a significant improvement of disease-free five-year-survival (DFS) (72 vs. 76%, p = 0.049) in univariate analysis. This benefit could not be shown for five-year overall survival (80 vs. 81% p = 0.1127). Furthermore, the individual studies differed concerning therapy modalities and included low patient numbers only [536]. The British QUASAR study is the largest individual randomized trial published concerning this issue [542].

In this study after median observation period of 5.5 years the relative risk for death from whatever cause was significantly lower in the adjuvant therapy group than in the observation group (HR 0.82; 95% CI: 0.70 – 0.95, p = 0.008), resulting in an absolute survival benefit of about 3.0% (95% CI: 1.0 – 6.0). However, this study as well showed methodical weaknesses in regards to its heterogeneous study group (71% colon carcinoma, 91% Dukes' stage B) and the heterogeneous therapy protocols containing 5-FU (with or without Levamisol, different dosing of folinic acid). Considering the isolated subgroup of stage II colon carcinoma, the relative risk was not significantly reduced; the effect however was the same throughout all subgroups leading to the assumption of a survival benefit for all prognosis groups. Considering the significance of this study with regards to the so-defined "high-risk-situation" (see below), no recommendations can be derived, since data about T-category and/or vascular invasion are merely available for about 20% of all patients. Out of the collective of these 20% only very few patients were really showing T4- or V1-status. At this time, there is no convincing data available concerning usage of Oxaliplatin in stage II: At ASCO 2007 [543]* the effect of adjuvant postoperative chemotherapy (FOLFOX4 versus LV5FU2) in a subgroup analysis in stage II was reported. Regarding stage II colon cancers, there was neither a significant improvement of disease-free survival (HR 0.84; 95% CI: 0.62 – 1.14; p = 0.258) nor an overall survival benefit (HR 1.0; 95% CI: 0.71 – 1.42) found for those patients being treated with Oxaliplatin combination therapy and having a stage II tumour. Taking all currently available randomized and controlled studies into account, a recommendation towards an obligatory use of adjuvant chemotherapy in stage II cannot be given [544 – 546]. However, due to the positive results of the largest trial until now, the QUASAR study, a benefit of adjuvant therapy in stage II without risk factors cannot completely be excluded – regardless of methodical problems of this study. For that reason, therapy should at least be taken into consideration at this stage [542]; in any case, potential benefits and risks of such a therapy should be discussed with the patient.

VI.1.5. UICC stage II with risk factors

Recommendation

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 Recommendation B, Level of evidence: 3, strong consensus.

Background

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

Several studies found that poor prognosis was associated with certain risk situations such as T4 tumour, tumour perforation, operation under emergency conditions and/or too low a number of examined lymph nodes [547, 548]. A recent retrospective trial including 1306 patients with a stage II tumour revealed in multivariate analysis that T4-category was associated with poor disease-free survival (HR 1.75) [549]. In the study by Moertel (n = 318), T4-category in stage II had no additional prognostic value [544]; yet in the study by Burdy (n = 108) [550], in the Erlanger analysis (n = 305) [547] and in the published meta-analysis by Gill [536] such prognostic relevance was demonstrated.

After emergency surgery a significantly lower five-year survival rate was observed, absolute numbers being 29.8% versus 52.4% (p < 0.001). This difference was seen in stage I/II as well as in stage III [551]. Cancer-specific survival after five years was reduced from 74.6% to 60.9% with evidence of anemia, to 51.6% with evidence of stenosis and to 46.5% with evidence of perforation (p < 0.001) [552]. In several studies, the number

of examined lymph nodes was found to be an independent prognostic factor as well [519, 553]. 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 [553]. Le Voyer (INT-0089, n = 3411) 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 analyzed [519]. In a study of 3592 cases of colorectal carcinoma an English working group [554] found a significant survival benefit for each subgroup of patients depending on the number of lymph nodes identified (0 – 4 lymph nodes, 5 – 10 lymph nodes, > 10 lymph nodes). This effect was demonstrated for every tumour stage. In multivariate analysis, the number of examined lymph nodes was shown to be an independent prognostic factor. An analysis of the SEER database [555] correlated the number of examined and/or removed lymph nodes with long-term survival.

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

A study in which patients with stage II tumours and high-risk characteristics were represented in a small sub-group, showed no benefit of adjuvant chemotherapy compared to sole operation [534]. In contrast to this, the MOSAIC study included a high-risk population consisting of patients with stage II tumours with T4-status, tumour perforation, ileus, blood vessel invasion and/or less than 10 lymph nodes examined; for this high-risk population postoperative adjuvant FOLFOX4 chemotherapy tended to result in an improvement of disease-free survival by 7.2% (HR 0.74; 95% CI: 0.52 – 1.06) in comparison to 5-FU/FA chemotherapy. However, possibly due to the small number of patients, a significant improvement of overall survival could not be shown [543]*.

Recommendation

At this time, 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, microsatellite status, DNA ploidy and TS/p53 expression, lymph and blood vessel invasion) should not be used as an indication for adjuvant chemotherapy.

Level of Recommendation: A Level of evidence: 4, strong consensus.

Background

It has been demonstrated in some, but not in all studies that certain parameters have a prognostic relevance for colorectal carcinoma. Yet, there are no prospective studies available relating to the benefit of adjuvant chemotherapy with the presence of one or more of these factors. In some studies, level of differentiation was shown to be an independent prognostic factor in stage III [513, 556] as well as in stage II and III [536]. In contrast to this, an analysis by Hermanek demonstrated that the level of differentiation only has a prognostic significance in a certain subgroup of stage III (any T N2M0) [557].

In several studies, loss of 18q-allele was shown to have an independent prognostic role in stage II cancers [558 – 562].

Regardless of this, a study of patients with stage II colorectal carcinoma (n = 70) came to the conclusion that 18q loss did not possess any prognostic significance [563]. Moreover, it is unclear whether tumours showing 18q loss might respond worse to chemotherapy.

In 10 – 15% of all sporadic colorectal carcinomas microsatellite instability (MSI) can be detected. Microsatellite instability is caused by defects of the DNA-mismatch-repair-(MMR)-system (MMR-system) caused by an inactivation of the MLH 1, MSH 2, MSH 6 and PMS 2 genes. The results of a study of 718 patients in Italy indicate that patients with MMR protein-negative tumours have a better long-term prognosis than patients with MMR protein-positive carcinomas. This positive prognostic effect was seen in stage II as well as stage III. Adjuvant chemotherapy induced an improvement of prognosis for patients who had MMR protein-positive tumours [564]. A study by Sinicrope demonstrated that microsatellite instability and DNA diploidy were also associated with a better prognosis [565].

A recently published meta-analysis clearly proved a negative prognostic significance of DNA aneuploidy. Patients with aneuploidic colorectal carcinoma had a significantly higher mortality rate five years after operation than patients with diploid tumours did. This applied for all subgroups analyzed and in particular for stage II [566].

Among 570 patients in stage II (55%) and stage III (45%) analyzed together in the IMPACT study, adjuvant chemotherapy led to an improvement in survival; with existence of higher-grade microsatellite instability however it resulted in a decreased survival [567]. A study of 876 patients with stage III tumours revealed that microsatellite status had no prognostic relevance for the group that had not received adjuvant chemotherapy (5 year survival rate: 43 vs. 36%), whereas for the group being treated with chemotherapy a significantly better survival rate was demonstrated for patients with MSI-positive tumours [568]. None of these studies were designed in a prospective manner concerning the investigation of prognostic and predictive parameters.

VI.1.6. Chemotherapy protocols

Chemotherapy protocols in stage III

Oxaliplatin in combination with 5-FU/folinic acid (FA)

Recommendation

For adjuvant chemotherapy of colon carcinoma in stage III, a therapy containing Oxaliplatin should be given.

Level of Recommendation A, Level of evidence: 1, strong consensus.

- FOLFOX (LV5FU2 + Oxaliplatin):
  e.g. FOLFOX4: 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, hereafter 600 mg/m^2 as a 22-hour infusion; day 1 and 2) in combination with Oxaliplatin (85 mg/m2 as a 2-hour infusion; day 1), repeated on day 15. 1 cycle enfolds 2 weeks, 12 cycles total.

Background

Several randomized studies demonstrated a significant reduction of disease recurrence rate as well as of total survival rate by applying a combination of 5-FU and folinic acid [533, 534, 537].

The MOSAIC study (2246 patients) compared adjuvant chemotherapy consisting of 5-FU/FA (LV5FU2) with a FOLFOX4 scheme (LV5FU2 + Oxaliplatin 85 mg/m2) every 2 weeks for 12 cycles. With regards to the total study population, the FOLFOX4 chemotherapy demonstrated a significant improvement in disease-free survival compared to LV 5FU2 chemotherapy (73.3 vs. 67.4%, p = 0.003) [543*, 569]. 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, too, was significantly improved by FOLFOX4 chemotherapy in stage III reflected by an increase of 4.4% (p = 0.029). Four years after therapy, occurrence of peripheral-sensory neuropathy was found at a rate of 12% (grade I), 2.8% (grade II) and 0.7% (grade III) [543*, 569].

The NSABP study C-07, 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 within 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 [570]. When choosing between 5-FU and an Oxaliplatin-containing regimen, the side-effects of the individual protocols should be considered. Due to the higher cumulative dose of Oxaliplatin in the MOSAIC study, a slightly lower rate of level 3 – 4 neuropathies was observed in the NSABP study (12.4 vs. 8.4%). However, level 3 and 4 diarrhea was observed more often in the bolus FLOX protocol 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 of chemotherapy due to a chemotherapeutically-induced enteropathy [570]. While showing comparable effectiveness, the toxicity of the FLOX protocol is not acceptable in comparison to that of the FOLFOX4 protocol. Hence, the FLOX protocol should not be used in adjuvant situations. Internationally, at this time the modified FOLFOX6 scheme, which consists of a 46-hour continuous infusion of 5-FU after an initial 5-FU bolus on day 1, is preferred; this scheme represents the control arm of international studies. This way, the patient avoids the 5-FU bolus and changing of the pump on day 2 of therapy (dose: Oxaliplatin 85 mg/m^2 IV, folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus, hereafter 2400 mg/m^2 continuously IV for 46 hours every 2 weeks). The combination of Capecitabin and Oxaliplatin in comparison to different bolus regimes of 5-FU/FA has only produced toxicity data so far [571]; study results on effectiveness are expected in 2008.

Adjuvant therapy with protocols including Irinotecan cannot be recommended on the available basis of phase III study data [572*, 573*, 574].

Monotherapy with Fluoropyrimidines

Recommendation

In case of contraindications against Oxaliplatin-containing regimes, a monotherapy with fluoropyrimidines should be given. Thereby, oral fluoropyrimidines should be preferred over infusional schemes. Bolus regimes should no longer be used due to higher toxicity.

Level of Recommendation A, Level of evidence: 1, strong consensus.

- Oral 5-FU prodrugs:
  e.g. Capecitabine 2x 1250 mg/m2 body surface p.o. day 1 – 14, every 3 weeks for 8 cycles.

Background

1987 patients with stage III colon carcinoma were randomized to either the Mayo Clinic scheme (983 patients) or were given Capecitabine as monotherapy (1004 patients) over a time period of 24 weeks each (X-ACT study). The primary aim of the study was achieved by proving that Capecitabine was at least equivalent to the Mayo scheme with regards 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 either. However, again a trend towards superiority of Capecitabine was found here (81.3 vs. 75.6% p = 0.05) [575].

Even though a randomized study with UFT + folinic acid versus 5-FU/FA [576] did not detect a difference concerning overall survival and disease-free survival and a Japanese meta-analysis of 3 studies demonstrated a significant improvement of overall survival and disease-free survival [577], UFT is currently not recommended, since it has no approval for adjuvant chemotherapy of colon carcinoma in Germany.

- Infusional 5-FU/folinic acid
  - LV5FU2
    e.g. folinic acid (FA) (200 mg/m^2 as 2-hour infusion, day 1 and 2) plus 5-FU (400 mg/m^2 as bolus, hereafter 600 mg/m^2 as 22-hour infusion; day 1 and 2)
    1 cycle enfolds 2 weeks, 12 cycles total
  - 5-FU/folinic acid scheme
    e.g. folinic acid (FA) (500 mg/m2 as 1 – 2-hour infusion) plus 5-FU (2600 mg/m^2 as 24-hour infusion) 1 × per week over a period of 6 weeks (day 1, 8, 15, 22, 29, 36). Repetition of therapy in week 8 (day 50). 3 cycles total.
  - Protracted venous 5-FU infusion (PVI)
    e.g. 5-FU as long-term infusion over 12 weeks total (300 mg/m^2/day)

Background

Compared to bolus schemes, several therapeutic studies with different types of infusional application showed no difference to giving 5-FU/FA as a bolus in relation to disease-free survival and overall survival. However, the noticeably better toxicity profile obviously speaks in favour of infusional application [578*, 579*, 580, 581].

A comparison of a 12 week therapy with the “protracted venous infusion” (PVI) of 5-FU (300 mg/m^2/day) versus a 6-months Mayo scheme showed no significant difference in recurrence-free survival (RFS) and in overall survival while monitoring lower toxicity for PVI 5-FU [582]. Beginning of adjuvant chemotherapy within a time period of 8 weeks after surgery demonstrated a significant survival benefit [583]. Optimal duration of chemotherapy was 6 months [580, 584, 585].

Stage II

Recommendation

If patients with stage II tumours are to receive adjuvant chemotherapy, fluoropyrimidines can be administered as monotherapy.

Level of Recommendation 0, Level of evidence: 1, strong consensus.

Background
See VI.1.4. UICC stage II.

VI.2. Perioperative therapy of rectal cancer
VI.2.1. Obligatory diagnostic procedures prior to neoadjuvant therapy
- Digital rectal exam
- Rigid rectoscopy
- Biopsy with histopathological diagnosis
- Endoscopic ultrasound and high-definition MRI of the pelvis or multislice CT of the pelvis
- Colonoscopy (exclusion of secondary tumours in the large intestine)
- Abdominal CT, chest X-Ray, chest CT in case of suspicion of pulmonary metastases
- Laboratory: CEA, LDH, AP, absolute leukocytes count

Background
With a digital rectal exam, tumours in the lower part of the rectum can be palpated.
Using this procedure, the size of the tumour, its exact position, mobility and spread should be determined. This is the basis of the clinical staging (CS) according to Mason (CS I: high mobility, CS II: mobile, CS III: little mobility, CS IV: immobile). Rectoscopy allows evaluation of the distal 15 – 20 cm of the rectal sigmoid. It does not only serve as a method for exact localization of exact position (measured with a rigid rectoscope from the anocutaneous line) and macroscopic evaluation of the tumour, but also allows biopsy and histological confirmation of cancer. Tissue penetration of tumours within colorectal wall layers (especially discrimination of T1 versus T2 tumours), involvement of perirectal lymph nodes and the involvement of the sphincter apparatus can be determined by endoscopic ultrasound [586]. Hence, this examination technique is especially used for planning of limited surgical procedures (local excisions of low-risk T1 tumours), for modern continence-sparing operations without sphincter involvement as well as for the decision for neoadjuvant radiotherapy or radiochemotherapy (indicated for stages uT3/4 or uN+). High-definition MRI examinations or multislice CT of the pelvis are especially indicated if the infiltration into neighbouring structures is suspected, possibly supplemented by gynecological examination when a questionable affection of the vagina, the uterus and the adnexes is found or by cystoscopy if bladder involvement is suspected. High-resolution thin-layer MRI (with body array coils) allows display of the mesorectal fascia and the distance of the tumour from the border of the mesorectum [587] in a highly accurate manner. Patients showing tumour tissue at a distance of 1 mm or less from the circumferential resection margin (CRM) or showing affection or even break-through of the CRM, have a considerably higher risk of disease-recurrence even after optimized surgery with total mesorectal excision. According to prospective study data of the MERCURY study group, high-resolution thin-layer MRI is able to predict infiltration of the tumour into the perirectal fatty tissue as well as a free mesorectal resection border (defined as CRM >1 mm) with high accuracy [588]. Certain study groups and centers limit indication to pre-operative radiotherapy or adiochemotherapy to patients with tumours who show, as defined by an MRI, more than a 5 mm penetration into the perirectal fatty tissue or an approach of up to 1 mm towards the circumferential resection margin [589, 590]. This selective procedure has to be validated in further (randomized) studies. MRI examination is useful for supporting further therapy decisions if a choice is to be made between a pre-operative short-term radiation and a radiochemotherapy with tumours showing only a small distance to the circumferential resection margin (see VI2.2.2). Colonoscopy is done in order to exclude synchronous secondary tumours in the large intestine. Computer tomography of the abdomen as well as a chest X-ray (p.a. and lateral) is an obligatory test prior to therapy in order to exclude distant metastases.
Suspicious pulmonary findings should be clarified by the use of further imaging techniques. In relation to laboratory results, the determination of the tumour marker CEA, of LDH, of alkaline phosphatase and of the absolute count of leukocytes is obligatory.

VI.2.2. Perioperative therapy – indications for perioperative radio- or radiochemotherapy
VI.2.2.1. Stage I
Recommendation
Perioperative therapy is not indicated for stage I tumours.
Level of Recommendation A, Level of evidence: 5, strong consensus.

