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<th>Annals of Oncology</th>
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| Complete List of Authors: | Schmoll, Hans-Joachim; University clinic Halle, Innere Med. IV; Aderka, Dan; Chaim Sheba Medical center, Oncology Institute; Tel Aviv University, Sackler School Medicine; Van Cutsem, Eric; University Hospital Gasthuisberg, Department of Internal Medicine; Stein, Alexander; Universitäts Hamburg, Hubertus Wald Tumor Center; Valenti, Vincenzo; Policlinico Universitario "A. Gemelli", Catholic University; Glimelius, Bengt; Uppsala University, Department of Oncology and Pathology; Haustermans, Karin; University Hospitals Leuven Campus Gasthuisberg, Department of Radiation Oncology; Nordlinger, Bernard; Assistance-Publique-Hopitaux de Paris, Department of Surgery; Balmana, Judith; University Hopital Vall d Hebron, Medical Oncology Department; Regula, J.; Maria-Sklodowska-Durie Mem. Cancer Center, Institute of Oncology; Nagtegaal, I.D.; Radboud University Nijmegen, Medical Center; Beets-Tan, Regina; Maastricht University Medical Center, Radiology; Arnold, Dirk; Universität Hamburg, Hubertus Wald Tumor Center; Ciardello, Fortunato; Division of Medical Oncology, Department of Experimental and Clinical Medicine; Hoff, Paolo; Hospital Sirio Libanes, Instituto do Cancer; Kerr, David; University of Oxford, Clinical Pharmacology; Köhne, Claus-Henning; Hospital Oldenburg, Oncology/Hematology; Labiance, R.; Ospedali Riuniti, Department of Haematology and Oncology; Price, Timothy; The Queen Elizabeth Hospital, Medical Oncology; Scheithauer, Werner; Medical University Vienna, Division of Oncology; Sobrero, Alberto; Azienda Ospedaliero-Universitaria, S Martino, Medical
Colorectal cancer is the most frequent tumour type in both sexes combined in western countries. Although screening programs including the implementation of FOBT and colonoscopy might be able to reduce mortality by removing precursor lesions and by making diagnosis at an earlier stage, the burden of disease and mortality is still high. Improvement of diagnostic and treatment options increased staging accuracy, functional outcome for early stages, as well as survival. Although high quality surgery is still the mainstay of curative treatment, the management of colorectal cancer must be a multimodal approach performed by an experienced multidisciplinary expert team. Optimal choice of the individual treatment modality according to disease localization and extent, tumour biology and patient factors is able to maintain quality of life, enables long term survival and even cure in selected patients by combination of chemotherapy and surgery. Treatment decisions must be based on the available evidence which has been the basis for this consensus conference based guideline delivering a clear proposal for diagnostic and treatment measures in each stage of rectal and colon cancer and the individual clinical situations. This ESMO guideline is recommended to be used as the basis for treatment and management decisions.
ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making


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The management of colorectal cancer must be a multimodal approach performed by an experienced multidisciplinary expert team. Optimal choice of the individual treatment modality according to disease localization and extent, tumour biology and patient factors is able to maintain quality of life, enables long term survival and even cure in selected patients by combination of chemotherapy and surgery. Treatment decisions must be based on the available evidence which has been the basis for this consensus conference based guideline delivering a clear proposal for diagnostic and treatment measures in each stage of rectal and colon cancer and the individual clinical situations. This ESMO guideline is recommended to be used as the basis for treatment and management decisions.

1 Introduction

Colorectal cancer (CRC) is the most frequently diagnosed cancer in Europe and one of the leading causes of cancer death worldwide. In the past years treatment and outcome of early and advanced disease has steadily improved. Progress in imaging enables more precise differentiation of prognostic subgroups in rectal cancer a selected treatment approach based on TNM stage and potential mesorectal fascia (MRF) involvement to improve local control. Even in metastatic disease some patients with metastases limited to liver and/or lung can be cured with a multimodal treatment approach of intensive chemotherapy, followed by secondary R0-resection of initially unresectable disease. Currently, a broad variety of trials and retrospective analyses gave further insight into clinical questions like selection and duration of treatment, combinations with targeted agents, and tailored treatment with respect to clinical, and molecular factors. In addition, knowledge of prognostic as well as predictive biomarkers (blood, tumour tissue) is significantly increasing to better guide selection of drugs and treatment strategy.