Background
Carcinomas of the rectum in UICC stage I (T1/2 N0) show a low rate of local recurrence and distant metastasis when the treatment consists of a sole radical operation with en-bloc dissection of lymph nodes and total mesorectal excision (TME) for tumours in the lower (up to 6 cm from the anocutaneous line) and middle third of the rectum (>6 – 12 cm from the anocutaneous line) or consists of a partial mesorectal excision (PME) for tumours in the upper third of the rectum (>12 – 16 cm from the anocutaneous line) [591]. For this reason, this tumour stage has been excluded from early American studies as well as from modern trials looking at the value of neoadjuvant radiochemotherapy [592].
Nevertheless, Swedish and Dutch studies on pre-operative short-term pre-radiation with 5×5 Gy versus an operation alone included tumour stage I. A subgroup analysis performed in the more recent Dutch study showed no significant difference in regards to the local recurrence rate between sole TME and additional radiotherapy for tumours in UICC stage I[591, 593]. The older Swedish study demonstrated a significant benefit of additional radiation for stage I, but here the concept of TME had not yet been implemented [594].
The value of radio(chemo)therapy before or after local excision of a T1 high-risk carcinoma (G3/4, L1, V1, diameter larger than 3 cm, R1 resection) is not verified [595]. A radical tumour excision including lymph node removal should be performed within 4 weeks for patients showing incomplete resection (R1) or risk-constellations (see above).
For patients with T1 high-risk carcinomas localized in the lower part of the rectum or T2-N0-tumours in UICC stage I who refuse an extirpation, pre-operative radio(chemo)therapy followed by local excision can be an option [596]. This, however, is a procedure that has not been validated.

VI.2.2.2. Stage II/III

Recommendation

For UICC stages II and III neoadjuvant radio- or radiochemotherapy is indicated. cT1/2 carcinomas with questionable lymph node involvement are an exception; here, primary surgery (if necessary followed by adjuvant radiochemotherapy in the presence of pN+) is a possible therapeutic option.

Level of Recommendation A, Level of evidence: 1b, strong consensus.

Background

Meta-analyses show an improved effectiveness of pre-operative radiation in comparison to postoperative radiation [597, 598]. An early randomized study on pre- versus postoperative sole radiation showed a significantly lower rate of local recurrences in the pre-operative arm [599]. The German study on adjuvant and neoadjuvant radiochemotherapy (RCT) of rectal cancer in UICC stages II and III (CAO/ARO/AIO-94) also demonstrated a significant reduction of the rate of local recurrences in the neoadjuvant arm [600]. The rate of postoperative complications was not increased for preoperative RCT in comparison to immediate operation; acute and chronic toxicity overall were significantly lower in the preoperative RCT-arm. For tumours localized in the distal rectum for which the surgeon had assessed an obligatory indication for extirpation prior to randomization, the rate of sphincter-retaining operation procedures was doubled by pretreatment in comparison to immediate surgery. A problem of every neoadjuvant therapy is the potential "overstaging" and, thus, the resulting "overtreatment" of patients for whom, falsely, a wall-penetrating (T3) or lymph node positive tumour (N+) has been diagnosed. Since sensitivity and specificity are limited especially for the evaluation of lymph node involvement, for T1/2 tumours showing questionable N+ status in imaging techniques the primary operation is considered an advisable option.

Several centers and study groups have stated – taking into account the chronic side effects associated with radiotherapy [601, 602] – further selection criteria for primary operation being T3 tumours infiltrating the mesorectal fatty tissue not more than 5 mm as well as tumours showing a distance of more than 1 mm to the mesorectal line of resection (MRI diagnosis is obligatory) [589, 590]. These selection criteria have to be further evaluated in clinical trials.

Recommendation

The value of radiation therapy for carcinomas in the upper third of the rectum is considered controversial. Adjuvant therapy as for colon carcinoma or perioperative radio(chemo)therapy as for rectal carcinoma can be performed.

Level of Recommendation 0, Level of evidence: 3a, strong consensus.

Background

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

- Data from American studies concerning adjuvant therapy, which established radiochemotherapy for treatment of rectal carcinoma, were based exclusively upon rectal tumours showing a margin of up to 12 cm in between the distal edge of the tumour and the anocutaneous line.
- The Dutch TME study showed no significant improvement of the local disease-recurrence rate by additional radiotherapy for tumours of the upper third of the rectum (here defined as: 10 – 15 cm from the anocutaneous line) [593].

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

- The analysis of the Dutch TME study represents the results of an explorative subgroup analysis. Thus, the authors of the trial did consequently not conclude that patients with tumours in the upper third of the rectum do not require radiotherapy.
- The British MRC-CR07 study, which has only been published in abstract form until now, has shown a significant advantage of general pre-operative short-term radiotherapy versus selective postoperative radiochemotherapy for all rectal thirds only when affection of the circumferential resection margin was present [603]*.
- A current subgroup analysis of the German CAO/ARO/AIO study 94 found no significant difference in the local disease-recurrence rate for tumours in the middle and upper third of the rectum.
- In contrast to the Dutch TME study, in Germany tumours in the upper third of the rectum are treated with a partial mesorectal excision (PME). This procedure is possibly associated with an increased rate of local disease-recurrence. The GAST-05 study being led by Prof. Becker and Dr. Liersch is to examine the question of whether tumours in the upper third of the rectum require a TME.

Recommendation

In situations in which a downsizing of the tumour is desirable (T4 tumours, insufficient safety margin to the mesorectal fascia in thin-layer MRI – margin of 1 mm or less – or desired sphincter preservation for tumours in the lower third), pre-operative radiochemotherapy should be preferred over short-term radiotherapy. For cT3 tumours or cN+ tumours for which downsizing is not being attempted, pre-operative therapy can be conducted in form of either radiochemotherapy or short-term radiation.

Level of Recommendation A, Level of evidence: 3b, strong consensus.

Background

For pre-operative radiotherapy, two radiation schemes are available in principle: Short-term radiation with 25 Gy in single doses of 5 Gy over five consecutive days, directly followed by the operation, and conventionally fractionated radiation up to a total reference dose of 45 to 50.4 Gy in 25 – 28 fractions, followed by the operation after 4 – 6 weeks. A randomized Polish study found that in comparison to short-term radiation neoadjuvant radiochemotherapy being conventionally fractioned was associated with a significantly superior result in relation to downsizing and downstaging as well as with a significantly lower rate of R1 resections [604]. Nevertheless, the rate of sphincter-preserving operation procedures (primary endpoint) as well as local control (secondary endpoint) showed no significant difference in both arms [605]. In order to maximize tumour shrinkage prior to operation, conventionally fractionated radiochemotherapy should be preferred over short-term radiation for those indications listed above. With the latter no relevant tumour shrinkage is achieved, due to the short duration of therapy and the operation following directly afterwards [606].

Recommendation

Neoadjuvant radiochemotherapy should include 5-Fluorouracil monochemotherapy with or without folinic acid.

Level of Recommendation A, Level of evidence: 1b, strong consensus.

Background

The value of combining conventionally fractionated pre-operative RT with a 5-FU/folinic acid chemotherapy conducted simultaneously was analyzed in the EORTC-22921- as well as in the FFCD-9203-study (the EORTC-study additionally analyzed the relevance of adjuvant chemotherapy [607, 608]). The essential result of both studies was the significant reduction of the local disease-recurrence rate by pre-operative radiochemotherapy in comparison to solitary radiotherapy. In the German CAO/ARO/AIO-94 study, 5-FU was administered in the first and fifth week of radiation with a dose of 1000 mg/m^2/day as a 120-hour long infusion. In the EORTC-22921 and the FFCD-9203 study, patients received 5-FU in a dose of 350 mg/m^2/day and folinic acid in a dose of 20 mg/m^2/day in the first and fifth week of radiation over a period of 5 days respectively.

Neoadjuvant radiochemotherapy including new substances and combinations (Capecitabine, Oxaliplatin, and Irinotecan) showed complete remission rates of up to 30% in several phase II studies [609]. The value of these combination therapies is currently being tested in phase III studies.

VI.2.2.3. Stage IV

Recommendation

For synchronously metastatic carcinoma of the rectum no standard recommendation concerning the therapeutic algorithm exists. Prognosis of the disease is usually determined by systemic metastases. Hence, in case of irresectable distant metastases primarily a systemic combination chemotherapy should be performed, unless symptoms caused by the primary tumour make a different approach necessary. If a primary radiochemotherapy is conducted, intensified combinational chemotherapy should be employed considering the presence of systemic metastases.

Level of Recommendation B, Level of evidence: 5, strong consensus.

VI.2.3. Adjuvant therapy

VI.2.3.1. Adjuvant therapy after primary surgery (without neoadjuvant therapy)

Recommendation

In stage I, adjuvant therapy is not indicated after a R0-resection.

Level of Recommendation A, Level of evidence: 1b, strong consensus.

Background

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

Recommendation

Patients with UICC stage II and III, who have not undergone neoadjuvant radiochemotherapy or short-term radiotherapy, should receive adjuvant radiochemotherapy.

Level of Recommendation A, Level of evidence: 1b, strong consensus.

Background

The addition of chemotherapy to postoperative radiation reduced not only the rate of local disease-recurrence was reduced, but also improved overall survival in comparison to (conventional) operation only [610, 611]. Data on the use of adjuvant radiochemotherapy after pathologically confirmed adequate excision of the mesorectum and a distance of more than 1 mm in between the tumour and the circumferential resection margin are not yet available. The rates of local disease-recurrence, even without an additional adjuvant therapy, are specified here with a total number of less than 10%, however, for subgroups such as tumours in the lower third of the rectum, they might be higher. Patients with tumours in UICC stage II and III should be entered into randomized studies. This would clarify whether, after quality-assured surgery, certain subgroups of patients exist (e.g. pT3N0-tumours with little infiltration of the perirectal fatty tissue or pT1/2-N+-tumours), whose disease-recurrence risk is comparable to that of patients in UICC stage I and who therefore do not benefit from adjuvant radio- and chemotherapy [612, 613]. Concerning the question of tumour therapy in the upper third of the rectum, see VI. 2.2.2.

The British MRC-CR07 study, which has only been published as an abstract until now, has shown that a risk-adapted algorithm (postoperative radiochemotherapy only for patients with positive circumferential resection margins after TME) is significantly inferior to a general pre-operative radiotherapy with 5 × 5 Gy for all carcinomas of the rectum in regards to local control and disease-free survival [603]*.

Recommendation

After a R1-resection or intraoperative tumour tears, a postoperative radiochemotherapy should be conducted unless neoadjuvant radio (chemo) therapy has been performed previously.

Level of Recommendation B, Level of evidence: 4, strong consensus.

Background

R1-resections and intraoperative tumour tears are associated with a high risk of local disease-recurrence and justify a postoperative RCT. An unplanned subgroup analysis of the Dutch TME study showed no significant improvement in the rates of local disease-recurrence by conducting a solitary postoperative radiotherapy with up to 50.4 Gy [614].

Recommendation

Adjuvant therapy should begin 4 – 6 weeks after the operation.

Level of Recommendation B, Level of evidence: 3a, strong consensus.

Recommendation

Radiation therapy can take place at the same time as the first and second chemotherapy cycle or as the third and fourth cycle.

Level of Recommendation 0, Level of evidence: 2a, strong consensus.

Recommendation

Radiation therapy should be combined with 5-FU monochemotherapy.

Level of Recommendation A, Level of evidence: 1b, strong consensus.

Background for the last three recommendations:
According to the "NCI scheme", adjuvant therapy begins 4 – 8 weeks after surgery by administration of two chemotherapy courses of 5-FU in a dose of 500 mg/m^2 body surface per day as a bolus application for five consecutive days (day 1 to 5 and 36 to 40). Radiotherapy begins on day 63. The pelvic area of lymphatic drainage is to receive a total dose of 45 Gy by applying a single dose of 1.8 Gy five days a week over five weeks followed by a low-volume dose saturation of up to 50.4 Gy in the area showing the biggest risk of local disease-recurrence. During the first and fifth week of radiation patients receive simultaneous 5-FU chemotherapy in the same dose and application form as for the two initial courses, however only over a period of three days. After completion of the radiotherapy, two additional courses of chemotherapy are to follow (day 134 – 138 and 169 – 173), however only in a reduced dose of 450 mg 5-FU/m^2 body surface per day over a period of five days [421].
According to study results published by O'Connell et al., during the entire period of radiation a low-dose 5-FU long-term infusion can be performed with a dose of 225 mg/m^2 body surface per day instead of applying 5-FU in bolus form [615]. The Intergroup-0144 study, however, had not been able to confirm superiority of 5-FU long-term infusional programmes in comparison to biochemically (folinic acid/levamisole) modulated 5-FU bolus applications [616]. In a four-arm American Intergroup-study (0114), modulation of 5-FU bolus applications with leukovorin and/or levamisole was shown not to be superior to the sole administration of a 5-FU bolus [617].
A further possible modification of the NCI scheme involves the time period between the operation and radiotherapy. Tumour and radiation biological reasons recommend a short time interval until the operation is performed. First analyses of a Korean study gave evidence that an early beginning of radiotherapy simultaneously to conducting the first 2 postoperative chemotherapy courses results in a significantly better disease-free survival rate [618]. This, however, was not confirmed by a long-term follow-up [619]*. The postoperative arm of the German CAO/ARO/AIO-94 study can be recommended as an alternative to the NCI scheme (start of RCT 4 weeks after surgery, 1000 mg/m^2/day of 5-FU as a 120-hour long-term infusion in the first and fifth week of radiation, 4 courses of adjuvant chemotherapy, 5-FU bolus in a dose of 500 mg/m^2/day over 5 days, 3 week break).

Recommendation
The standard for adjuvant therapy of rectal carcinoma is a combined radiochemotherapy.
There is no indication for sole (adjuvant) chemotherapy or radiotherapy for rectal carcinoma. An exception is given only in the case of a contraindication against one or the other form of therapy.
Level of Recommendation A, Level of evidence: 1a, strong consensus.

Background
Sole postoperative radiotherapy reduces the rate of local disease-recurrence, but has – in contrast to the combination of radio- and chemotherapy – no influence on overall survival [620]. Contraindications for radiotherapy are prior radiations in the pelvis as, for instance, in the context of prostate or cervical carcinoma treatment. Sole chemotherapy reduced the rate of disease-recurrence, the combination with radiotherapy, however, was shown to be superior to chemotherapy alone [421]. A Japanese phase III study recently published showed a survival benefit for patients in UICC stage III by applying a sole postoperative chemotherapy with Uracil-Tegafur after TME and selective lateral lymph node dissection [621].

VI.2.3.2. Adjuvant therapy after neoadjuvant radiotherapy or radiochemotherapy

Recommendation
In patients with rectal cancer who have undergone neoadjuvant radiochemotherapy adjuvant chemotherapy is indicated after surgery regardless of postoperative tumour stage (thus, being indicated also with complete remission or for UICC stages I and II).
Level of Recommendation A, Level of evidence: 1b, strong consensus.

Background
The reason for this recommendation is that adjuvant chemotherapy was an obligatory component of the CAO/ARO/AIO-94 study as well as of the FFCD-9203 study after preoperative radiochemotherapy. The EORTC study (22921) randomized in a four-armed study and a "two-by-two factorial design" between the groups of postoperative chemotherapy and no postoperative chemotherapy after preoperative radiotherapy or radiochemotherapy. Postoperative chemotherapy did not lead to a statistically significant improvement of survival. Nonetheless, the survival benefit amounted to 6% in absolute terms for progression-free survival and to 4% for overall survival and was attained by conducting a therapy of a comparatively low toxicity [600].
Subgroup analyses revealed that adjuvant chemotherapy showed a significant survival benefit especially for those patient groups whose histopathological status was ypT0/1/2 after preoperative therapy. In studies on preoperative short-term radiotherapy with 5 × 5 Gy, generally no adjuvant chemotherapy was applied. In a current Dutch phase III study patients with rectum carcinoma treated by 5 × 5 Gy radiation and surgery are randomized to alone adjuvant chemotherapy with Capecitabine and observation [607, 622].

Recommendation
Adjuvant chemotherapy should either be conducted as 5-FU monotherapy or as a combination of 5-FU/folinic acid.
Level of Recommendation B, Level of evidence: 1b, strong consensus.

Background
In the CAO/ARO/AIO-94 study, 4 cycles of adjuvant chemotherapy with 5-FU in a dose of 500 mg/m^2 were administered as an IV bolus over 5 days every 4 weeks. In the EORTC-22921 and FFCD-9203 studies, patients received 4 cycles of adjuvant chemotherapy with 5-FU in a dose of 350 mg/m^2/day and folinic acid in a dose of 20 mg/m^2/day over 5 days respectively every 4 weeks.

Topic VII: Management of patients with metastases and in palliative intention

▼

VII.1. Patients with primarily resectable liver and/or pulmonary metastases

VII.1.1. Primarily resectable pulmonary metastases

VII.1.2. Primarily resectable liver metastases
VII.1.2.1. Preoperative imaging
VII.1.2.2. Perioperative therapy of primarily resectable liver metastases
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VII.2. Patients with indication for intensified systemic therapy
VII.2.1. Patients with potentially resectable metastases
VII.2.1.1. Algorithm for isolated primarily irresectable pulmonary metastases
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VII.2.1.2.1. Systemic neoadjuvant therapy
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VII.4. Treatment protocols
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VII.4.1.2. Combination therapy
VII.4.2. Duration of therapy/treatment disruption in first-line therapy – reinduction
VII.4.3. Second- and third-line therapy chemotherapy protocols
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VII.4.3.2. Third-line monotherapy with biological agents
VII.5. Management of local recurrence or non-hepatic and non-pulmonary metastasis
VII.5.1. Local recurrence
VII.5.2. Non-hepatic or non-pulmonary metastases

The following part of this S3-guideline contains updated recommendations for tumour therapy of metastatic colorectal carcinoma, which will especially reflect novel findings from studies of the past four years. Primarily resectable metastases will be discussed as well as the special situation of a secondary resectability in a therapy concept being primarily palliative. Taking into account the availability of new biological substances, a detailed listing will be presented with comments on possible combinations depending on the goal of therapy and the individual situation of the patient. Dividing patients up into subgroups should simplify decision-making.

Definition of subgroups according to clinical situations/therapy goals

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

Strong consensus.

Background

For synchronous as well as metachronous metastases of liver and/or lungs, complete surgical resection offers a chance of permanent cure for a part of the patients. The evaluation of resectability is the first step of the decision-making process for the therapeutic management in patients with pulmonary and/or hepatic metastases (citation: NCCN 2007). In patients with R0-resectable metastases surgical resection should be the primary choice (see VII.1.). Patients without a possibility for a primary surgical intervention should receive systemic chemotherapy. The choice of the chemotherapy regimen (crucially) depends upon the therapeutic goal. The therapeutic strategy for metastases in palliative situation should e.g. be determined in the context of an interdisciplinary tumour boards.

Patients have to be thoroughly informed about therapeutic options according to their individual needs and involved in decision-making. Besides tumour therapy, which will be illustrated in the following, the securing of adequate analgesic therapy and nutrition, of a need-based psycho-social and psycho-oncological care as well as supportive therapy schemes are integral parts of a palliative therapy concept (see topic-specific guideline at www.awmf-leitlinien.de) (available sources, as of 8/07: Guidelines of the German Society for Nutritional Medicine/ESPEN Guidelines on Enteral Nutrition ([www.awmf-leitlinien.de, register no. 073/006e and 073/005e] guideline "tumour pain" registered by DIVS and DKG, currently under development, planned to be published in 2008). Concerning therapy goals in palliative situations, the disease- and therapy-related quality of life as an easily measurable parameter is now more frequently used as a secondary endpoint in studies. The wish of patients to be informed about all relevant and available measures (tumour-specific, supportive, psycho-social, psycho-oncological therapy options) and offers of help (e.g. cancer counseling offices, self-help groups) has to be met. In addition, complementary/unconventional treatment methods should be discussed with the patient, also to avoid unfavourable interactions with other therapeutics.

VII.1. Patients with primarily resectable liver and/or pulmonary metastases

VII.1.1. Primarily resectable pulmonary metastases

Recommendation

Resectable pulmonary metastases should be resected.

Level of Recommendation A, Level of evidence: 3a, strong consensus.

Background

The indication for primary resection of pulmonary metastases depends on their number and localization, the level of potential pulmonary pre-damage and the expected residual volume after resection. The premise for this is that a R0 resection seems generally possible. Resections should be performed parenchyma-preserving, whereby a sufficient degree of radicality should be guaranteed. Patients should be treated in specialized centers with surgeons being considerably experienced in this matter [623].

In a currently published systematic review by Pfannschmidt et al., a majority of the studies consulted agreed only on preoperative CEA tests as an independent prognostic factor, while data concerning the prognostic relevance of the preoperative number of metastases are inconsistent, but show a trend towards a survival benefit for patients with single metastasis (**Table VII.1**). Further possible influencing factors, such as the disease-free interval or the initial tumour stage have not been confirmed with regards to their prognostic significance [624–627].

VII.1.2. Primarily resectable liver metastases

Definition: Resectable liver metastases are present if

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

[628].

Recommendation

R0-resectable metastases limited to the liver should be resected.
Level of Recommendation A, Level of evidence: 3b, strong consensus.

Background

The five-year survival rate after resection of colorectal liver metastases ranges between 25 and 40% [629–632].

Recommendation

The resectability of metastases should be evaluated by a surgeon with considerable experience in liver surgery.
Strong consensus.

Table VII.1 Five-year overall survival after R0 resection of pulmonary metastases (according to Pfannschmidt et al. [627]).

reference	n	5 year OS	median follow-up (Mo)	level of evidence
Lee 2007	59	50,3%	34,7	III
Pfannschmidt 2003	167	32,4%	58,6	III
Saito 2002	165	39,6%	56,5	III

Background

The prognosis can be estimated preoperatively based on easily obtainable clinical criteria according to the so-called FONG score (**Table VII.3**). This preoperative prognosis score from the Memorial Sloan Kettering Cancer Center in New York was calculated on basis of a large number of patients and is internationally recognized.
Prognostically unfavourable criteria [633]:

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

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

VII.1.2.1. Preoperative Imaging

Recommendation

For patients with liver metastases and a Fong score > 2, a preoperative FDG-PET CT-scan should be conducted since in approximately 25% of patients a change is made in therapeutic strategy due to the proof of further metastases.
Level of Recommendation B, Level of evidence: 3, strong consensus.

Background

The goal of preoperative diagnostics prior to a partial liver resection is not only to determine the number and anatomical localization of the liver metastases, but also to rule out the presence of extra-hepatic manifestations with highest possible confidence.
The FDG-PET is the most appropriate imaging procedure in this context. The important role of FDG-PET in therapeutic decision-making has been demonstrated by several studies in recent years. A prospective work by Joyce et al. showed that for 17 out of 71 (24%) patients with potentially resectable hepatic metastases a change in the therapeutic proceeding was made after conducting a PET-(CT) due to further identified extra-hepatic and/or non-resectable lesions [634]. In another study, which has also been designed in a prospective manner, the data of a preoperative CT-scan were re-evaluated by PET-CT. This resulted in changing the therapeutic planning in 21% of the cases [635]. By comparing conventional imaging with FDG-PET, Amthauer et al retrieved 48 discrepant findings (46

Table VII.2 Survival rate after resection of colorectal metastases.

reference	n	surgical mortality	5-year survival rate Surgery	5-year survival rate no surgery	p	level of evidence
Nordlinger 1996[1]	1568	2,3%	28%	–	–	III
Fong 1997[2]	456	2,8%	38%	–	–	III
Scheele 2001[3]	516	8,3%	38%	–	–	III
Kato 2003[4]	763 (585 OP vs. 178 w/o surgery)	n. a.	39,2%	3,4%	< 0.001	III

[1] 5% of all cases received adjuvant therapy.
[2] 128 of all patients received adjuvant therapy.
[3] 43 patients with different regimens of chemotherapy prior to resection of metastases, 26 patients received adjuvant treatment.
[4] Adjuvant therapies among 54.5% of all cases without significant difference in the survival rate.

Table VII.3 Survival after resection of colorectal liver metastases (according to Fong et al. Annals of Surgery, 1999) [633].

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

of which were actually positive), which resulted in a modified strategy for 37% of patients [636]. Recent trials indicate that especially patients with an unfavourable risk profile (Fong score of 3 – 5) benefit from a preoperative PET examination, while this was not the case for patients with a favourable risk constellation [637]*. Due to limited availability of PET-CT, a preoperative MRI examination seems to be a possible alternative according to the opinion of experts.

VII.1.2.2. Perioperative therapy of primarily resectable liver metastases

VII.1.2.2.1. Neoadjuvant therapy of resectable liver metastases

Recommendation

Neoadjuvant systemic therapy of resectable liver metastases can be considered in reasonable exceptional cases.

Level of Recommendation 0, Level of evidence: 3, strong consensus.

Background

A neoadjuvant therapy shall improve the results of a curatively intended surgical intervention and is therefore linked to the realistic option of a following R0 resection. In order to compare neoadjuvant (preoperative) or combined (perioperative) versus adjuvant (postoperative) strategy in regards to the target dimension of R0 resectability and long-term survival with primarily resectable liver metastases, there are no prospective, randomized studies available.

In a currently published, prospective randomized phase III study of the EORTC, the value of perioperative therapy with liver metastases primarily classified as R0 resectable was investigated. In relation to progression-free survival, the intention-to-treat analysis revealed no significant benefit for perioperative therapy with FOLFOX4 in comparison to a sole operation. The difference in progression-free 3-year-survival was 7.3% (28.1 to 35.4%) and just missed the level of significance (HR: 0.79; [0.62 – 1.02] p = 0.058) (**Table VII.4**). Per protocol analysis, which only considers patients who were actually resected, showed that a significant prolongation of progression-free survival can be achieved with perioperative therapy (3-yr. PFS: 33.2 vs. 42.4% HR: 0.73; [0.55 – 0.97] p = 0.025). Opposing to the possible benefit of perioperative therapy is the significantly increased perioperative morbidity in the chemotherapy arm (25 vs. 16% with sole operation, p = 0.04), whereas overall mortality showed no difference [638]. The decision for neoadjuvant therapy of liver metastasis should take into account that – besides increased perioperative morbidity – perioperative chemotherapy might reduce therapeutic options for recurrent disease. In addition, there is a certain risk that the optimal time window for a resection might be missed, and that all combination protocols cause a significant amount of damage to healthy liver tissue (see section VII.2.1.2.2). In contrast, a potential advantage is the possibility of an early treatment of micro-metastases and the evaluation of response to chemotherapy, which can be helpful in regards to postoperative planning and estimating prognosis [639]. The guideline of the US-American National Comprehensive Cancer Network (NCCN) therefore recommends that for patients with synchronous, resectable metastases neoadjuvant therapy (plus adjuvant therapy postoperatively) should be considered as an option besides the sole adjuvant strategy. For metachronous metastases, surgery is the primary recommendation if the patient has received chemotherapy within the past 12 months (National Comprehensive Cancer Network. Clinical Guidelines in Oncology: Colon Cancer V2.2007. Available at: www.nccn.org Access on June 4, 2007).

Table VII.4 Prospective studies on neoadjuvant therapy of patients with resectable liver metastases.

reference	n	regimen	overall Response rate (ORR)	resection rate (R0)	long-term survival	level of evidence
Lorenz 2003 [640, 1	42	FOLFOX	47,7%	80,9%	–	IIb – III
Wein 2003 [641, 2	20	5FU /FS /OX	100%	80%	2-yr. Tumour-related survival 80%	IV
Gruenberger 2008 [642]	56	XELOX + Bevacizumab	73%	93%	–	IIb
Nordlinger 2008 [638, 3	364	FOLFOX 4 preoperative and postoperative vs. surgery only	43%	83,0 vs. 84%	3-yr. PFS 35,4% vs. 28,1% HR: 0,79 (0,62 – 1,02); p = 0.058	Ib

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

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

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

Taking into consideration the potential risks of neoadjuvant therapy the restrictive recommendation and the striving for a timely resection appears to be justified.
The concept of perioperative chemotherapy for primarily resectable liver metastases is currently being evaluated in ongoing studies with chemotherapy regimens of different intensities.

VII.1.2.2.2. Adjuvant therapy of resectable liver metastases

Recommendation

After R0 resection of synchronous or metachronous liver metastases adjuvant chemotherapy can be considered.

Level of Recommendation B, Level of evidence: 2, strong consensus.

Background

Despite R0 resection of liver metastases only approximately 30% of patients remain free of disease-recurrence in the long term. The rationale for systemic adjuvant therapy after resection of metastases is based on indirect evidence, derived from studies which have demonstrated the effectiveness of adjuvant chemotherapy in stage III colon cancer. The available data for systemic adjuvant therapy after resection of metastases are however limited; there are no placebo-controlled/blinded studies available (neither for neoadjuvant settings).
In two randomized studies and the following pooled analysis of the collected data the effectiveness of a 5-FU monotherapy was examined [643*, 644*, 645] (**Table VII.5**). Neither study accomplished sufficient recruitment in order to demonstrate a significant effect of chemotherapy on survival and both studies were terminated early. An interim analysis of the study results showed a trend towards improvement of progression-free interval in one study and a borderline significant improvement of progression-free survival in the second study. The overall survival was not influenced by adjuvant therapy. Of remark, both studies contained a chemotherapy regimen of low effectiveness (5-FU bolus application). A current study which compared a more effective protocol with sole operation was terminated early due to inadequate recruitment (ADHOC study). The meanwhile widely-spread use of adjuvant therapy after resection of metastases, particularly in the US, entails that the question whether a systemic chemotherapy offers a benefit for the patients compared to surgery only, might no longer be conclusively clarified. Evidence that supports the decision for a systemic adjuvant therapy is given in the EORTC study which was cited in the previous chapter and from a retrospective analysis of the registry data of two reference centers (Memorial Sloan-Kettering Cancer Centre and the Royal Infirmary of Edinburgh). Over a time period of 8 years (1991 – 1998) all patients who received a liver resection due to colorectal carcinoma metastases were registered there (n = 792) and a benefit for 5-FU-based adjuvant chemotherapy was found in comparison to surgey only with regards to overall survival (n = 274 vs. 518; median survival 47 versus 36 months, 5-year survival rate 37 vs. 31% p = 0.007) [646]. The guidelines of the US-American National Comprehensive Cancer Network and the national guidelines of Australia recommended adjuvant chemotherapy after resection of metastases while pointing out the limited evidence resulting from the limited data available (National Comprehensive Cancer Network. Clincal Guidelines in Oncology: Colon Cancer V2.2007. Available at: www.nccn.org Accessed on June 4, 2007; Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. The Cancer Council Australia and Australian Cancer Network, Sydney 2005. Available at www.cancer.org.au Accessed on June 4, 2007).

Clinical groups II and III – Indications for systemic chemotherapy – General recommendations

Recommendation

Active systemic tumour therapy is indicated in principle since a survival benefit has been proven.

Level of Recommendation A, Level of evidence: 1a, strong consensus.

Background

At the beginning of the 1990's two prospective, randomized studies with a total of 223 patients demonstrated a survival benefit of systemic chemotherapy compared to best supportive care (BSC).

Table VII.5 Prospective studies on adjuvant therapy after R0 resection of colorectal liver metastases.

reference	n	regimen	survival	median follow-up	level of evidence
Portier 2006	173	5-FU/FA vs. observation	DFS: 33,5 vs. 26,7% (p = 0.028) OS: 51 vs. 41% (p = 0.13)	87 mo	IIa
Langer 2002[1]	129	5-FU/FA vs. observation	DFS: 39 vs. 20 Mo (p = 0.35) OS: 53 vs. 43 mMo (p = 0.39)	n. a.	–
Mitry 20 06[1,2]	302	5-FU/FA vs. observation	PFS 2,2 vs. 1,55 Jahre (p = 0.059 OS 5,09 vs. 3,91 Jahre (p = 0.125)	n. a.	–
Figueras 2001 [647]	235	specially 5-FU/FA	DFS: 34 Mo 5-yr. OS 36%	20 mo	III
Parks 2007[3]	792	5-FU based vs. observation	Improved survival with CTX (p = 0.007, log rank)	1991 – 1998	IIIb

[1] Only available in abstract form; hence limited ability to jugde the evidence.
[2] The summary in Mitry et al. is a pooled analysis of the studies by Langer and Portier.
[3] Limited validity of registry data.

By this means, a prospective, randomized comparison between best supportive care and chemotherapy with Cisplatin and bolus application of 5-FU/FA including 40 patients found a median overall survival of 5 months versus 11 months with the administration of chemotherapy (p = 0.006) [648]. In the studies of the NGTACG the median survival rate was 14 versus 9 months in the control group (log rank p = 0.13) [649].

Recommendation

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 indication, potential contraindications should be considered. Age per se does not represent a contraindication.

Level of Recommendation A, Level of evidence: 1a, strong consensus.

Background

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

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

By these means, it was shown for the FOLFOX regimen that older study patients benefited in the same way as younger patients did from an intensified therapy in relation to remission rate and progression-free as well as overall survival, although especially haemotoxicity was slightly increased (grade 3 neutropenia 43 vs. 49% p = 0.04, thrombopenia 2 vs. 5%, p = 0.04) [531]. Mattioli et al. showed a high effectiveness for a bifractionated FOLFOX protocol with a patient group having an average age of 75 years [650]. A phase II study by Feliu et al. analyzed the feasibility of CAPOX respectively Capecitabine mono as first-line therapy for patients who were older than 70 years [651]. A Spanish working group treated a selection of older patients being older than 72 years with FOLFIRI [652], an exploratory subgroup analysis of the BICC-C study on patients who were older than 65 years showed no difference in effectiveness and toxicity of an Irinotecan-containing protocol in comparison with younger patients [653]*. An analysis of randomized studies published in 2008 showed an improvement of response-rates with an Irinotecan-based chemotherapy for younger as well as for older patients (>70 years) (46.6 vs. 29.0%, p < .0001; and 50.5 vs. 30.3%, p < .0001). The same applied for PFS (HR, 0.77; 95% CI, 0.70 – 0.85; p < 0.0001 for younger patients respectively HR 0.75; 95% CI, 0.61 – 0.90; p = .0026 for patients >70 years) and, with limitation, for overall survival, where a trend towards an improvement was observed for the older patients (HR, 0.83; 95% CI, 0.75 – 0.92; p = 0.0003 und HR 0.87; 95% CI, 0.72 – 1.05; p = 0.15 for patients >70 years) [654]. For patients older than 80 years, the amount of data available is still sparse. Thus, older patients as well should receive chemotherapy when presenting with relevant indications. When choosing the appropriate therapy, the change of organ functions with age; any possible comorbidities as well as age-related limitations of functional status should be considered.

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

Recommendation

If systemic therapy (e.g. inoperable liver/pulmonary filiae) is indicated, the primary tumour can remain in place. Exceptions can be symptomatic tumour stenoses and/or Hb-relevant bleeding.

Level of Recommendation 0, Level of evidence: 4, strong consensus.

Recommendation

In general, patients should have access to all available drugs during the course of their therapy.

Level of Recommendation A, Level of evidence: 5 [655].

VII.2. Patients with indication for intensified systemic therapy

VII.2.1. Patients with potentially resectable metastases

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

VII.2.1.1. Management of isolated primarily irresectable pulmonary metastases

Recommendation

For primarily irresectable pulmonary metastases, systemic chemotherapy should be conducted.

Level of Recommendation A, Level of evidence: 4, strong consensus.

VII.2.1.2. Management of isolated primarily irresectable liver metastases

VII.2.1.2.1. Systemic neoadjuvant therapy

Recommendation

For primarily irresectable liver metastases, systemic therapy should be initiated. It is important to perform a constant evaluation of a possible secondary resectability after the induction of remission. If the goal of therapy is the induction of remission with secondary resection of metastases, then the most effective available systemic combination therapy should primarily be used (intensified therapy).

Level of Recommendation A, Level of evidence: 4, strong consensus.