1.1 Methodology

In this rapidly developing field of management of CRC, definition of standards for diagnosis and treatment is of utmost importance to apply the optimal available treatment strategy in an individual patient. Therefore, an international consensus conference was established by ESMO in order to give guidance in translating all data into a standard clinical practice guideline. The multidisciplinary ESMO consensus conference, held in Lugano 23.-25.09.2010, assembled 37 experts from all involved disciplines and most countries and regions worldwide. All the available literature (including abstracts and full papers) was reviewed regarding diagnosis, staging and treatment and the management modality was defined stage-by-stage for colon and
rectal cancer. A set of recommendations was pre-formulated as the basis for discussion. After discussion a set of recommendations was formulated on the basis of consensus achieved by the panel. These were further developed after the meeting. Levels of evidence and grades of recommendation (given in square brackets in the text) were defined by the meeting chairmen using an adapted version of the Infectious Diseases Society of America. The extended manuscript was circulated and the final version consented by all participants. When a universal agreement on a given topic was not achieved statements are based on the majority decision.

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, experts opinions</td>
</tr>
</tbody>
</table>

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<tr>
<th>Grade of Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,...) optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>

Table 1: Level of evidence and strength of recommendation given in square brackets in the text according to..

2 Epidemiology

In 2008 436,000 new cases of colorectal cancer (CRC) were diagnosed in Europe, thus being the most common cancer with 13.6% of all diagnosed cancer. Worldwide 1.23 million CRC were responsible for 9.7% of the total cancer burden, after lung (1.61 million) and breast cancer (1.38 million). CRC was responsible for 212,000 (12.2%) deaths in Europe in 2008, representing the second most common cause of cancer death after lung cancer (19.9%). About 20-25% of patients with CRC present with metastatic disease at time of diagnosis, and 20-25% of patients will develop metastases later resulting in a relatively high overall mortality rate of 40-45%. However, during the past two decades mortality from CRC has declined, especially in northern and western Europe, potentially related to improved earlier detection (screening and early diagnosis) and advances in adjuvant and definitive treatment.
3 Diagnosis, management and counselling of hereditary colorectal cancer

All patients with CRC should have a collection of family history regarding polyps and any type of cancer (at least first and second-degree relatives) [V, A]. About 5% of CRC are of hereditary origin. If a clinical suspicion of polyposis or Lynch syndrome is made, the patient should be referred to a specialist in human genetics [V, C]. Average risk populations should have an organized access to population-CRC screening, if resources are available on national level [V, A]. Methodology and choice of screening modality is a matter of discussion. An overview of management of hereditary CRC syndromes is summarized in table 2.

3.1 Lynch syndrome

Clinical suspicion is based on fulfilment of clinical criteria (Amsterdam, Bethesda) or by an altered molecular screening (microsatellite instability (MSI) and/or IHC for mismatch repair proteins (MMR) in the context of a suggestive personal or family history [III, B].

3.1.1 Detection of mutation

Germline genetic testing will be performed according to results of molecular screening (MSI and/or IHC of MMR). If a tumour block is not available, the gene specific prediction models may help to guide a genetic strategy [III, B]. If loss of MLH1 expression is observed (especially in non-familial cases), somatic hypermethylation of the MLH1 promoter should be considered, which can be ruled out by testing of the somatic BRAF V600E mutation or analysis of hypermethylation of the MLH1 promoter [III, B].

Full germline genetic testing should include DNA sequencing and large rearrangement analysis of the MMR genes [I, A]. Adequate pre- and post-test genetic counselling should always be performed.

3.1.2 Surveillance for healthy mutation carriers

For individuals with Lynch syndrome carrying an MLH1 or MSH2 mutation, colonoscopy should start at the age 20-25 years and should be repeated every 1-2 year [II, A].

No specific upper limit for surveillance endoscopies is established and it should be based on the individual’s health status.

For healthy individuals with Lynch syndrome carrying an MSH6 or PMS2 mutation, colonoscopy should start at the age of 30 years and be repeated every 1-2 year. Again, no specific upper limit is established [II, A].

Endometrial and ovarian cancer screening may be performed in a yearly basis starting at the age of 30-35 years with gynaecological examination, pelvic ultrasound, analysis of CA125, and aspiration biopsy [IV, C]. Pros and cons should be adequately discussed with the individual subject at risk given the evidence of benefit only from observational studies.

Surveillance for other Lynch-associated cancers is recommended based on the family history and may include upper endoscopy, abdominal ultrasound and urine cytology from the age of 30-35 years in a 1-2 year interval [IV, C].
3.1.3 Chemoprevention
Neither specific chemoprevention nor specific dietary interventions is being recommended at the current time in individuals with Lynch syndrome to prevent CRC, although data are emerging supporting the use of aspirin [II, B].