Background

About 35% of all patients with colorectal carcinoma present with metastases at diagnosis.

15 – 20% of the synchronous and metachronous metastases can be resected with curative intent. In most cases, however, the metastases are classified as primarily irresectable due to various reasons. The possibility to achieve a downsizing of primarily irresectable liver metastases and thus a secondary resectability and potential cure with systemic chemotherapy was evaluated in several studies as primary/secondary endpoint and in the context of exploratory subgroup analyses of studies with primarily palliative intention (**Table VII.6**).

A retrospective analysis by Giacchetti and Bismuth showed a five-year overall-survival of about 50% after neoadjuvant chemotherapy and subsequent resection, comparable to the long-term results after primary resection of liver metastases of patients with a FONG score of less than 3 [656]. For certain chemotherapy regimens particularly good response and resection rates have been described. By this means, Falcone achieved a significant improvement of response rates (34 vs. 60%, $p < 0.001$) and the R0 resection rate (6 vs. 15%, $p = 0.033$) with FOLFOXIRI compared to FOLFIRI. This benefit was even more obvious with patients having isolated liver metastases (12 vs. 36%, $p = 0.017$) [657].

The combination of FOLFIRI and the EGFR antibody Cetuximab achieved an ORR of 46.9% (vs. 38.7% for FOLFIRI alone) in a phase III design. The portion of R0 resections as a secondary endpoint was increased in the experimental arm (4.3 vs. 1.5%) [658]*. The greatest benefit was achieved for patients who had a wild type k-ras expressing tumour. In this retrospective analysis, a statistically significant difference was seen for PFS in patients with k-ras wild type-expressing tumours who were treated with Cetuximab ($p = 0.0167$; HR: 0.68 [95% CI: 0.051 – 0.934]), but response rates also were clearly improved (59.3% [Cetuximab + FOLFIRI] vs. 43.2% [FOLFIRI], $p = 0.0025$) [659]*. A significant correlation between the remission rate and resection rate was found for patients with isolated liver metastases ($r = 0.96$, $p = 0.002$). Furthermore, in large studies with primarily palliative intent and an unselected collective of patients the response rate likewise correlated with the resection rate ($r = 0.74$, $p < 0.001$). When interpreting study data one should take note of patient selection and the fact that between individual studies the definition of resectability was often not uniform [660].

VII.2.1.2.2. Chemotherapy-related liver damage and localization of metastases

Recommendation

The hepatotoxicity of the protocols listed above such as "Blue Liver"/chemotherapy-associated steatohepatitis (CASH) should be considered in differential therapeutic decision-making and planning of surgery.

Level of Recommendation B, Level of evidence: 3, strong consensus.

Background

In the past few years, several working groups have dealt with the question of how much preoperative chemotherapy influences the risk of complications with partial liver resection. Aloia et al. examined a cohort of 303 patients for whom a partial liver resection was carried out due to colorectal liver metastases. 92 patients were randomly chosen, 75 had received preoperative chemotherapy, 17 patients had not. Those who had received preoperative chemotherapy required significantly more-frequent intraoperative transfusions. The predominant histopathological changes in healthy liver tissue were vascular lesions in terms of sinusoidal obstruction syndrome (SOS) and – when appearing in a severe form – correlated positively with

Table VII.6 Response rates and survival of patients after achieving secondary resectability (modified according to [660]).

reference	n	regimen	response-rate (%)	R0 resection-rate (%)	long-term survival of patients who received resection	level of evidence
Falcone 2007[1] [657]	244	FOLFIRI vs. FOLFOXIRI	34 vs. 60 ($p < 0.0001$)	6 vs. 15 ($p = 0.033$)	–	Ib
Van Cutsem 2007 (CRYSTAL)[2]	1198	FOLFIRI vs. FOLFIRI + Cetuximab	38,7 vs. 46,9 ($p = 0.0038$)	1,5 vs. 4,3 ($p = 0.0034$)	–	Ib
Adam 2001[3]	701	Oxa + FU/FA (chron)	pCR: 6,3	13,5	5-yr. survival: 35%	IIb
Giacchetti 2006[4]	564	FOLFOX2 vs. LOHP 5FU FA chron.	44 vs. 42	R0: 12,4 vs. 13,1 pCR: 1,1 vs. 2,8	–	IV
Tournigand 2006[4]	620	FOLFOX 4 vs. FOLFOX 7 + maintenance	58,5 vs. 59,2 n. s.	11,3 vs. 9,4	38,9 vs. 43 mo. ($p = 0.93$)	IV
Souglakos 2006[4] [661]	283	FOLFOXIRI vs. FOLFIRI	43 vs. 33,6 ($p = 0,168$)	8,8 vs. 3,4	–	IV
Saltz 2008[4] [662]	1401	XELOX/FOLFOX 4 + Beva vs XELOX/FOLFOX 4 + Placebo	38 vs. 38 ($p = 0.99$)	n. a.	21,3 vs. 19,9 mo. ($p = 0,077$)	IV

[1] Resection rate is a secondary endpoint, FOLFOXIRI as continuous infusion, higher doses of chemotherapy in FOLFOXIRI arm as with Souglakos et al.

[2] Resection rate a secondary endpoint, benefit only when treating patients with k-ras wild type tumours.

[3] Prospective observation study, resection rate is the primary endpoint, patients potentially cured by surgery, R0 status not reported.

[4] Resection rates as a result of exploratory subgroup analyses.

the need of intraoperative transfusions. Postoperative morbidity depended on the duration of the preoperative chemotherapy [663]. In a further retrospective study, 61% of the examined patients received preoperative chemotherapy. Therapy with Oxaliplatin was more frequently associated with sinusoidal obstruction in healthy liver tissue without noteworthy mortality (1.6%). Irinotecan-containing therapy on the other hand was rather associated with steatohepatitis. Patients with steatohepatitis had a higher 90-day mortality than those without steatohepatitis (14.7 vs. 1.6%) [664].

Recommendation

An intraoperative exploration of the liver should be conducted with regards to the localization of metastases at initial imaging. A surgical resection should be pursued for all previously known lesions.

Level of Recommendation B, Level of evidence: 3b, strong consensus.

Background

A current work by Benoist et al. showed that, despite a complete remission verified radiologically by CT, in 83% of the cases residual tumour tissue was still found either macroscopically or microscopically, or a disease-recurrence was seen in-situ within one year. 38 patients with a total of 66 liver metastases were included. Hence, the resection of metastases should be performed as early as possible when having the option of a R0 resection, and should be guided by the primary borders of the lesions prior to therapy [665].

VII.2.1.2.3. Loco-regional therapeutic procedures

Recommendation

The benefit of local therapy (e.g. laser therapy, radiofrequency ablation and stereotactic radiotherapy) with regards to survival has not been determined.

Level of Recommendation 0, Level of evidence: 4, consensus.

Recommendation

The use of SIRT (selective internal radiation therapy) and HAI (hepatic arterial infusion) is not indicated outside of clinical trials.

Consensus.

Background

For local tumour control with functionally inoperable metastases a series of procedures such as laser therapy and radiofrequency ablation are available, whose effectiveness and usability have been examined predominantly in case series and small cohort studies. The value of these locally ablative procedures within the whole therapeutic concept is vague [666, 667]. Therefore, patients with inoperable metastases should primarily receive systemic chemotherapy. Since regional forms of chemotherapy (e.g. HAI, SIRT) are not superior to systemic chemotherapy, they should not be used outside of clinical trials [668]. Data from a prospective, randomized phase III study on 74 patients showed a significant improvement of response rate (respectively measured as number of metastases [44 vs. 17.6%, $p = 0.01$], size of metastases [50 vs. 24%, $p = 0.03$] and CEA [72 vs. 74%, $p = 0.004$]) and progression-free survival (number of metastases [9.7 vs. 15.9 months, $p = 0.001$], size of metastases [7.6 vs. 12.0 months, $p = 0.04$] or CEA [5.7 vs. 6.7 months, $p = 0.06$]) for a combination of HAI and SIRT in comparison to HAI alone. The overall survival was not significantly longer [669]. Nonetheless, the use of selective intravascular radionuclide therapy is still experimental which should only be considered if all other options have been exhausted [670–672].

VII.2.2. Patients with indication for intensified palliative therapy

The management of this patient group matches for the most part the management described in section VII.2.1.

Recommendation

Patients with tumour-related symptoms, organ complications or rapid progress should receive the most effective combination therapy with consideration of the general condition of the patient (intensified therapy).

Level of Recommendation B, Level of evidence: 5, strong consensus.

VII.3. Patients with the option for less-intensive therapy

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

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

Recommendation

Patients with multiple metastases without option for resection after regression of metastases, without tumour-related symptoms or organ complications and/or severe comorbidities can receive a monotherapy as first-line therapy.

Level of Recommendation 0, Level of evidence: 1, strong consensus.

Background

Several studies have worked on the question of optimal sequence of the different chemotherapy protocols in the treatment of colorectal carcinoma. The CAIRO study investigated the question whether a sequential monotherapy is equivalent to an initial combination therapy in relation to overall survival. 820 patients were randomized into one of the two therapy arms and were either treated with sequential monotherapy (consisting of Capecitabine → Irinotecan → CAPOX) or with combination therapy (CAPIRI → CAPOX). No significant difference in overall survival was found, while observing comparable toxicities (16.3 vs. 17.4 months, $p = 0.3281$) [673]. However, the results of this study should be critically examined in regards to study design and patient selection and are not transferable without limitation [674].

The FOCUS trial, which was the largest single study on colorectal carcinoma with a total of 2,135 patients, demonstrated that a combination therapy as first- and/or second-line therapy is superior to a sequence of monotherapies (arm A). Starting with a 5-FU monotherapy followed by 5-FU in combination with either Oxaliplatin or Irinotecan (arm B) resulted in a overall survival of 15.2 and 15.0 vs. 13.9 months in arm A ($p = 0.24$); with combination therapy as first- and second-line therapy (arm C) the benefit in overall survival reached statistical significance (FOLFOX 15.4 months, FOLFIRI 16.7 months vs. 13.9 months, $p = 0.02$) [675]. Another reason contradicting the

general use of monotherapy as first-line therapy has been shown by a currently published, retrospective subgroup analysis of the N9741 study. There, achieving complete remission was found to be associated with an improved overall survival. The rate of complete remissions after 5-FU monotherapy was only about 1%, whereas after FOLFOX4 complete remission rates of 6.2% have been described [676]. In summary, it can be stated that, as first-line therapy, a therapy as active as possible should be conducted, although 5-FU monotherapy followed by combination therapy is an acceptable alternative in specific cases (e.g. group 3) and should therefore be discussed with the patient. Sequential monotherapy (e.g. 5-FU monotherapy followed by Irinotecan monotherapy) cannot be recommended on basis of these data. Therapy sequence of 5-FU bolus followed by 5-FU infusional protocols, without extension to a second or even third substance is obsolete. It appears important that patients have access to all active substances during the course of their therapy [655]. The value of biological substances within the respective oncological overall-concept will be discussed in the relevant sections.

VII.4. Therapy protocols

VII.4.1. Chemotherapy protocols in first-line therapy

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

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

VII.4.1.1. Monotherapy (5-FU)

Recommendation

In case that a Fluoropyrimidine-monotherapy is conducted, oral administration should be preferred over intravenous administration of 5-FU. With the infusional protocols available, the de-Gramont scheme should be preferred over the AIO scheme, since the de-Gramont scheme puts less strain on the patient due to a 14-day application while probably showing similar effectiveness.

Level of Recommendation B, Level of evidence: 4, consensus.

Background

5-FU was the standard chemotherapeutic agent from the 1950's onwards in treating colorectal carcinomas and led to remission rates of 10 – 15% and a median overall survival of about 6 – 9 months. At the end of the 1980's, the combination of bolus 5-FU with biomodulators such as folinic acid resulted in remission rates of about 20% and a median survival time of about 12 months [677, 678].

Randomized studies which compared 5-FU bolus application with continuous administration until noting progress, showed higher response rates (7 vs. 30%, $p < 0.001$) without influence on overall survival (10.3 vs. 11.3 months, $p = 0.379$). The continuous administration showed higher incidence of hand-foot syndromes (23 vs. 0%, $p < 0.001$) but less grade 3 – 4 neutropenia (1 vs. 22%, $p < 0.001$). Four deaths due to neutropenic sepsis were documented in the bolus arm [679]. In 1997, de Gramont demonstrated a statistically significant improvement in response rates (32.6 vs. 14.5%, $p = 0.0004$) and average progression-free survival (27.6 vs. 22 weeks, $p = 0.001$) with a two-week infusional protocol while showing lower toxicity [680]. A meta-analysis from the same year confirmed this benefit in overall survival. Although the numbers were not statistically significant in the individual studies, the analysis of six studies with a total of 1219 patients showed a significant difference in overall survival of 12.1 months with continuous 5-FU administration versus 11.3 months with bolus protocols ($p = 0.04$) [681]. Oral fluoropyrimidines can increase the quality of life even more, since they allow for out-patient therapy without port systems and pumps, which are associated with a complication rate of about 10% (thromboses, infection, dislocation) [682 – 684]. Furthermore the costs are lower. The side-effects of Capecitabine are mainly hand-foot syndrome, haemotoxicity and diarrhea. Studies have shown that patients prefer oral administration, as long as effectiveness is not compromised [685, 686]. Twelves examined 97 patients with mCRC. In direct comparison with Capecitabine only the modified out-patient de Gramont scheme resulted in similar patient satisfaction. In fact, the gain in quality of life for the study patients was actually higher for the out-patient infusional scheme ($p < 0.05$) [687]. The effectiveness of Capecitabine in comparison with a 5-FU protocol was studied in two randomized multi-center phase III studies. In both studies, the control arm consisted of a bolus 5-FU protocol (Mayo protocol), which at the time corresponded to the standard of therapy. Van Cutsem demonstrated response rates of 18.9% for Capecitabine and 15% for 5-FU/FA, median overall survival was 13.2 versus 12.1 months ($p = 0.33$). The administration of Capecitabine led to a lower incidence of grade 3 and 4 stomatitis and neutropenia ($p < 0.00001$), but more-frequent appearance of hand-foot syndromes ($p < 0.00001$) [688]. Hoff demonstrated similar results in his study of 605 patients [689]. A pooled analysis of these two studies, published in 2004, included a total of 1,207 patients and demonstrated highly significantly different response rates of 26% for those patients treated with Capecitabine versus 17% in the 5-FU arm ($p < 0.0002$). Overall survival was not prolonged (12.9 versus 12.8 months) [690]. A direct randomized comparison of Capecitabine with an infusional 5-FU protocol is at this time only available in combination with Irinotecan/Oxaliplatin with or without Bevacizumab. Here, Capecitabine represents an effective and well-tolerable alternative to infusional 5-FU protocols (**Table VII.7**).

For patients who received a 5-FU/folinic acid-based therapy, favourable prognostic factors that have been identified are

Table VII.7 Capecitabine (Cape) in comparison with bolus 5-FU/FA in first-line therapy.

reference	n	regimen	overall response-rate (%)	TTP (Mo)	OS (Mo)	level of evidence
Van Cutsem 2004	1 207	Cape/Mayo	26 vs. 17 (p < 0.0002)	4,6 vs. 4,7 (p = 0.95)	12,9 vs. 12,8 (p = 0.48)	Ia
Van Cutsem 2001	602	Cape/Mayo	18,9 vs. 15	5,2 vs. 4,7 (p = 0.65)	13,2 vs. 12,1 (p = 0.33)	Ib
Hoff 2001	605	Cape/Mayo	24,8 vs. 15,5 (p = 0.005)	4,3 vs. 4,7 (p = 0.72)	12,5 vs. 13,3 (p = 0.974)	Ib

ECOG performance status (0 – 1), leukocyte count (< 10×10^9/L), alkaline phosphatase (< 300 U/l) and evidence of only one metastatic site [691].

VII.4.1.2. Combination therapy

In recent years, a series of large phase III studies on first-line therapy of mCRC were published, where patients were randomized into one group with a fluoropyrimidine-monotherapy and another group with combination chemotherapy consisting of fluoropyrimidine and Irinotecan or Oxaliplatin. Combination therapy improved response rates and progression-free survival in all of these studies; in two of the three Irinotecan-based therapy studies a significant survival benefit was shown for combination therapy, although the influence of second- and third-line therapies on overall survival should not be left out of consideration when evaluating the value of first-line therapy.

Oxaliplatin + 5-FU/folinic acid

Background

The combination of infusional 5-FU/FA with Oxaliplatin resulted in a significant increase of progression-free survival as compared to the sole administration of an infusional 5-FU therapy (median PFS of 9 months versus 6.2 months for 5-FU/FA alone; p = 0.0003) (**Table VII.8**).

Additionally, response rates were significantly better with the intensified therapy (50.7 vs. 22.3%, p = 0.0001), although more grade 3 – 4 toxicities were observed. Especially neutropenias and neurological complications occurred significantly more frequently in the Oxaliplatin arm (p < 0.001). Overall survival was not significantly longer (16.2 vs. 14.7 months, p = 0.12) [692].

Irinotecan + 5-FU/folinic acid (FA)

Background

The combination of Irinotecan and bolus 5-FU/FA (IFL) shows an unfavourable effect/side-effect ratio and is therefore obsolete.

The comparison of a 5-FU/FA monotherapy with a combination therapy consisting of infusional 5-FU/FA and Irinotecan revealed a significant benefit for the combination therapy; the decision whether the patients were treated according to the AIO scheme (weekly) or the de Gramont scheme (every two weeks) was made by the individual centers. A total of 387 patients were treated [695] (**Table VII.9**). The response rates were 35% for the Irinotecan-containing protocol and 22% for the 5-FU/FA monotherapy (p < 0.005). Progression-free survival and overall survival were significantly prolonged (6.7 vs. 4.4 months, p < 0.001 and 17.4 vs. 14.1 months, p = 0.031).

The spectrum of side effects included CTC-grade 3 and 4 diarrheas in 44.4% (versus 25.6% in the 5-FU monotherapy arm, p = 0.055) and grade 3 and 4 neutropenias in 28.8% of the patients in the Irinotecan group (versus 2.4% in the 5-FU monotherapy arm, p = 0.001) [695]. In another study in which 430 patients were treated with Irinotecan and a weekly 5-FU

Table VII.8 Oxaliplatin-containing protocols in first-line therapy – phase III studies.

reference	n	regimen	overall response rate (ORR)	PFS (Mo)	OS (Mo)	level of evidence
de Gramont 2000 [692]	420	FOLFOX4 vs. 5FU/FA	50,7 vs. 22,3 (p = 0.0001)	9,0 vs. 6,2 (p = 0.0003)	16,2 vs. 14,7 n. s.	Ib
Giacchetti 2006 [693]	564	FOLFOX2 vs. Oxaliplatin/5FU (chronomodulated)	44,3 vs. 42,0	8,4 vs. 8,4 n.s	18,7 vs. 19,6 n.s	Ib
Giacchetti 2000 [694]	200	Oxaliplatin/5FU vs. 5FU (both chronomodulated)	53 vs. 16 (p < 0.001)	8,7 vs. 6,1 (p = 0.048)	19,4 vs. 19,9	Ib

Table VII.9 Irinotecan-containing protocols in first-line therapy – phase III studies.

reference	n	regimen	overall response rate (ORR) (%)	PFS (Mo)	OS (Mo)	level of evidence
Kohne 2005 [696]	430	AIO + CPT 11 vs. AIO	62,2 vs. 34,4 (p < 0.0001)	8,5 vs. 6,4 (p < 0.0001)	20,1 vs. 16,9 n. s.	Ib
Douillard 2000 [695]	387	FOLFIRI vs. 5-FU/FA	35 vs. 22 (p < 0.005)	6,7 vs. 4,4 (p < 0.001)	17,4 vs. 14,1 (p = 0.031)	Ib
Saltz 2000 [697]	683	IFL vs. Mayo (vs. CPT 11 mono)	39 vs. 21 (p < 0.001)	7,0 vs. 4,3 (p = 0.004)	14,8 vs. 12,6 (p = 0.04)	Ib

Table VII.10 Oxaliplatin- versus Irinotecan-containing protocols in first-line therapy.

reference	n	regimen	overall response rate (ORR) (%)	PFS (Mo)	OS (Mo)	level of evidence
Tournigand 2004 [698]	220	FOLOFOX6 – FOLFIRI vs. rev sequence	54 vs. 56 n.s	8,0 vs. 8,5 n.s	20,6 vs. 21,5 n. s.	Ib
Goldberg 2004 [700]	795	FOLFOX vs. IFL (vs. IROX)	45 vs. 31 (p = 0.002) (vs. 35)	8,7 vs. 6,9 (p = 0,0014) (vs. 6,5)	19,5 vs. 15 (p = 0.0001) (vs. 17,4)	Ib
Goldberg 2006 [701]	305	rIFL vs FOLFOX	32 vs. 48 (p = 0.006)	5,5 vs. 9,7 (p < 0.0001)	16,3 vs. 19 (p = 0.026)	Ib
Colucci 2005 [699]	360	FOLFIRI vs. FOLFOX	31 vs. 34 (p = 0.6)	TTP: 7 vs. 7	14 vs. 15	Ib
Comella 2005 [702]	274	OXAFAFU vs. IRIFAFU	44 vs. 31 (p = 0.029)	7 vs. 5,8 (p = 0.046)	18,9 vs. 15,6(p = 0.032)	Ib

scheme (AIO scheme) in two different levels of dosage, the comparison with the AIO scheme alone showed a benefit for combination therapy as well. The differences in response rates and progression-free survival were highly significant, overall survival, however, was not shown to be significantly longer [696]. Grade 3 and 4 toxicities in this study were especially diarrheas (29% for Irinotecan-containing protocols vs. 21% for 5-FU monotherapy). Saltz showed in his three-armed study that combination therapy consisting of bolus 5-FU and Irinotecan (IFL) also resulted in considerably improved response rates and significant elongation of progression-free survival and overall survival in comparison to monotherapy consisting of either bolus 5-FU/FA or Irinotecan; the results for Irinotecan monotherapy and bolus 5-FU monotherapy were comparable. However, the bolus 5-FU arm had the highest rate of grade 3 – 4 neutropenias (66.2 vs. 53.8% with combination therapy and 31.4% after Irinotecan monotherapy) and neutropenic complications in 14.6% (vs. 7.1 respectively 5.8%). Gastrointestinal toxicity with diarrhea and vomiting was higher in the combination arm [697]. Considering the different combinations of 5-FU/FA and Irinotecan, FUFIRI and FOLFIRI (infusional 5-FU) are of approximately equal effectiveness, although the rate of alopecia is probably lower in the weekly protocol. Irinotecan plus bolus 5-FU (Saltz protocol) shows the most unfavourable ratio of effect and side-effects and should therefore no longer be used.

Comparison of Irinotecan- versus Oxaliplatin-containing combination therapies

Background

If an indication for combination chemotherapy is given, FOLFOX or FOLFIRI can be employed in first-line therapy.

Although a survival benefit was demonstrated for two of the three Irinotecan-containing combination chemotherapies in opposition to the Oxaliplatin-based protocols (see above), when directly compared, FOLFOX and FOLFIRI have been observed to be of similar value in effectiveness [698].

Hence, the spectrum of toxicities should be especially taken into consideration when choosing between a fluoropyrimidine-based Irinotecan- or Oxaliplatin-containing combination. Colucci and colleagues documented the same effectiveness of FOLFIRI and FOLFOX in direct comparison (see below) while observing different toxicities. The most frequently observed side-effects were alopecia and side-effects affecting the gastrointestinal tract in arm A (Irinotecan) and thrombocytopenia and neuropathies in arm B (Oxaliplatin). Grade 3 and 4 toxicities were observed in both arms, by means of neutropenia (27 respectively 28%) and diarrheas (28%) especially for the Irinotecan-containing protocols, and neuropathy (12%) for the Oxaliplatin-containing protocols [699] (Table VII.10).

Capecitabine in combination with Oxaliplatin or Irinotecan

Oxaliplatin and Capecitabine

Background

Two large phase III studies with a total of 822 patients are available in which infusional 5-FU/FA was compared with the oral prodrug Capecitabine each in combination with Oxaliplatin. The Spanish working group chose the FUOX regimen as the standard arm, the AIO study group employed a weekly infusional protocol of 5-FU/FA/Oxaliplatin (FUFOX) [703, 704]. The German study documented a progression-free survival of 7.1 months (versus 8 months in the FUFOX arm; HR: 1.17; 95% CI: 0.96 – 1.43; p = 0.117) and an overall survival of 16.8 months (versus 18.8 months in the FUFOX arm; HR: 1.12; 95% CI: 0.92 – 1.38; p = 0. 26) for the CAPOX arm. Response rates were 48% for CAPOX (95% CI: 41 – 54%) respectively 54% for the FUFOX regimen (95% CI: 47 – 60%). The most-frequent non-haematological side effect was polyneuropathy in 27% versus 25% of the cases; only the hand-foot syndrome in grades 2 and 3 was significantly more frequent within the CAPOX arm (p = 0.028) [704]. Study design and results were comparable in both studies and therefore both therapy regimens represent an active first-line therapy.

Another large phase III study clearly showed the non-inferiority of Capecitabine and Oxaliplatin (in the XELOX protocol) in relation to progression-free and overall survival in comparison with FOLFOX4 (HR: 1.04; 97.5% CI: 0.93 – 1.16 for PFS and HR: 0.99; 97,5% CI: 0.88 – 1.12 for OS) [705] (**Table VII.11**).

Irinotecan and Capecitabine

Background

The data currently available on effectiveness and toxicity of Capecitabine and Irinotecan are less uniform than for the combination of Capecitabine/Oxaliplatin. Two studies analyzed the effectiveness of CAPIRI in comparison to an infusional 5-FU protocol. In the BICC-C study, CAPIRI was clearly inferior to FOLFIRI with regards to progression-free survival. The very high toxicity with nearly 50% of grade 3 – 4 diarrheas probably plays a crucial role here ($2 \times 1\,g/m^2$ Capecitabine/day 1 – 14, 250 mg Irinotecan/m^2 on day 1). Response rates and overall survival were not significantly different [706]. A study published in 2007 reported of intolerable side effects of the CA-

Table VII.11 Capecitabine and Oxaliplatin combinations in first-line therapy – phase III studies.

reference	n	regimen	overall response rate (ORR) (%)	PFS (Mo)	OS (Mo)	level of evidence
Cassidy 2008 [705] NO 16966	2034	XELOX vs. FOLFOX4	37 vs. 37	8 vs. 8,5 (HR: 1,04; 97,5 % CI: 0,93 – 1,16)	19,8 vs. 19,6 (HR: 0,99; 97,5 % CI: 0,88 – 1,12)	Ib
Porschen 2007 [704]	474	CAPOX vs. FUFOX	48 vs. 54	7,1 vs. 8,0 (HR: 1,17; 95 % CI: 0,96 – 1,43; p = 0.117)	16,8 vs. 18,8 (FUFOX HR: 1,12; 95 % CI: 0,92 – 1,38; p = 0.26)	Ib
Diaz-Rubio 2007 [705]	348	CAPOX vs. FUOX	37 vs. 46 n. s.	8,9 vs. 9,5 (p = 0.153)	18,1 vs. 20,8 (p = 0.145)	Ib

PIRI regimen, which also led to early termination of the study (2 × 1 g/m^2 Capecitabine/day 1 – 15 and 22 – 36, 250 mg Irinotecan/m^2 day 1 + 22). In the CAPIRI group especially haemotoxic side effects in 61% of the cases made a dose reduction necessary, in the FOLFIRI arm were only 7% dose reductions necessary. Six of eight deaths occurred in the group treated with CAPIRI, three patients died of a thromboembolic event and three due to high-grade diarrheas [707]. With a total of 820 patients, the CAIRO study is so far the largest study which dealt with the combination of Capecitabine and Irinotecan. In this study, Capecitabine was administered in a dose of 2 × 1 g/m^2/day 1 – 14 along with Irinotecan 250 mg/m^2/day 1 in a 3-week cycle. The frequency of grade 3 – 4 toxicities was not significantly different between the two groups, with the exception of the more-frequent appearance of grade 3 hand-foot syndromes in the sequential treatment arm [673].

In this study the rate of severe diarrheas was significantly lower than in the BICC and EORTC studies, which may be explained with the fact that the Dutch centers in the CAIRO study were specifically trained for executing the study and managing of possible side-effects. Due to its toxicity, the CAPIRI regimen can currently not be considered as a standard therapy. Preliminary data from the AIO, however, indicate that, with a dose-reduction (200 mg/m^2 Irinotecan day 1 + 2 × 800 mg/m^2 Capecitabine/day 1 – 14), CAPIRI can be administered with tolerable side-effects. The most-frequent CTC grade 3 – 4 toxicities were diarrheas in 17/15.5%, hand-foot syndrome in 5.9/2.7% and neurotoxicity in 15.3/0% of all patients [708]* (**Table VII.12**).

Irinotecan, Oxaliplatin + 5-FU as combination therapy – FOLFOXIRI

Background

In a phase III study published in 2006, no statistical superiority of the FOLFOXIRI regimen could be demonstrated in comparison with the FOLFIRI regimen. Median overall survival was 21.5 vs. 19.5 months, response rates were 43 vs. 33.6% (p = 0.337 resp. p = 0.168). The rate of side-effects (alopecia, diarrhea, neurotoxicity) was significantly higher than in the FOLFIRI arm (p = 0.0001 resp. p = 0.001 for neurotoxicity) [661]. Falcone et al. however demonstrated a significant improvement of progression-free as well as overall survival with FOLFOXIRI. This survival benefit was accompanied by significantly more-frequently appearing grade 2 – 3 peripheral neurotoxicity and grade 3 – 4 neutropenias (0 vs. 19% resp. 28 vs. 50%, p < 0.001 resp. p = 0.0006) [657]. In both studies response rates were better in comparison to FOLFIRI alone; in Falcone's study this benefit reached the level of significance. However, the results of the two studies are only partially comparable due to different protocols and study populations. Response rates and resection rates, which were the primary and secondary endpoints of the Italian study, were convincing, so that the FOLFOXIRI protocol should especially be considered for induction of remission and possible secondary resection of liver metastases (see also VII.2.1.2) (**Table VII.13**).

5-FU/folinic acid + Bevacizumab

Background

This combination is particularly fitting for patients who do not qualify for an Oxaliplatin-containing/Irinotecan-containing protocol or for patients for whom a lengthening of progression-free and overall survival along with good quality of life is the primary goal of therapy (matching group 3). In a prospective, randomized placebo-controlled phase II study Kabi-

Table VII.12 Capecitabine in combination with Irinotecan in first-line therapy – phase III studies.

reference	n	regimen	overall response-rate (ORR) (%)	PFS (Mo)	OS (Mo)	level of evidence
Koopman 2007 (CAIRO) [673]	820	CAPIRI vs. Cape mono	41 vs. 20 (p < 0.0001)	7,8 vs. 5,8 (p = 0.0002)	17,4 vs. 16,3	Ib
Fuchs 2007 (BICC-C) [706]	430	FOLFIRI vs. mIFL vs. CAPIRI	47 vs. 43 vs. 39 n. s.	7,6 vs. 5,9 vs. 5,8 (p = 0.004 and 0.015 resp.)	23,1 vs. 17,6 vs. 18,9 n. s.	Ib
Kohne 2007 [707] (EORTC 40015)	85	CAPIRI vs. FOLFIRI (± Celecoxib)	48 vs. 46	5,9 vs. 9,6	14,8 vs. 19,9	IIb

Table VII.13 FOLFOXIRI in first-line therapy.

reference	n	regimen	overall response rate (ORR) (%)	PFS (Mo)	OS (Mo)	level of evidence
Falcone 2007[1]	244	FOLFOXIRI vs. FOLFIRI	60 vs. 34 (p = 0.0001)	9,8 vs. 6,9 (p = 0.0006)	22,6 vs. 16,7 (p = 0.032)	Ib
Souglakos 2006[2]	283	FOLFOXIRI vs. FOLFIRI	43 vs. 33,6 (p = 0.168)	8,4 vs. 6,5 (p = 0.17)	21,5 vs. 19,5 (p = 0.337)	Ib

[1] 5-FU as continuous infusion.

[2] 5-FU as bolus, protocol with reduced doses of Irinotecan and Oxaliplatin.

navaar et al. analyzed the effectiveness of a combination of Bevacizumab with a 5-FU/FA monotherapy according to the Roswell Park scheme in comparison with a sole 5-FU/FA monotherapy [709]. The results show a highly significant lengthening of progression-free survival in combination with Bevacizumab (9.2 vs. 5.5 months, p = 0.0002), without achieving a significant improvement in response rates (26 vs. 15.2%, p = 0.055). The difference in overall survival was also not significant (16.6 vs. 12.9 months, p = 0.16). The therapy was well tolerated although this study involved patients of a high-risk population (the median age was 72, the performance status was > 0 for 72% of the patients).

Oxaliplatin + 5-FU/folinic acid + Bevacizumab

Background

The recently published randomized multi-center study NO16966 was initially designed as a two-armed study, which was to examine the non-inferiority of Capecitabine and Oxaliplatin (as XELOX protocol) in comparison with FOLFOX4 [705]. After publication of data of the phase III study by Hurwitz (see below), which revealed a significant benefit by adding Bevacizumab, the original study protocol was expanded to a 2x2 factorial design and extended by Bevacizumab. The study showed a significant improvement of progression-free survival for the combination of chemotherapy and Bevacizumab (XELOX/FOLFOX ± Bevacizumab). PFS as the primary endpoint was increased in median from 8.0 to 9.4 months (HR: 0.83; 97.5% CI: 0.72 – 0.95; p = 0.0023) [662]. A possible explanation for this relatively small difference of only 1.4 months in PFS under a triple combination therapy could be that the average therapy duration in both arms was only about six months (190 days); the administration of the combination chemotherapy and Bevacizumab was stopped hereafter, probably due to toxicity reasons. In line with this, only 29% of the patients who were treated with Bevacizumab were treated until progression. A planned subgroup analysis of these patients indicates that continuing therapy up to progress could result in a lengthening of the "time of tumour control." Overall survival as a secondary endpoint was not significantly improved (21.3 vs. 19.9 months, HR: 0.89; 97,5% CI: 0,76 – 1,03; p = 0.077), response rates were the same (38 vs. 38%, OR 1.00; 97.5% CI: 0.78 – 1.28, p = 0.99). 59 patients (8.4%) in the Bevacizumab arm and 43 patients (6.1%) in the placebo arm were operated with curative intention; the effect on R0 resectability cannot yet be conclusively determined. Resectability was not defined as a secondary endpoint in this trial [662] (see also VII.2.1.2).

Irinotecan + 5-FU/folinic acid + Bevacizumab

Background

The direct comparison of IFL plus placebo with IFL plus Bevacizumab showed a significant lengthening of overall survival from 15.6 months to 20.3 months (p < 0.001). The median time until progress could also be extended from 6.2 months to 10.6 months by combination with the antibody (p < 0.001). In the non-placebo group response rates were significantly higher with 44.8% compared to the placebo group (34.8% p = 0.004). The spectrum of toxicity included a grade 3 hypertension for 11% of the patients treated in the experimental arm in contrast to 2.3% in the standard arm. Further grade 3 and 4 toxicities were leucopenia in 37% and diarrhea in 32.4%. Since then, Bevacizumab was permitted for use in combination with 5-FU/FA with or without Irinotecan for first-line therapy of colorectal carcinoma [710].