3.1.4 Risk reduction: prophylactic surgical options
Prophylactic colectomy in healthy mutation carriers is not recommended. Prophylactic gynaecological surgery might be an option in female carriers from the age of 35 onwards and after childbearing is completed [IV, C].

3.1.5 Cancer treatment
The need of intensive surveillance after surgery versus the option of an extended colectomy should be discussed at the time of diagnosis of an advanced adenoma or CRC, especially in young patients [IV, C]. For female CRC patients with good prognosis, surveillance/surgical options for gynecologic cancer should also be discussed. Chemotherapy regimens are the same as those for sporadic CRC.

3.2 Familial colorectal cancer X syndrome
Relatives of individuals with CRC who fulfil the Amsterdam criteria and who do not exhibit MMR deficiency have a moderate risk of CRC. Surveillance would include colonoscopy at a 3-5 year interval, starting 5-10 years before the youngest case in the family. Surveillance of extracolonic cancers is not recommended.

3.3 FAP
Clinical diagnosis of classical FAP is based on the identification of >100 colorectal adenomas. Lifetime risk for development of CRC is 100%.

3.3.1 Attenuated FAP
Clinical diagnosis of attenuated FAP is based on the following criteria:
• at least two patients with 10-99 adenomas at age >30 years; or
• one patient with 10-99 adenomas at age >30 years, a first-degree relative with CRC and few adenomas, and no family members with >100 adenomas before the age of 30 years.

3.3.2 Genetics
Genetic testing (germline APC mutation) should start by investigating the affected individual. If the causative mutation is detected, pre-symptomatic diagnosis can be offered to at-risk family members. When the causative mutation is not identified, all at-risk family members should undergo colorectal endoscopic screening [V, C].

3.3.3 Colorectal screening
In families with classic FAP, flexible sigmoidoscopy is an adequate technique and it should be performed every 2 years, starting at the age of 12-14 years, and continued lifelong in mutation carriers [V, C]. If adenomas are found, colonoscopy should be done annually until colectomy.
In families without an identified APC mutation, surveillance should be performed every 2 years until the age of 40, and be repeated every 3-5 years between 40-50 years and may continue with general screening at age 50 if no polyposis has developed [V, C]. When an attenuated form is suspected, total colonoscopy is needed. In this setting, examination should be performed every 2 years until polyposis is diagnosed. Screening should be started at the age of 18-20 years and continued lifelong.
3.3.4 Screening for extracolonic manifestations

It should start when colorectal polyposis is diagnosed or at age 25-30 years, whichever comes first [V, C]. Gastroduodenal endoscopy should be performed every 5 years until adenomas are detected [V, C]. Screening for thyroid cancer should be performed by annual sonography of the neck [V, C]. Regular physical examination and if indicated abdominal CT should be performed in search for desmoids tumours [V, C]. Screening for other extracolonic manifestations is not justified because of their low prevalence and/or limited clinical impact. Since gastrointestinal adenomas may also develop in the jejunum and ileum, it has been suggested that regular screening by barium contrast series or wireless capsule endoscopy could be performed [V, C].

3.3.5 Treatment

Surgical resection is the standard of care in patients with classical FAP [IV, A]. It can be considered in some patients with an attenuated form. Surgical resection includes either total colectomy with ileoanal pouch anastomosis or subtotal colectomy with ileorectal anastomosis, once adenomas are detected [IV, C]. Duodenal adenomas are managed with endoscopic polypectomy, and in Spigelman stage IV (see below), duodenal–pancreatectomy may be considered. Because of the high recurrence rate of desmoid tumours, surgical resection should be delayed unless complications occur. The first line treatment in patients with large or growing intra-abdominal or abdominal wall desmoid tumours is based on e.g COX 2 inhibitors, tamoxifen and tyrosine kinase inhibitors.

3.3.6 Surveillance for healthy mutation carriers

Colon-Rectum

Regular endoscopic surveillance every 6-12 months after subtotal colectomy is recommended to detect rectal adenoma recurrence [V, C]. When total colectomy is performed, surveillance of the pouch can be repeated every 1-2 years. In patients with attenuated FAP conservative management with endoscopic polypectomy, examination of the entire colon and rectum should be performed annually [V, C].

Duodenum

Surveillance of duodenal manifestation will depend on its extension. When it corresponds to Spigelman stage I or II, upper endoscopy should be performed every 5 or 3 years, respectively, and every 1-2 years in stage III or every 6 months in stage IV [IV, C].