A direct comparison of FOLFIRI plus Bevacizumab with mIFL plus Bevacizumab in the BICC-C study revealed a clear superiority for the 5-FU protocol in progression-free survival, overall survival (not yet reached vs. 19.2 months with mIFL + Bevacizumab, p = 0.007). Response rates were not significantly different (57.9 vs. 53.3%) [706]. Also due to the more-favourable toxicity profile, the infusional 5-FU protocol should be preferred over the IFL protocol.

Oxaliplatin + Capecitabine + Bevacizumab

Background

The results of the N016966 study are presented in detail above. Both XELOX in combination with Bevacizumab and XELOX without the antibody are not inferior to the infusional protocol. The response rates which were acquired by an independent review committee were equal being 38% for both the FOLFOX and the XELOX arm. A predefined subgroup analysis indicates a benefit of 1.9 months in median progression-free survival for the combination of Bevacizumab with XELOX compared to XELOX alone (7.4 vs. 9.3 months, HR: 0.77; 97.5% CI: 0.63 – 0.94; p = 0.0026). The availability of Bevacizumab in the FOLFOX arm resulted in no significant lengthening of progression-free survival in this subgroup analysis (8.6 vs. 9.4, HR: 0.89; 97.5% CI: 0.73 – 1.08; p = 0.1871) [662].

Oxaliplatin + 5-FU-folinic acid + Cetuximab

Background

A randomized multicenter phase II study from Europe analyzed the effectiveness of a combination of FOLFOX ± Cetuximab (OPUS study). 337 patients were randomized. Response rates were 45.6% in the experimental arm and 35.7% in the standard arm, while showing comparable grade 3 – 4 toxicity. Survival data were not yet available at the time of the presentation in 2007. The most-frequent side-effects were neutropenia, diarrhea in both groups and acne-like skin rash in the group treated with Cetuximab [711]*.

There are no phase III data that support a treatment of mCRC with a combination of FOLFOX and Cetuximab in first-line therapy.
Hence, a general recommendation concerning the use of this combination cannot be given at this time.
However, Cetuximab is permitted for first-line therapy of CRC in combination with Oxaliplatin for those patients who have wild type k-ras tumours.

5-FU-folinic acid + Irinotecan + Cetuximab

Background

Until now, there are no phase III data available by means of a fully published manuscript concerning the use of Cetuximab in first-line therapy. The data of the phase III study (CRYSTAL) presented at ASCO in 2007 are promising and demonstrate a statistically-significant increase in response rates and progression-free survival in comparison with FOLFIRI alone. The combination of FOLFIRI and Cetuximab resulted in a response rate of 46.9% (in comparison with 38.7% for FOLFIRI; p = 0.005). The rate of R0 resections as a secondary endpoint was increased in the experimental arm as well [658]*. The high response rates from phase I/II studies (ORR 67%) which had been discussing an outstanding role for Cetuximab as a possible therapy for downsizing marginally resectable liver metastases [712], were not achieved.
A retrospective analysis of the CRYSTAL study which was currently presented at ASCO showed that exclusively patients with wild type k-ras tumours benefit from a therapy with Cetuximab [659]*.
Cetuximab can be used – after its approval, which is expected for August of 2008 – for this group of patients in combination with an Irinotecan-containing therapy as a first-line therapy of CRC.

VII.4.2. Duration of therapy/Interruption of therapy in first-line therapy/Reinduction

Recommendation

There is no sufficient evidence that would justify stopping a once-begun systemic chemotherapy before disease progression occurs.
Level of Recommendation B, Level of evidence: 1b, consensus.

Background

Since overall survival and duration of tumour control can be considerably extended in each line of therapy with new chemotherapeutic agents and combination chemotherapies, the question of chemotherapeutic-associated side-effects and the resulting quality of life are also becoming more and more decisive. As a result, studies have been performed that analyzed the value of a maintenance therapy with less-intensive therapy schemes (OPTIMOX 1) or a complete stopping of therapy after an induction phase in contrast to therapy until progression (OPTIMOX 2). The OPTIMOX 1 study analyzed the administration of FOLFOX4 up to progression in comparison with FOLFOX7 followed by a maintenance therapy with 5-FU/FA and reinduction of FOLFOX7 with the appearance of progression. The differences in progression-free and median survival were not significant, the rate of grade 3 neurotoxicities was more favourable (13 vs. 18%, p = 0.12) [713]. Such a de-escalation strategy with reinduction of Oxaliplatin with documented progression should also be used in clinical routine and be discussed with patients as a possible option. The OPTIMOX 2 study examined the possibility of a complete halt of therapy in comparison with a maintenance therapy as in OPTIMOX 1. With this study concept, median progression-free survival was significantly longer in the control arm (OPTIMOX 1) than in the experimental arm (8.3 vs. 6.7 months; p = 0.04); median overall survival was considerably better as well (24.6 vs. 18.9 months; p = 0.05). So far, the data are only available reporting abstract form and were not fully conclusive in the presentation [714]*. A recommendation for a planned complete interruption of therapy without maintenance therapy cannot be given on the basis of these data. The working group around Maughan observed a considerably lower toxicity with an intermittent administration of a 5-FU-containing protocol with no clear survival benefit for the continuous administration (HR 0.87 for intermittent administration, 95% CI: 0.69 – 1.09; p = 0.23) [715].
Labianca found no difference in overall survival as the primary endpoint between an intermittent FOLFIRI protocol in comparison with a continuous administration up to progress while observing comparable toxicity (HR = 1.11; 95% CI; 0.83 – 1.48) [716]*.
In contrast to a conceptual interruption of therapy, there are short-term interruptions in chemotherapy due to the personal

Table VII.14 Studies concerning the question of treatment interruption/maintenance therapy [713 – 716].

reference	n	regimen	overall response rate (ORR) (%)	PFS (Mo)	OS (Mo)	level of evidence
Labianca 2006[1]	336	FOLFIRI intermitt vs. cont.	29 vs. 35	8,8 vs. 7,3 (HR: 1,00, 95% CI: 0,74 – 1,36)	16,9 vs. 17,6 (HR: 1,11 95% CI: 0,83 – 1,48)	Ib
	620	Ctx bis PD vs. maintenance with 5FU/FA	58,8 vs. 59,2 n. s.	9 vs. 8,7 n. s.	19,3 vs. 21,2 n. s.	Ib
Maindrault 2007 (OPTIMOX 2)[1]	202	maintenance vs. stop of therapy	63 vs. 61	8,3 vs. 6,7 (p = 0.04)	24,6 vs. 18,9 (p = 0.05)	Ib
Maughan 2003	354	5-FU/FA 12w Ctx vs. cont.	21 vs. 8	3,7 vs. 4,9 (HR:1,2 95% CI: 0,96 – 1,49)	10,8 vs. 11,3 (HR: 0,87; 95% CI: 0,69 – 1,09)	IIb

[1] So far the study has only been published in abstract form.

living situation of the patient (e.g. vacation). In this case, short-term interruptions of therapy are tolerable (**Table VII.14**).

VII.4.3. Chemotherapy protocols in second- and third-line therapy

Overall, studies on first-line therapy of mCRC show a high variability concerning overall survival ranging from 14.1 to more than 22 months. Assuming that there were no great differences in patient selection, the type of chosen second- and third-line therapy and certainly their different availability as well are possibly responsible for these discrepant results. The choice of second- and third-line therapy depends on previous therapies and the time interval without therapy as well as on the individual situation of the patient and the particular goal of therapy. Although in first-line therapy currently options are taken into consideration concerning the reduction of the duration of therapy or "stop-and-go" strategies (see above), second- and third-line therapies should still follow the principle that the therapy should be administered up to disease-progression.

Recommendation

Due to the lack of sufficient evidence none of the therapeutic agents described above should be continued after a documented progression under therapy with the exception of fluoropyrimidines or the administration of Irinotecan in combination with Cetuximab after failure of an Irinotecan-containing therapy. This also applies to Cetuximab and Bevacizumab.

Level of Recommendation A, Level of evidence: 2, strong consensus.

Background

The value of an effective second-line therapy for overall survival has been analyzed in several phase III studies. Thus, a second-line therapy with Irinotecan after failure of Fluorouracil monotherapy resulted in a significant benefit in overall survival in comparison with BSC [717] or infusional 5-FU/FA [718]. Combination therapy with Oxaliplatin and Fluorouracil after failure of an Irinotecan-containing protocol in first-line therapy was superior to 5-FU/FA and/or Oxaliplatin monotherapy in relation to the resulting response rates as well as in relation to the time until progress [719]. 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) up to 15% (FOLFOX) and a progression-free survival of about 2.5 – 4.2 months in second-line therapy. The median survival of the patients was about 20 months for both therapy sequences (FOLFOX → FOLFIRI and/or FOLFIRI → FOLFOX) respectively [698]. The introduction of monoclonal antibodies such as Cetuximab, Bevacizumab and Panitumumab has extended the possibilities for second- and third-line therapy as well. The BOND-1 study for the first time verified the effectiveness of Cetuximab in combination with Irinotecan as second-line therapy for advanced CRC's after Irinotecan failure (RR 22.9%, overall survival 8.6 months) [720]. The EPIC study showed that the combination of Cetuximab plus Irinotecan was also effective after a previously administered therapy containing Oxaliplatin and in direct comparison was more effective than an Irinotecan-monotherapy [721].

VII.4.3.1. Combination therapy in second- and third-line therapy

Irinotecan or Oxaliplatin + Fluoropyrimidine

Background

In his work published in 2004, Tournigand compared FOLFOX and FOLFIRI as first- and second-line therapy, respectively, and vice versa. Median survival of the respective sequences was not significantly different between the two arms (20.6 months for FOLFOX vs. 21.5 months for FOLFIRI in first line treatment) [698]. With relation to response rates or progression-free survival again no significant benefit could be shown for one sequence or the other (**Table VII.15**).

627 patients with progress under Irinotecan-containing therapy were treated either with XELOX or FOLFOX in the second line. The average time to progression was 4.8 months in the XELOX arm vs. 4.7 months in the FOLFOX arm.

Grade 3 – 4 toxicities were noted in 60.1% of the cases in the XELOX arm and in 72.4% of the patients treated with FOLFOX. They mainly involved diarrheas (20 vs. 5%), neutropenia in 5% respectively 35% and nausea and vomiting in 5 – 6% of the cases [723]*. Consequently, Capecitabine in combination with Oxaliplatin can replace 5-FU in second-line therapy as well.

Irinotecan + Cetuximab

Background

In the BOND study, 329 patients who showed progress within three months after receiving Irinotecan-containing therapy were treated. The patients were either randomized for chemotherapy with Irinotecan and Cetuximab or for Cetuximab monotherapy. Compared to monotherapy, the combination therapy resulted in significantly higher response rates (22.9 vs. 10.8%, $p = 0.007$). Progression-free survival was significantly lengthened as well (4.1 vs. 1.5 months, $p < 0.001$). Overall survival was 8.6 respectively 6.9 months ($p = 0.48$) [720]. The EPIC study analyzed the effectiveness of this combination with patients who had shown progress under treatment with an Oxa-

Table VII.15 Oxaliplatin-containing protocols in second-line therapy.

reference	n	regimen	overall response rate (ORR) (%)	PFS (Mo)	level of evidence
Giantonio 2007 [722]	829	FOLFOX 4 vs. FOLFOX + Bevacizumab vs. Bevacizumab mono	8,6 vs. 22,7 ($p < 0.0001$) vs. 3,3	4,7 vs. 7,3 ($p < 0.0001$) vs. 2,7	Ib
Rothenberg 2007 [723, 20	627	XELOX vs. FOLFOX	n. a.	TTP: 4,8 vs. 4,7	Ib
Tournigand 2004 [698]	220	FOLFIRI → FOLFOX 6 vs. rev. sequence	4 vs. 15	2,5 vs. 4,2	Ib
Rothenberg 2003	463	FOLFOX 4 vs. FA-5 FU vs. Oxaliplatin mono	9,9 vs. 0 vs. 0	TTP: 4,6 vs. 2,7 ($p < 0.0001$)	Ib

[1] So far only published in abstract form.

liplatin-based therapy. In this phase III study, patients were either treated with Cetuximab + Irinotecan (n = 648) or with Irinotecan mono (n = 650). Response rates were significantly improved with the administration of combination therapy (16.4 vs. 4.2%, p < 0.0001). Median PFS was extended from 2.6 months to 4.0 months with the availability of Cetuximab (HR: 0.692, p < 0.0001). Median overall survival as a primary endpoint was comparable in both arms, since after progression a "crossover" in the other study arm was permitted (10.7 vs. 10 months, hazard ratio for overall survival = 0.975, 95% CI: 0.854 –1.114, p = 0.71). An accompanying analysis of the quality of life showed an improvement for the general health status (p = 0.047) and for functional and individual symptoms (fatigue, nausea/vomiting [p < 0.0001], pain [p < 0.0001]) in the combination arm, so that – assuming approval of the drug – this combination can be considered for symptomatic patients [721, 724*].

Bevacizumab + 5-FU-folinic acid + Oxaliplatin

Background

The value of Bevacizumab in combination with Oxaliplatin and 5-FU/FA in second-line therapy after failure of an Irinotecan-containing therapy with patients who had not before been treated with Bevacizumab was analyzed in a phase III study. 829 patients were randomized into one of the three therapy arms, being FOLFOX-Bevacizumab or FOLFOX or Bevacizumab as monotherapy, respectively. The additional consideration of Bevacizumab resulted in a significant survival benefit of 2.1 months in comparison to FOLFOX alone (12.9 vs. 10.8 months, HR: 0,75; p = 0.0011). Progression-free survival as well was significantly longer than in the solitary chemotherapy arm (7.3 vs. 4.7 months, HR: 0.61, p < 0.0001).

Bevacizumab alone had no clinical value. The combination with the VEGF antibody increased the rate of grade 3 and 4 toxicities by 14%. Bleeding, vomiting and hypertension occurred significantly more frequent in the experimental arm. The fact that the risk of neuropathy was increased as well is most likely due to longer therapy duration in the combination arm (10 vs. 7 cycles in the FOLFOX arm). The follow-up period was 28 months [722].

Mitomycin C + Fluoropyrimidines

Background

In a work by Chong with 36 patients an objective response rate of 15.2% was achieved in third-line therapy. Median overall survival was 9.3 months. Data from phase I/II studies are encouraging; results from phase III studies are not available. Fluoropyrimidine and Mitomycin C can be used as a salvage therapy [725 – 728].

VII.4.3.2. Monotherapy with biological substances in third-line therapy

Cetuximab

Background

In 2006, Lenz published a large one-armed phase II study with 346 patients which also demonstrated the benefit of Cetuximab monotherapy for Irinotecan-refractory patients and had a response rate of 11.6%. More than half of the patients were showing progression at the time of the first imaging (median progression-free survival: 1.5 months); overall survival was 6.6 months. The BOND study, which was already mentioned above, showed comparable response rates of about 10% in monotherapy. In the studies named lastly, again, the grade of skin rash correlated with effectiveness [720, 729]. A currently published study, which compared Cetuximab monotherapy with BSC, achieved an overall survival of 6.1 months versus 4.6 months in the group with sole BSC [730]. In consideration of these data and the results of the BOND-1 study, Cetuximab monotherapy is especially recommendable for patients who do not qualify for Irinotecan-containing therapy (approval of Cetuximab in monotherapy: non-responder to Oxaliplatin and Irinotecan-containing chemotherapy and Irinotecan-intolerance). Translational data on a heterogeneous patient collective indicate that for Cetuximab as well the k-ras mutational status is an independent predictive factor. Thus, a k-ras mutation was found in 27% of the Irinotecan-refractory patients and was associated with a resistance against Cetuximab (0 vs. 40% responders among the 24 patients with k-ras mutation respectively among the 65 patients with k-ras wild type expressing tumours, p < 0.001) as well as with a worse survival (median PFS: 10.1 vs. 31.4 weeks for patients without mutation, p = 0.0001; median OS: 10.1 vs. 14.3 months for patients without mutation; p = 0.026) [731].

The k-ras mutation status is relevant for approval as of August, 2008. Only patients with a wild type k-ras expressing tumour should receive Cetuximab.

Panitumumab

Background

Panitumumab is the first fully human monoclonal antibody which binds to the epidermal growth factor receptor (EGFR). An effectiveness study in phase II with 148 patients with pretreated metastasized colorectal carcinoma (dose of Panitumumab 2.5 mg/kg/week) showed a partial response to therapy in 9% of the cases; in 29% of the cases the disease remained stable. The average overall survival time was 9 months; the average time up to progression was 14 weeks [732]. A subsequently performed randomized and controlled multicenter phase III study included 463 patients with metastasized colorectal carcinoma after failure of cytostatic standard therapy with 5-FU/FA, Irinotecan and Oxaliplatin. Patients were randomized to Panitumumab along with best supportive care (n = 231) or to best supportive care only (n = 232). With Panitumumab a significant improvement in progression-free survival was achieved (HR: 0.54; 95% CI, 0.44 – 0.66, p < 0.0001). Median progression-free survival was 8 weeks for patients who were treated with Panitumumab, in contrast to 7.3 weeks for those who had only received best supportive care. 176 of the patients, who had primarily been assigned to best supportive care, received Panitumumab by crossover after progression of their tumour [733]. For 168 patients k-ras mutation status was available, 20 patients (12%) showed response; with 32% the disease remained stable. The effectiveness of Panitumumab was limited to tumours that showed no k-ras mutations. These translational studies were currently published [734]. In the US, Panitumumab was approved in September 2006, in Europe in December 2007. The approval is limited to patients who have wild type k-ras gene expressing tumours and for whom chemotherapy regimens containing Fluoropyrimidine, Oxaliplatin and Irinotecan have failed (third-line therapy).

VII.5. Management of local recurrence or non-hepatic and non-pulmonary distant metastases

VII.5.1. Local recurrence

For local recurrence of rectal carcinomas, who have not yet received a pre-treatment (radio(chemo)therapy) in the context of the primary operation, this form of therapy should now be primarily considered. For pre-treated patients who show the possibility for a R0 resection, surgery can primarily be performed [735]. For those pre-treated patients who show questionable R0 resectability of a relapse, decision-making in relation to multimodal surgical proceeding must be done individually and in consideration of the intensity of pre-therapy. For loco-regional lymph node relapse in the context of colorectal carcinoma, an attempt for a complete curative resection should be made, if possible [736].

VII.5.2. Non-hepatic or non-pulmonary distant metastases

Recommendation

Peritonectomy and hyperthermic abdominal perfusion cannot be recommended at this time due to the lack of sufficient trial data.
Level of Recommendation 0, Level of evidence: 4, strong consensus.

Background

In a selected patient collective an overall survival, which varied between 12 and 32 months, was observed after cytoreductive surgery and subsequent hyperthermic intraperitoneal chemotherapy. Morbidity and mortality were 14 – 55% and 0 – 19% respectively [737]. A randomized study published in 2003 compared cytoreductive surgery with subsequent HIPEC and systemic chemotherapy with the conventional proceeding by means of solitary systemic chemotherapy with 5-FU with or without palliative surgical intervention. The primary endpoint, overall survival, demonstrated an interval of 12.6 months in the standard arm versus 22.3 months in the experimental arm ($p = 0.032$). Treatment-related mortality was 8% in the experimental arm [738].
Nevertheless, this treatment approach is reserved to individual cases; a general recommendation cannot be given on the basis of these data.
For isolated bone metastases with pain symptoms local radiation therapy should be conducted. In this context, a meta-analysis showed that single, high-dose therapy is equally potent to fractionated therapy [739]. Single, high-dose therapy should therefore be preferred with consideration of the oncologic overall-concept. Biphosphonate administration can additionally follow. Surgery is indicated in case of an increased fracture risk and imminent paraplegia. With isolated brain metastases a surgical resection should be performed if possible [740]. If inoperable, radiation therapy, if applicable as stereotactic radiation, are possible options [741].

VIII. Topic Area: Follow-up care

▼

VIII.1 Follow-up care for patients with UICC stage I
VIII.2 Follow-up care for patients with UICC stages II and III
VIII.3 Value of diagnostic procedures in follow-up care
VIII.4 Time course of follow-up care
VIII.5 Age limitations for follow-up care
VIII.6. Special cases
VIII.7 Rehabilitation after resection of colorectal carcinoma

After diagnosis and therapy of a colorectal carcinoma, adequate medical care makes sense regardless of the tumour stage. After curative therapy of a colorectal carcinoma there is an increased risk for a local or local-regional recurrence (3 – 24%), distant metastases (25%) or a metachronous second tumours (1.5 – 10%) [476, 742 – 750]. The risk is increased in case of a genetic predisposition [746] and with advancing tumour stages [751, 752]. The quality and type of a chosen operating procedure influence the frequency of local-regional recurrence and the survival rate [476, 744]. In addition, the following are the fundamentals for establishing a follow-up care for these patients: A recurrence should be discovered so early that a second operation is possible with a curative goal. Follow-up should also enable the diagnosis and treatment of tumour and therapy related sequelae. Subjective goals of follow-up care are oriented towards the improvement of the patient's quality of life [753]. An additional goal is quality control of the diagnostic and therapeutic measures which were carried out.
However, the effect of follow-up care seems marginal, with on average a 1% improved survival for the complete group of treated patients [754]. Data from 267 articles relating to this topic were evaluated in a meta-analysis [755]. In order to enable long term survival of one patient with colorectal carcinoma, 360 positive follow-up tests and 11 secondary operations were necessary. The remaining 359 follow-up measures and 10 operations resulted in either no therapeutic advantage or had negative consequences [755].

VIII.1 Follow-up care with patients in UICC stage I

Recommendation

A regular follow-up for patients with colorectal carcinomas and early tumour stage (UICC I) is not to be recommended after R0 resection considering of the low rate of recurrence and the favourable prognosis.
Level of Recommendation B, Level of evidence: 4, strong consensus.

Background

Patients in UICC stage I have a good prognosis after a curative resection. In patients with pT2 tumours recurrence occurs more frequently (UICC Ib) (13%) than in those with pT1 tumours (UICC Ia) (4%). Altogether the long-term survival in stage UICC I patients according to a prospective cohort study are very good with 86%. Deviations can be made from this in individual cases with an expected higher local recurrence risk due to endoscopic or Intraoperative findings (e.g. after intraoperative tumour opening) or pathological findings (e.g. higher risk for distant metastases with invasion of the periocolonic veins [757, 769], angiolymphatic invasion [759, 760], G3/G4 tumours or pT2 tumours) (see topic area IV).

VIII.2 Follow-up care with patients in UICC stage II and III

Recommendation

After R0 resection of colorectal carcinoma of UICC stage II and III, regular follow-up examinations are indicated Table **VIII.1***).*
Level of Recommendation B, Level of evidence: 1a, strong consensus.

Recommendation

Follow-up should however only be performed if a recurrence would result in therapeutic consequences.

Table VIII.1 Programmed examinations in the context of follow-up with colorectal carcinoma UICC II or III.

examination	months										
	3	6	9	12	15	18	21	24	36	48	60
medical history, physical exam, CEA		×		×		×		×	×	×	×
colonoscopy		× [1]							× [2]		
abdominal ultrasound[3]		×		×		×		×	×	×	×
sigmoidoscopy (rectoscopy)[4]		×		×		×		×			
spiral CT[5]	×										
chest x-ray (no consensus)											

[1] If no complete colonoscopy has been carried out preoperatively.
[2] With negative findings (no adenoma, no carcinoma) next colonoscopy after 5 years.
[3] A meta-analysis showed an advantage for an image procedure to detect liver metastases during follow-up. For this reason, the expert commission decided that the simplest and least expensive procedures should be used.
[4] Only for rectal carcinoma without neoadjuvant or adjuvant radiochemotherapy
[5] Only for rectal carcinoma 3 months after completion of the tumour-specific Therapy (operation and/or adjuvant radio/chemotherapy) as initial finding.

Level of Recommendation A, Level of evidence: 5, strong consensus.

Background

With advanced colorectal carcinomas (UICC stage II and III) the risk of recurrence is significantly higher [476, 742 – 752]. Concerning the use of follow-up of CRC-patients there are 6 randomised, controlled studies [761 – 766] (**Table VIII.1**) 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" [764, 766]. Nearly all studies also included patients in UICC stage I.

One of the two positive studies compared the efficiency of a risk-adapted follow-up with a minimal follow-up with additional stratification in a high- and low-recurrence risk group [766]. A high risk was present if one of the following criteria was fulfilled: adenocarcinoma of the distal rectum with anterior resection, adenocarcinoma of the left colon flexure with infiltration of the serosa (Dukes B; T3), CEA preoperative ≥ 7,5 ng/ml, Dukes C, poor tumour differentiation (G3), mucinous adenocarcinoma or signet-ring carcinoma. There was no difference in the number of curative resections for symptomatic and asymptomatic patients. Nevertheless, the risk adapted follow-up resulted in more curative operations and a better five-year survival rate. Before such a risk-adapted follow-up can be recommended, further studies are necessary. In the second positive study [764], the type of examination methods used (clinical examination, ultrasound, CEA, chest x-ray, colonoscopy) were not significantly different between intensified and standard follow-up. In the more intensive follow-up group in addition an annual CT examination was performed and the intervals for examinations were shorter. The standard follow-up consisted of two examinations separated by six months and afterwards annually, while the more intensive follow-up included a control visit every three months for the first two years, then half-yearly controls over three years, and afterwards annual examinations. Chest x-rays, colonoscopies and CT's were scheduled once a year. If patients became symptomatic, examinations were performed earlier. In the group with standard follow-up diagnosed local recurrences were more often associated with distant metastases, they were less often found in the context of a follow-up visit and on average were discovered 10 months later. Those with more intensive follow-up had a higher rate of resections with curative intention (65 vs. 10%) and a better five-year survival (73 vs. 58%) [764].

Another study came to a different result. In this study follow-up visits every three months over 2 years, then biannual over 5 years were performed. Only the more intensive follow-up included an annual chest x-ray, computer tomography and colonoscopy. After five years of post-observation, there was no difference in the survival of the two groups, so that the authors stated that these additional examination methods were unnecessary [765]. This was confirmed in the study as well from Pietra et al. [764] in which the number of curative operations on distant metastases in the liver and lungs showed no difference, even though both groups were examined with these invasive techniques. Possibly the testing interval played a more important role than the kind of diagnostic procedure used. However in one controlled, randomised study short follow-up intervals were not found to influence survival [763]. In this study the methods were similar, but the interval varied between the two groups. The follow-up consisted of biannual intervals for the intensive follow-up group for three years [763], which is similar to the interval used in the "standard follow-up" of the Pietra et al. study [764].

Different meta-analyses of five of the randomised and controlled studies (1 positive, 4 negative) [754, 755, 767 – 770] demonstrated a small survival benefit for performing more compared to fewer tests. Liver imaging as part of follow-up was also shown to be significantly better. The significance was lost, however, if both results were calculated as risk differences and not as odds ratios [769]. An active follow-up lead only to a marginal survival benefit of 0.5 to 2% after five years [754]. A psychological benefit through follow-up can be assumed. No clear recommendations concerning extend and intervals of follow-up examinations can be given due to lack of good studies [772 – 774]. Follow-up adapted to UICC stages or effectiveness of a complete abandonment of follow-up have not been examined in prospective studies.

Due to the unsatisfactory quality of data, the expert conference gave a recommendation grade of B despite an evidence-level 1a with the availability of several meta-analyses for the programmed procedure for follow-up of colorectal carcinoma of UICC stage II and III.

VIII.3 Value of diagnostic methods for follow-up

The following recommendations were given concerning diagnostic tests for follow-up.

Medical history

Recommendation

A symptom-oriented medical history and physical examination are the principle components of follow-up.

Level of Recommendation A, Level of evidence: 5, strong consensus.

Background

The medical history and physical examination play a small part in the early detection of colorectal carcinoma. However, these basic physician measures should procede any further examinations [773, 775]. All participants of the consensus conference agreed with this.

CEA testing

Recommendation

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 with suspicion of a metastasized tumour stage.

Level of Recommendation B, Level of evidence: 4, strong consensus.

Background

CEA was shown to be superior to colonoscopy, computer tomography and ultrasound for the early detection of liver metastases [764, 776, 777]. A meta-analysis of 7 non-randomised studies showed a survival benefit of 9% for patients for whom the follow-up program included CEA [767]. Other studies showed no or only minimal benefit [429, 762]. CEA was not recommended for follow-up in a literature review [774].

However American (ASCO) and European (EGTM, European Group on Tumour Markers) Guidelines for follow-up include however the use of CEA [773, 775, 777], whereby the testing is recommended every 2 – 3 months in the first 2 years. 30% of all colorectal tumours do not release CEA [778, 779], while 44% of the patients with normal preoperative values show an increase postoperatively [780]. The further clarification of increased CEA values requires diagnostic imaging and if necessary 18-fluorodeoxyglucose positron emission tomography [781, 782]. Due to the general controversial data for the use of CEA in follow-up of colorectal carcinoma, the expert conference deviated from the recommendations of ASCO and EGTM and determined a biannual rather than three-month testing interval in the first two years.

Recommendation

The routine testing of laboratory values in the context of follow-up is not advisable.

Level of Recommendation B, Level of evidence: 3b, strong consensus.

Background

In several studies the testing of liver enzymes was part of the follow-up programs. A study showed that CEA and other imaging procedures became positive earlier than liver function tests [772]. For these reasons, a routine testing of these serum parameters is not advised. The same applies for the complete blood count [775].

FOBT

Recommendation

The testing of occult blood in the stool is not appropriate for follow-up.

Level of Recommendation A, Level of evidence: 3b, strong consensus.

Background

The testing of occult blood in the stool is not appropriate for follow-up. Only 12% of the local tumour recurrences led to a surface injury of the mucosal membrane [779]. Serial testing of 1,217 patients with curative resection of colorectal carcinoma showed a very low sensitivity and specificity of the test for recurrent tumours or polyps [783].

Ultrasound

Recommendation

Abdominal ultrasound is technically appropriate for the detection of liver metastases. The routine use for follow-up is not assured by data. However the expert round assessed ultrasound as the simplest and least-expensive procedure and therefore recommends its use for the diagnosis of liver metastases.

Level of Recommendation A, Level of evidence: 5, strong consensus.

Background

The sensitivity of abdominal ultrasound for th edetection of liver metastases varies widely between 53% and 82% [774]. In most studies it was not as accurate as computer tomography. In a controlled, randomised study [761], 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 randomised studies the use of an imaging test for the evaluation of the liver presented statistically significant survival benefits [769]. If the calculation of these results was done as a risk difference and not as an odds ratio this advantage was no longer detectable [769]. 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.

Endoscopic ultrasound

Recommendation

Endoscopic ultrasound (EUS) is appropriate for the detection of local recurrences in rectal carcinoma, especially in combination with EUS-guided biopsy. No recommendation can be given for routine use in follow-up.

Level of Recommendation B, Level of evidence: 3b, strong consensus.

Background

In one study endoscopic ultrasound examinations were shown to be helpful for the detection of local-regional recurrences after sphincter-retaining rectal resection if this procedure was combined with EUS-guided biopsy [784]. 68 perirectal lesions detected by EUS consisted of 36 actual local recurrences in a group of 312 patients. 12 recurrences could be detected with a proctoscope. For 22 of the endosonographically seen 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 [784]. EUS is

not recommended as a primary diagnostic technique for follow-up due to the invasiveness of the procedure when combined with biopsy. It is however useful as workup of suspected local-regional recurrences of rectal carcinoma that have been detected by other tests.

Computer tomography/Chest x-Ray

Recommendation

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 Recommendation B, Level of evidence: 1b, strong consensus.

Background

In a randomised, controlled study, the use of computer tomography (CT) as part of follow-up was shown to have no influence on patient survival [765]. It is true that 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 tumour recurrence earlier than regular CT examinations [764, 765, 786].

Recommendation

The value of chest x-rays for CRC follow-up did not find a consensus.

Evidence strength: 1b, no consensus

Background

Chest x-rays are used in several follow-up programs. 6% of the patients included in a randomised and controlled study developed lung metastases in the course of follow-up [765]. Four asymptomatic metastases (among 157 patients) were discovered with repeated chest x-rays, of which three were isolated and could be resected. Only one of these patients survived the duration of the observation period. In the patient group without regular chest x-ray, four isolated metastases of the lung were found, one of which underwent surgery without extending the life of the patient [765]. In an additional study including 1356 patients, 12 patients were diagnosed with curable lung metastases (0.9%) using chest x-ray [786]. Most of the other studies are case series without comparative groups [776]. Given the available data, no recommendation can be given for regular chest x-ray tests [774]. Due to this, no consensus could be reached in the consensus conference. About half the participants were of the opinion that, despite the lack of evidence, a regular chest x-ray should be part of a follow-up program.

Endoscopic Procedures

Recommendation

Colonoscopy is appropriate to detect local recurrences or new tumours. All patients should receive a complete colonoscopy preoperatively or within 6 months postoperatively. A colonoscopy should be performed after 3 years and after that every five years in order to detect metachronous carcinomas or polyps.

Level of Recommendation B, Level of evidence: 2b, strong consensus.

Recommendation

Sigmoidoscopies are appropriate to detect local recurrences and secondary tumours in the areas within reach. Additional sigmoidoscopies are only to be performed in patients with a rectal carcinoma in UICC stages II and III who have not received neoadjuvant or adjuvant radiochemotherapy.

Level of Recommendation B, Level of evidence: 4, strong consensus.

Recommendation

The rigid rectoscopy is appropriate to detect local recurrences and anastomoses changes in patients with rectal carcinoma. It can be used as an alternative procedure to sigmoidoscopy.

Level of Recommendation B, Level of evidence: 4, strong consensus.

Colon contrast enema, virtual colonography and PET

Recommendation

Colon contrast enema, virtual colonography and PET should not be part of follow-up program.

Level of Recommendation B, Level of evidence: 5, strong consensus.

Background

Colonoscopy is an invasive detection method which causes costs and complications (0.2% perforations), in order to discover a relatively low rate of local recurrence or metachronous tumours in follow-up. In patients with colorectal carcinoma, the cumulative incidence for metachronous carcinoma was 1.5% after 5 years [747]. The relative risk incidence is 1.6 times higher than in the general population and 6.8 times higher than in patients with a history of adenomatous polyps [747].

Out of 1247 intensively followed-up patients, 44% developed a recurrence [787]. Among 40% of these cases, an operation with curative intention was planned, but could only actually be carried out in half of them. The five-year survival rate for these patients was 23%. Overall, 28 of the 1,247 patients profited from the follow-up. Only 33% of the curative operations were performed because of a recurrence detected by endoscopy or chest x-rays [787].

In a retrospective cohort study, the mortality of patients with colorectal carcinoma who underwent at least one colonoscopy after diagnosis was compared with patients who had no further endoscopy. In the cohort with at least one colonoscopy, the first 'surveillance colonoscopy" took place in 52% in the first year, 78% within the first 18 months and in 88% within 2 years. The absolute reduction of mortality after 5 years in the group with at least one surveillance colonoscopy was 12%, and the relative risk reduction was 29% [788]. Not all colonoscopies in this study were performed exclusively because of surveillance.