3.4 MUTYH-associated polyposis (MAP)

MUTYH-associated polyposis (MAP) is inherited as an autosomal recessive trait with high penetrance. Clinically, MAP resembles the attenuated form of FAP syndrome, with an average age of onset around the mid-50s with often <100 adenomas and, accordingly, patient management is very similar.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Diagnosis of index case (with cancer)</th>
<th>Management of the affected individual (with cancer)</th>
<th>Management of individuals at high risk (healthy mutation carriers or individuals at 50% risk of being mutation carrier)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical</td>
<td>Molecular</td>
<td>Cancer risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screening (tumour tissue)</td>
<td>Treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Germine genetic testing (blood)</td>
<td></td>
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<tr>
<td>Lynch</td>
<td>Amsterdam, Bethesda</td>
<td>MSI and/or IHC for MMR proteins</td>
<td>Tumour resection</td>
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<tr>
<td></td>
<td></td>
<td>MLH1, MSH2, MSH6, PMS2</td>
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<tr>
<td></td>
<td></td>
<td>Clinical</td>
<td>Discuss colectomy, especially in young patients</td>
</tr>
<tr>
<td>Familial CRC X</td>
<td>Amsterdam, Bethesda</td>
<td>no MMR deficiency</td>
<td>As average population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unknown</td>
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<tr>
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<td>Screening (tumour tissue)</td>
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<tr>
<td></td>
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<td>Clinical</td>
<td></td>
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<td>Colonoscopy: &gt; 100 adenomas</td>
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<td>APC</td>
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<tr>
<td>Attenuated FAP (aFAP)</td>
<td>Colonoscopy: a) 2 relatives 10-99 adenomas (&gt;30 y of age)</td>
<td>APC</td>
<td>Total or subtotal colectomy when adenomas occur.</td>
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<td>MUTYH</td>
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(m: month, y: years)

Table 2: Management of hereditary colorectal cancer
3.4.1 Screening for Family members

Individuals should undergo total colonoscopy every 2 years, starting at the age of 18-20 years and continuing lifelong [V, C]. Genetic testing allows the most cost-effective screening to be performed by focusing colorectal examinations only on gene carriers. However, when the causative mutation is not identified, all at-risk family members should undergo colorectal screening.

3.4.2 Treatment for healthy gene carriers

Colorectal management is similar to that proposed for patients with attenuated FAP.

4 Prognostic factors

Prognosis is determined by several factors, in particular the specific tumour stage and - biology and patient related factors, which can potentially be modified by treatment intervention. There is a broad variety of patient or tumour related and biochemical prognostic factors (Table 3a-d), some are combined to define a prognostic classification score \(^8-14\). However, identification of prognostic subgroups by scoring is not relevant out of clinical trials, since it does not influence treatment decision. In contrast, definition of clinically defined subgroups according to patient’s characteristics (performance status, clinical presentation and parameters reflecting tumour biology) can be helpful for guiding treatment decision with respect to intensity and selection of drugs/combinations for first line treatment (table 12). The relevance of molecular and genetic markers emerge, with status of high frequency microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) and KRAS-Codon 12 or G13D – or BRAF mutation gaining importance in determination of prognosis for early and advanced colorectal cancer \(^15,16\).

At this moment determination of any prognostic factor for therapeutic decisions is not recommended (except for MSI status for early stage colon cancer) [II, B].

Early colorectal cancer

- **MSI status** is a strong prognostic factor, whereas data on **KRAS and BRAF status** are conflicting \(^17-20\).
  - MSI-H/dMMR patients have a proven better prognosis in stage II and III than low frequency MSI (MSI-L) or microsatellite stable (MSS) patients.
  - **BRAF mutated** tumours showed no increased risk of relapse in stage II/III in QUASAR and PETACC 3, and a worse overall survival in PETACC 3 (particularly in patients with MSI-low or MSS tumours) - however not due to higher recurrence rate but potentially to poor survival after relapse (as known from trials in metastatic disease).
  - **KRAS mutation** was associated with a significantly higher risk of recurrence in QUASAR compared to wild type (wt), but not in PETACC 3.

- **Genomic signatures** have a potentially high prognostic value, but are currently not predictive for guiding decision on adjuvant treatment. The panel agreed, that although this is a rapidly emerging field with great potential and several studies ongoing, none of these signatures is ready for clinical use, and further validation studies are needed \(^21-23\).