Prospective randomised trials investigated the effects of regular colonoscopy next to other tests on the survival after curative resection of colon carcinoma. An intensively-cared for (surveillance) group received annual colonoscopies, CT of the liver and X-ray examinations, while in the control group the testing was done only in those who became symptomatic and for the whole group after 5 years [765]. In the intensively cared-for group an additional 505 colonoscopies and 24 colon contrast enemas were conducted. In the control group 13 symptomatic metachronous or recurrent carcinomas were discovered; in the intensively cared-for group 10 carcinomas

were found, 9 of which went along with symptoms or abnormal findings in other follow-up diagnostic tests. Colonoscopy discovered five carcinomas in the first group and three in the second group [765]. Only one patient in the latter group was asymptomatic, so that only one from 167 patients with regular colonoscopic surveillance examinations profited from this. In a meta-analysis of several randomised, controlled studies it was confirmed that colonoscopic surveillance is less effective than the search for extramural recurrences [770]. Regular colonoscopies in 175 patients after curative resected colorectal carcinoma beginning after one year and then followed by a two-year interval discovered 11 recurrent cancers at the anastomosis, of which 8 could be resected again [789]. Because recurrences were only found in sigmoid and rectal cancers with advanced stages (Dukes B and C), the authors recommended a sigmoidoscopy after 6, 15 and 24 months only for this group. Secondary cancers or significant polyps were exclusively detected during pre- and directly postoperative colonoscopies. Accordingly, surveillance colonoscopies should be performed every 3 (in case of additional polyps during the index-colonoscopy) or 5 years (in case of cancers with no additional polyps) [789, 790].

One has to differentiate between colon and rectal carcinomas during follow-up because the rate of local recurrences with rectal carcinoma is significantly higher [476, 744, 748 – 750]. This applies especially if no total mesorectal excision [476, 750] and/or neoadjuvant or adjuvant [138, 792] radiochemotherapy was performed. A curatively treatable local-regional recurrence was found in only 3.8% (37 of 978) of all R0-operated rectal carcinomas in one retrospective study [749], so that regular rectosigmoidoscopies for follow-up for rectal carcinomas should only be performed in patients without neoadjuvant or adjuvant therapy.

It is important to carry out a complete colonoscopy in all colorectal carcinomas preoperatively, or if a stenosis cannot be passed 3 – 6 months postoperatively, in order to exclude synchronous tumours [138]. Surveillance colonoscopies should follow after three years and if there are no additional findings, every five years thereafter [138].

VIII.4 Time course of follow-up

In the first two years after the operation of a colorectal carcinoma, 80% of all recurrences are detected, whereas practically no new recurrences are detected after 5 years [793]. This applies for rectal carcinoma as well, although with this tumour entity, a few local-regional recurrences were observed after that period [749]. 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 [761, 762, 764, 765]. A three-month interval was found to be superior to a 6 month interval in one study with otherwise similar examination methods [764]. The patients in the three-month follow-up group received an additional annual CT, which in one other study was shown to be without benefit [765]. The consensus conference decided due to the lack of clear data an examination interval of 6 months in the first 2 years. After 5 years only colonoscopies should be performed to exclude secondary carcinoma.

VIII.5 Age limit for follow-up

In controlled studies of follow-up, patients up to 87 years of age [761 – 766] 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.

VIII.6 Special cases

Recommendation

After local removal of a pT1 low-risk carcinoma, local endoscopic examinations should follow after 6, 24 and 60 months (see also IV.4).

Recommendation level: B, Level of evidence: 4, strong consensus.

Recommendation

After palliative tumour resection (R2 resection), programmed follow-up examinations are not necessary.

Level of Recommendation A, Level of evidence: 4, strong consensus.

Recommendation

For HNPCC patients who have a carcinoma after hemicolectomy, colonoscopic examinations and after subtotal colectomy, rectoscopic examinations should be performed in annual intervals (see also III.2.5.3).

Level of Recommendation A, Level of evidence: 2a, strong consensus.

Recommendation

For FAP patients with a colon carcinoma who have undergone proctocolectomy, a pouchoscopy should be performed annually (see also III.2.5.1).

Level of Recommendation A, Level of evidence: 2a, strong consensus.

Recommendation

After iliorectostomy a rectoscopy is necessary every 4 – 6 months (see also III.2.5.1).

Level of Recommendation A, Level of evidence: 2a.

VIII.7 Rehabilitation after resection of colorectal carcinoma

The goal of rehabilitation is the elimination – or at least compensation of tumour – or therapy-related consequences as well as support in acceptance of remaining handicaps with the goal of a self-controlled participation in society.

Recommendation

The benefit of post-hospital curative treatment and rehabilitation measures (in regard to better quality of life, better performance capabilities, better work capability, longer disease-free survival, longer overall survival) has not yet been studied prospectively. Patients who fulfil the legal requirements should be offered post-hospital curative treatment or rehabilitation

Level of Recommendation B, Level of evidence: 5.

Background

The goal for every rehabilitation is the securing and, if possible, improvement of the quality of life for those affected, whereby the necessity for these measures should be assessed for each individual. Rehabilitation is defined in the law as a

social right (SGB I, paragraph 19). The type and amount of necessary payments are defined in SGB (paragraph 29), SGB V (health insurance), and SGB VI (pension insurance), SGB III (work promotion), and also in RehAngG and in SGB IX.
The need for rehabilitation after treatment of colorectal tumours is quite variable and significantly dependent on the type and amount of operative procedure as well as the consequences of therapy (continence problems, sexual function disturbances, stoma, etc.). Rehabilitation processes should take place according to defined rehabilitation needs and individual rehabilitation capabilities following the primary therapy.
In patient rehabilitation procedures can be necessary, especially after special therapeutic procedures, in order to employ and coordinate the necessary concentrated measures.
Data on the value of rehabilitation procedures do not exist. Psychosocial counselling and, if necessary, support is desirable in case of problems with psychological coping with the tumour disease, with the consequences of therapy, with social adjustment difficulties and with professional reintroduction [771, 794]796.
Contacts with those who have been affected by the same disease can present significant assistance for psychic processing or adjustment to a changed life situation for those who have recently encountered these experiences. Those who have been affected by the same events can, through using their own examples and experience in everyday life with the disease and handicaps be convincing to others that a higher quality of life can be possible. Therefore, contacts should be arranged with patient organizations.

Appendix 1

▼

Amsterdam Criteria [178, 179]

1. At least three family members with HNPCC-associated carcinomas (colon/rectum, endometrium, small intestine, urothelial [ureter/renal pelvis])
2. At least two following generations affected
3. A first-degree family member related with two others
4. A person with the disease at the time of the diagnosis who is younger than 50
5. Exclusion of a familial adenomatous polyposis

Appendix 2

▼

Bethesda Criteria [180]

1. Patients with cancer disease in the families which fulfil the Amsterdam criteria.
2. Patients with two HNPCC-associated carcinomas, including synchronous and metachronous colorectal carcinomas or associated extra-colonic carcinomas (endometrium, ovarian, stomach, small intestine, gall bladder carcinomas, carcinomas in the area of renal pelvis or ureter)
3. Patients with colorectal carcinoma and a first-degree relative with colorectal or associated extracolonic carcinoma and/or a colorectal adenoma; one of those with cancer was diagnosed at an age < 45, the adenoma < 40 years of age.
4. Patients diagnosed with colorectal carcinoma or endometrial carcinoma at an age < 45 years.
5. Patients with right-sided colon carcinoma with an undifferentiated (solid/crib-form) cell type in histopathology, diagnosed at an age < 45 years

Appendix 3

▼

Updated Bethesda Criteria [181]
Tumours from patients who fulfil one of the following criteria should be examined for microsatellite instability:

1. Diagnosis of a CRC before the age of 50
2. Diagnosis of synchronous or metachronous colorectal or other HNPCC-associated tumours (colon, rectum, endometrium, stomach, ovaries, pancreas, ureter, renal pelvis, biliary system, brain (among others, glioblastoma), skin (salivary gland adenoma and carcinoma, keratoacanthoma, small intestine)) independent of the age of diagnosis.
3. Diagnosis of a CRC before the age of 60 with typical histology of an MSI-H tumour (tumour-infiltrating lymphocytes, Crohn's-like lesions, mucinous or seal ring differentiation, medullary carcinoma).
4. Diagnosis of a CRC with at least one first-degree relative with an HNPCC-associated tumour, from which a diagnosis of at least one tumour before the age of 50.
5. Diagnosis of a CRC with two or more first-degree relatives with an HNPCC-associated tumour, independent of age.

Appendix 4 Participants in the Consensus Conference, 2004

participants in the Consensus Conference, 2004					
Prof. Dr. H. H. Abholz[1]	Düsseldorf	DEGAM	Prof. Dr. H. Lochs	Berlin	DGVS
Prof. Dr. G. Adler	Ulm	DGVS	Dr. C. Maar	München	Felix-Burda-Stiftung
Dr. L. Altenhofen	Köln	ZI	Prof. Dr. M. Manns	Hannover	DGVS
Prof. Dr. W. O. Bechstein	Frankfurt	DGC/DGVC	Dr. G. Mauer	Berlin	KBV/ZI
Prof. Dr. H. Becker	Göttingen	DGVS	B. Metzinger[2]	Bergisch-Gladbach	IKK Bundesverband
Prof. Dr. H. J. Brambs	Ulm	DRG	PD Dr. G. Möslein	Düsseldorf	DGC/DGVC
Prof. Dr. W. Budach	Tübingen	DEGRO	Prof. Dr. J. Mössner	Leipzig	DGVS
Prof. Dr. R. Büttner	Bonn	DGP	Prof. Dr. H. Neuhaus	Düsseldorf	DGVS
Prof. Dr. M. Classen	München	DGVS	PD Dr. J. Ockenga	Berlin	DGVS
Dr. M. Dürsch	Erlangen	DGC	Dr. F. Overkamp	Recklinghausen	DGHO
Prof. Dr. J. Dunst	Halle	DEGRO	Prof. Dr. J. Pausch	Kassel	DGP/DGVS
Dr. A. Eickhoff	Ludwigshafen	DGVS	Prof. Dr. S. Petrasch	Duisburg	DGVS/DGHO
Prof. Dr. A. Encke	Frankfurt	AWMF	Dr. G. Pommer	Oldenburg	DGVS/DGCP
Prof. Dr. G. Englert	Freising	ILCO	Prof. Dr. R. Porschen	Tübingen	DGVS
Prof. Dr. J. Epplen	Bochum	DGHG	Dr. C. Pox	Bochum	DGVS
Prof. Dr. S. Feuerbach	Regensburg	DRG	Prof. Dr. P. Propping	Bonn	DGHG/DGH
Dr. C. Fibbe	Hamburg	DGVS	Prof. Dr. H. R. Raab	Oldenburg	DGC/DGVC
Prof. Dr. W. Fischbach	Aschaffenburg	DGVS	Dr. P. Reichert	Berlin	DGHO
Prof. Dr. W. Fleig	Halle	DGVS	Dr. B. Reingruber	Erlangen	DGC
Prof. Dr. I. Flenker	Dortmund	ÄK Münster	Dr. M. Reiser	Bochum	DGVS
Prof. Dr. U. Fölsch	Kiel	DGIM	Prof. Dr. J. F. Riemann	Ludwigshafen	DGVS
Prof. Dr. P. Frühmorgen	Ludwigsburg	DGVS	Prof. Dr. M. Rothmund	Marburg	DGC/DGCV
Prof. Dr. H. Gabbert	Düsseldorf	DGP	Prof. Dr. J. Rüschoff	Kassel	DGP
Dr. D. Galandi	Freiburg		Prof. Dr. R. Sauer	Erlangen	DEGRO
Dr. B. Gibis	Berlin	KBV/ZI	Prof. Dr. T. Sauerbruch	Bonn	DGVS
PD Dr. U. Graeven	Bochum	DGVS/DGHO	Prof. Dr. W. Scheppach	Würzburg	DGVS
PD Dr. S. Hahn	Bochum		Prof. Dr. W. Schmiegel	Bochum	DGVS/DKH
M. Haß	Freising	ILCO	Prof. Dr. W. Schmitt	München	DGVS
Prof. Dr. S. Hegewisch-Becker	Hamburg	DGHO	Prof. Dr. H. J. Schmoll	Halle	DGHO
PD Dr. M. Heike	Dortmund	DGHO	Prof. Dr. J. Schölmerich	Regensburg	DGVS
Prof. Dr. W. Hinkelbein	Berlin	DRG	Dr. K. Schulmann	Bochum	DGVS
Dr. S. Hoecht	Berlin	DEGRO	Prof. Dr. S. Seeber	Essen	DGHO
Prof. Dr. R. D. Hofheinz	Mannheim	DGHO	Prof. Dr. H. K. Selbmann	Tübingen	Institut für Medizinische Informationsverarbeitung
Prof. Dr. W. Hohenberger	Erlangen	DGC/DGVC/DKH			
Prof. Dr. A. Holstege	Landshut	DGVS	Prof. Dr. A. Sieg	Östringen	DGVS
Dr. D. Hüppe	Herne	DGVS	Prof. Dr. E. Stange	Stuttgart	DGVS
Prof. Dr. K. W. Jauch	München	DGC	U. Steder-Neukamm	Leverkusen	DCCV e. V.
Prof. Dr. T. Junginger	Mainz	DGC/DGVC	Dr. M. Steiner	Ihringen	Berufsverband der Frauenärzte e. V.
Prof. Dr. Th. Kirchner	Erlangen	DGP			
PD Dr. G. Kleber	Aalen	DGVS	Dr. M. Strauch	München	DGVS/BDI
Prof. Dr. Ch. Köhne	Dresden	DGHO	PD Dr. D. Strumberg	Essen	DGHO
Dr. I. Kopp	Marburg	AWMF/DGC	PD Dr. U. Vanhoefer	Essen	DGHO
K. D. Kossow[2]	Köln	BV /Allgemeinärzte Deutschlands	PD Dr. M. Vieth	Magdeburg	DGP
PD Dr. S. Kubicka	Hannover	DGVS	Prof. Dr. T. Vogl	Frankfurt	DRG
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PD Dr. F. Kullmann	Regensburg	DGVS	PD Dr. J. Weitz	Heidelberg	DGVS/DGC
Dr. E. Kunstmann	Bochum	DGVS	Prof. Dr. H. Wilke	Essen	DGHO
Dr. P. Langer	Marburg	DGC	Prof. Dr. C. Wittekind	Leipzig	DGP
Prof. Dr. P. Layer	Hamburg	DGVS	Prof. Dr. N. Zamboglou	Offenbach	DEGRO
Prof. Dr. T. Lehnert	Heidelberg	DGC/DGVC	Prof. Dr. M. Zeitz	Homburg	DGVS/DGC
Prof. Dr. S. Liebe	Rostock	DGVS			

German Surgical Society (DGC); German Visceral Surgery Society (DGVC);German; Society of Haematology and Oncology (DGHO); German Society for Human Genetics (DGHG); German Society of Internal Medicine (DGIM); German Society for Coloproctology (DGKP); German Society of Pathology (DGP); German Society for Radiooncology (DEGRO); German Society for Digestive and Metabolic Diseases (DGVS); German Cancer Society (DKG); German X-Ray Society (DRG); German United Society for Clinical Chemistry and Laboratory Medicin e. V. (DGKC); German Society for General Medicine (DEGAM); German Organisation for Physicians under Health Insurance (KBV); Central Institute for Health Insurance Care in Germany (ZI).

[1] Invited to participate.

Appendix 5 Work Groups IV – Coordinators and Members, 2007/2008

topic area IV	Endoscopy: Implementation and Polyp Management
coordinators:	
Prof. Dr. W. Schmitt	1. Medical Department, Gastroenterology and Hepatology, Neuperlach Hospital, Munich
Prof. Dr. J F Riemann	Medical Clinic C Hospital of the City of Ludwigshafen
members:	
Prof. Dr. G. Baretton	Institute for Pathology University Hospital of Dresden
PD Dr. S. Faiss	III. Medical Department Asklepios Hospital Barmbek, Hamburg
Prof. Dr. H. E. Gabbert	Institute for Pathology University Hospital Dusseldorf
S. In der Smitten	German Crohn's Disease/Ulcerative colitis Society DCCV Federal Office, Leverkusen
Prof. Dr. J. Mössner	Medical Hospital and Clinic II University Hospital Leipzig
Prof. Dr. H. Neuhaus	Medical Clinic Evangelical Hospital Dusseldorf
Dr. G. Pommer	Gastroenterology Practice Oldenburg
Dr. C. Pox	Medical University Clinic Knappschafts Hospital, Ruhr University Bochum
PD Dr. M. Reiser	Hospital for Internal Medicine Paracelsus Hospital, Marl
PD Dr. K. Schoppmeyer	Medical Hospital and Clinic II University Hospital Leipzig
Dr. B. Schumacher	Medical Clinic, Gastroenterology Evangelical Hospital, Dusseldorf
Prof. Dr. Ch. Wittekin	Institute for Pathology University Hospital Leipzig

Appendix 6 Work Groups VI – Coordinators and Members, 2007/2008

Topic area VI	Adjuvant and Neoadjuvant therapy
coordinators:	
Prof. Dr. R Porschen	Hospital for Internal Medicine Bremen East Hospital
Prof. Dr. R Sauer	Clinic for Radiotherapy University Hospital of Erlangen
members:	
Dr. D. Arnold	Medical Clinic IV University Hospital Halle
Prof. Dr. W. Budach	Hospital and Clinic for Radiotherapy and Radiooncology, University Hospital Dusseldorf
Dr. G. Folprecht	Medical Hospital I and Clinic
Prof. Dr. M. Geißler	University Hospital of Dresden Hospital for Oncology, Gastroenterology and General Internal Medicine, City Hospital of Esslingen
PD Dr. R. D. Hofheinz	III. Medical Clinic
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Appendix 7 Work Groups VII – Coordinators and Members, 2007/2008

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Topic area VII	Therapeutic procedure for metastases and in the palliative situation
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