Advanced colorectal cancer
• Elevated alkaline phosphatase (ALP) or leucocytes, low serum albumin, more than one tumour site, poor performance status (PS), high platelet count and elevated lactate dehydrogenase (LDH) are indicators of poor prognosis.

• BRAF-mutation and KRAS-codon G13D mutation indicates worse prognosis. The prognostic value of other KRAS mutations is not completely elucidated yet.

<table>
<thead>
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<th>factor</th>
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<tbody>
<tr>
<td>clinical/pathological</td>
<td>T4</td>
</tr>
<tr>
<td></td>
<td>N+ after preoperative chemoradiation (rectal)</td>
</tr>
<tr>
<td></td>
<td>MRF involvement (rectal)</td>
</tr>
<tr>
<td></td>
<td>obstruction/perforation</td>
</tr>
<tr>
<td></td>
<td>rupture during surgery</td>
</tr>
<tr>
<td></td>
<td>less than 12 analysed (retrieved) lymph nodes (and ratio)</td>
</tr>
<tr>
<td></td>
<td>vascular (venous/lymphatic) &amp; perineural invasion (V1, L1, PN1)</td>
</tr>
<tr>
<td></td>
<td>poor differentiation (G3/4)</td>
</tr>
<tr>
<td>molecular/genetic</td>
<td>MSI-H/dMMR</td>
</tr>
</tbody>
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Table 3a: Established prognostic factors in early CRC

<table>
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<th>group</th>
<th>factor</th>
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<tbody>
<tr>
<td>patient related</td>
<td>age (&gt;60 yrs)</td>
</tr>
<tr>
<td></td>
<td>N2</td>
</tr>
<tr>
<td></td>
<td>appropriateness of the pathology report</td>
</tr>
<tr>
<td></td>
<td>lymphocytes infiltration</td>
</tr>
<tr>
<td></td>
<td>tumour budding</td>
</tr>
<tr>
<td></td>
<td>tumour type</td>
</tr>
<tr>
<td></td>
<td>sentinel lymph node</td>
</tr>
<tr>
<td>center related</td>
<td>low volume/ less experience</td>
</tr>
<tr>
<td>molecular/genetic</td>
<td>KRAS mutation</td>
</tr>
<tr>
<td></td>
<td>TS positivity (&gt;25% of cells)</td>
</tr>
<tr>
<td></td>
<td>18qLOH</td>
</tr>
<tr>
<td></td>
<td>p53 (high)</td>
</tr>
<tr>
<td></td>
<td>SMAD4 (any loss)</td>
</tr>
<tr>
<td></td>
<td>multi-gene signatures</td>
</tr>
</tbody>
</table>

Table 3b: Potential prognostic factors in early CRC

<table>
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<tr>
<th>group</th>
<th>factor</th>
</tr>
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<tbody>
<tr>
<td>patient related</td>
<td>performance status ≥2</td>
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<tr>
<td></td>
<td>(biologic) age ≥70 yrs</td>
</tr>
<tr>
<td>biochemical</td>
<td>CEA &gt;50 µg/l</td>
</tr>
<tr>
<td></td>
<td>alkaline phosphatase ≥300 U/l</td>
</tr>
<tr>
<td></td>
<td>platelets ≥400x10^9/l</td>
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<tr>
<td></td>
<td>haemoglobin &lt;11g/dl</td>
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<tr>
<td></td>
<td>white blood cell count ≥10x10^9/l</td>
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<td></td>
<td>high LDH</td>
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<tr>
<td></td>
<td>low serum albumin</td>
</tr>
<tr>
<td>molecular/genetic</td>
<td>BRAF-mutation; KRAS codon G13D mutation</td>
</tr>
</tbody>
</table>

Table 3c: Established poor prognostic factors in advanced CRC
### Table 3d: Potential Prognostic Factors in Advanced CRC

<table>
<thead>
<tr>
<th>Group</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Related</td>
<td>Presence of severe co-morbidities</td>
</tr>
<tr>
<td></td>
<td>High socio-economic status</td>
</tr>
<tr>
<td>Tumour Related</td>
<td>Symptomatic disease</td>
</tr>
<tr>
<td></td>
<td>Metastatic sites</td>
</tr>
<tr>
<td></td>
<td>• Liver +/- lung only vs. multiple sites/organs</td>
</tr>
<tr>
<td></td>
<td>• Peritoneal involvement</td>
</tr>
<tr>
<td></td>
<td>Previous adjuvant treatment with oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>Early relapse after adjuvant therapy (&lt;=6 months)</td>
</tr>
<tr>
<td></td>
<td>Previous lines of treatment</td>
</tr>
<tr>
<td>Center Related</td>
<td>Low volume/ less experience</td>
</tr>
<tr>
<td></td>
<td>Deviation from standard clinical practise</td>
</tr>
<tr>
<td>Molecular/Genetic</td>
<td>MSI-H</td>
</tr>
<tr>
<td></td>
<td>EGFR (IHC)</td>
</tr>
<tr>
<td></td>
<td>KRAS-mutation (other than codon G13D)</td>
</tr>
<tr>
<td>Treatment Related</td>
<td>Skin rash during treatment with anti-EGFR-mAB</td>
</tr>
</tbody>
</table>

5 Predictive factors

Despite the numerous potential markers for prediction published, in the routine use outside clinical trials only those markers should be determined, which are essential for selection of treatment and drugs, as well as dosing. At this moment only the proven factors (Table 4a) are recommended.

#### 5.1 Predictive Factors for Early Colorectal Cancer

- There is no evidence for a predictive marker regarding the effect of adjuvant chemotherapy for early CRC and therefore the use of any marker is not indicated outside of a clinical trial setting [IV, C].

- Pooled analyses have suggested a detrimental effect for adjuvant treatment with 5FU in patients with stage II MSI-H/dMMR tumours, what could not be confirmed by recent analyses from randomized trials (PETACC 3, QUASAR)\(^{18, 28-30}\). Potential explanation for the discordance of the data might be due to insufficient analyses of the patients with respect to germline vs. sporadic MMR defects\(^{17}\). Data on the predictive effect of MSI on efficacy of irinotecan are equivocal as well\(^{28, 31}\).

#### 5.2 Predictive Factors for Advanced CRC

Epithelial growth factor receptor (EGFR) inhibitors

- **KRAS mutation** precludes efficacy of treatment with anti-EGFR antibodies and KRAS status determination is therefore mandatory before treatment\(^{32}\) [I, A]. KRAS analysis (either by IHC or gene sequencing) can be done on paraffin embedded tumour block of primary tumour or metastases.

- **KRAS codon G13D mutation** (5%) does not indicate efficacy of anti-EGFR treatment in KRAS mutant patients\(^{33-35}\), although data are conflicting\(^{36}\) [IV, C].

- **BRAF mutation** (8% of KRAS wild-type patients) seem to predict lack of benefit from treatment with EGFR antibodies\(^{26, 36-38}\), whereas analyses of CRYSTAL/OPUS suggested some benefit\(^{39}\).
• **BRAF, NRAS, PI3K, PTEN, EGFR mutations, and EGFR ligands (epiregulin, amphiregulin)** expression should not be determined in clinical routine, since treatment decision is not yet based on these markers [IV, C].

**Vascular endothelial growth factor (VEGF) inhibitors**

• There is no predictive marker for bevacizumab yet [IV, C]. Efficacy of bevacizumab does not depend on KRAS or BRAF mutational status, sVEGFR or plasma VEGF-levels 40, 41, whereas VEGF D in tumour tissue at baseline might be a potentially useful marker in the future 42. Changes in levels of angiogenic factors (e.g. basic fibroblast, placental, or hepatocyte growth factor) during treatment with bevacizumab might indicate development of resistance, however, these are not predictive but only progression associated markers 43, 44.

**Chemotherapy**

• **Topoisomerase-1 (Topo 1)** overexpression was found to be predictive for a benefit of treatment with irinotecan and potentially with oxaliplatin as well in the MRC FOCUS trial, which could not be confirmed for irinotecan in the CAIRO study 45, 46 [IV, C].

• **ERCC1** (excision repair cross-complementing gene 1) polymorphisms, thymidine phosphorylase (TP), or thymidylate synthase (TS) expression are associated with efficacy of oxaliplatin or 5FU, however for clinical routine these factors are not used for treatment selection (trials ongoing) 45, 47, 48 [IV, C].

5.3 **Predictive factors for toxicity**

• **DPD deficiency**: despite the risk of severe potential lethal toxicity under therapy with fluoropyrimidines (FU) in case of DPD deficiency (0.3-1.5% of patients), routine testing for DPD deficiency is not recommended [IV, C]. Only in case of severe toxicity due to the treatment with FU testing for DPD deficiency is strongly recommended, before further administering FU [IV, A]; in case of proven DPD deficiency further exposure of standard dose FU must be avoided.

• **UGT1A1 Polymorphism**: Only if severe toxicity potentially related to treatment with irinotecan occurs, testing for UGT1A1 polymorphisms should be considered [IV, C]. This is particularly important when irinotecan is used at high doses (300-350 mg/m²) but of less importance when it is administered at lower doses (125-180 mg/m²).

<table>
<thead>
<tr>
<th>group</th>
<th>factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>tumour related</td>
<td>symptomatic peritoneal carcinomatosis</td>
</tr>
<tr>
<td></td>
<td>multiple sites of metastases/ very extensive disease</td>
</tr>
<tr>
<td>centre related</td>
<td>deviation from standard clinical practise</td>
</tr>
<tr>
<td>biochemical</td>
<td><strong>efficacy after start of treatment</strong></td>
</tr>
<tr>
<td></td>
<td>• CEA flare and drop</td>
</tr>
<tr>
<td></td>
<td><strong>for toxicity of chemotherapy</strong></td>
</tr>
<tr>
<td></td>
<td>• creatinine clearance &lt;30ml/min for capecitabine</td>
</tr>
<tr>
<td></td>
<td>• bilirubin &gt;3 ULN for irinotecan</td>
</tr>
<tr>
<td>molecular/</td>
<td><strong>for treatment with anti-EGFR-mAB</strong></td>
</tr>
<tr>
<td>genetic</td>
<td>• KRAS mutation</td>
</tr>
<tr>
<td></td>
<td><strong>for chemotherapy toxicity</strong></td>
</tr>
<tr>
<td></td>
<td>• UGT1A1 *28 genotype for irinotecan</td>
</tr>
<tr>
<td></td>
<td>• DPD deficiency for fluoropyrimidines</td>
</tr>
</tbody>
</table>

table 4a: predictive factors in advanced CRC
<table>
<thead>
<tr>
<th>group</th>
<th>factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient related</td>
<td>performance status &gt;1</td>
</tr>
<tr>
<td></td>
<td><strong>efficacy after start of treatment</strong></td>
</tr>
<tr>
<td></td>
<td>• hand foot syndrome for capecitabine efficacy</td>
</tr>
<tr>
<td></td>
<td>• hypertension for anti-VEGF-mAB efficacy</td>
</tr>
<tr>
<td></td>
<td>for bevacizumab related toxicity</td>
</tr>
<tr>
<td></td>
<td>• cardiovascular disease/arterial thrombembolism</td>
</tr>
<tr>
<td>molecular/</td>
<td><strong>predictive for chemoradiation in localized rectal cancer</strong></td>
</tr>
<tr>
<td>genetic</td>
<td>• high TS</td>
</tr>
<tr>
<td></td>
<td>• low EGFR</td>
</tr>
<tr>
<td></td>
<td>• TS polymorphism *3/*3 or *3/*4 (less benefit from CRT, than *2/*2,</td>
</tr>
<tr>
<td></td>
<td>*2/*3, or *2/*4)</td>
</tr>
<tr>
<td></td>
<td><strong>for treatment with anti-EGFR-mAB</strong></td>
</tr>
<tr>
<td></td>
<td>• BRAF mutation</td>
</tr>
<tr>
<td></td>
<td>• ligands: amphiregulin and epiregulin levels</td>
</tr>
<tr>
<td></td>
<td>• PI3K (exon 20 versus exon 9) mutation</td>
</tr>
<tr>
<td></td>
<td>• PTEN mutation</td>
</tr>
<tr>
<td></td>
<td>• NRAS mutation</td>
</tr>
<tr>
<td></td>
<td><strong>for treatment with bevacizumab</strong></td>
</tr>
<tr>
<td></td>
<td>• VEGF &gt;98 pg/ml</td>
</tr>
<tr>
<td></td>
<td>• bFGF, HGF, PIgF increase before progression under bevacizumab</td>
</tr>
<tr>
<td></td>
<td>(+chemotherapy)</td>
</tr>
<tr>
<td></td>
<td><strong>for chemotherapy toxicity or efficacy</strong></td>
</tr>
<tr>
<td></td>
<td>• high ERCC1 for oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>• high TOPO 1 for irinotecan +/- oxaliplatin</td>
</tr>
</tbody>
</table>

Table 4b: potential predictive factors in advanced CRC

6 Rectal cancer

6.1 Diagnosis and staging of rectal cancer

Physical examination, family history for CRC, polyps and other cancers, and CEA should be obtained. Full colonoscopy has to be performed either at diagnosis preoperatively or postoperatively in case of obstructing tumors or for other reasons. Minimal requirements for distant staging of colon and rectal cancer are CT of the chest (if not available, X-ray of chest is acceptable) and abdomen and complete colonoscopy (either pre- or postoperatively). In addition, pelvic MRI is required for all rectal cancer patients.

6.1.1 Definition of localization of rectal cancer

The accurate diagnosis of local tumour extension, location, N-stage, potential circumferential resection margins (CRM)/ mesorectal fascia (MRF) involvement, and extra-mural or venous invasion is essential for defining the treatment strategy [III, A]. The primary lesion is identified by digital palpation and rigid or flexible endoscopy, with biopsy. The anatomical landmark / reference point is the anal verge for digital examination and endoscopy. Rectal cancers are categorized according to their distal edge measured from the anal verge and are located from anal verge up to 15cm. According to the methodology used (rigid vs. flexible endoscopy) the measurements are different. Definition for low vs. mid/high with rigid proctoscopy is accurate and more reliable than flexible endoscopy.

Furthermore, MRI is accurate in measuring the distance between the anorectal junction and the distal part of the tumour. It is also accurate for determining the
length of the tumour. However, definition of tumour heights with different methods is dependent on the position of the patient during the investigation and the different measurement point, e.g. anal verge for rigid proctoscopy and anorectal junction for MRI. Definition of tumour location/heights is only important if it is relevant for the treatment strategy, in particular for low rectal tumours as well as high (separation from colosigmoid cancer) (table 5).

<table>
<thead>
<tr>
<th>location</th>
<th>rigid proctoscopy</th>
<th>flexible endoscopy</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td>up to 5cm</td>
<td>up to 5cm</td>
<td>up to 4 cm</td>
</tr>
<tr>
<td>mid</td>
<td>from &gt;5 to 10cm</td>
<td>from &gt;5 to 10cm</td>
<td>from &gt;4 to 8 cm</td>
</tr>
<tr>
<td>high</td>
<td>from &gt;10 up to 15cm</td>
<td>from &gt;10 up to 15cm</td>
<td>from &gt;8 up to 12 cm</td>
</tr>
<tr>
<td>reference level</td>
<td>anal verge</td>
<td>anal verge</td>
<td>anorectal junction</td>
</tr>
</tbody>
</table>

Table 5: Measurement of rectal cancer with respect to reference level and method

If available, MRI is the recommended modality for initial staging [III, A]. MRI is highly accurate for definition of localisation, and for determining the total extension, and the relationship of the tumour to the peritoneal reflection (table 6). However, the stage specific management is always based on the best available staging method.

<table>
<thead>
<tr>
<th>parameter</th>
<th>method of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location (distance from anal verge/anorectal junction)</td>
<td>MRI rigid proctoscopy flexible endoscopy</td>
</tr>
<tr>
<td>T stage</td>
<td>T1 ERUS</td>
</tr>
<tr>
<td></td>
<td>T2 MRI ERUS</td>
</tr>
<tr>
<td></td>
<td>T3 MRI ERUS</td>
</tr>
<tr>
<td></td>
<td>T4 MRI (ERUS low rectum) MDCT (high and mid rectum)</td>
</tr>
<tr>
<td>sphincter infiltration</td>
<td>MRI ERUS</td>
</tr>
<tr>
<td>mesorectal fascia involvement</td>
<td>MRI MDCT (high and mid rectum)</td>
</tr>
<tr>
<td>N stage</td>
<td>MRI MDCT or ERUS</td>
</tr>
</tbody>
</table>

Table 6: Diagnostic procedures for staging of the primary tumour in rectal cancer

**Attention** should be paid to recognise an adenocarcinoma of the anal canal when the infiltration is more towards the anal canal than the rectal wall. These are however very rare, and treated in the same way as a very low rectal cancer.

### 6.1.2 Definition of clinical T-stage

- Sub classification of T1 cancers is based upon depth of invasion into the submucosal layer: sm1 upper third, sm2 middle third and sm3 lower third.
- *Endorectal ultrasound* (ERUS) and *endorectal MRI* have similar accuracy in the differentiation between superficial (T1 and/or T2) and T3 tumours, except in T1 tumours where ERUS is preferred [III, B]. Endorectal MRI is less patient friendly and not recommended.
- In early rectal tumours (<T3) ERUS or MRI should be used, to accurately define clinical T stage [III, B].
Endorectal ultrasound is not an adequate method for the assessment of local tumour extent in T3 or T4 tumours, except possibly in low tumours in the anterior part [IV, B].

Endorectal ultrasound and MRI often fail in the differentiation between T2 and borderline T3, mainly due to overstaging. Overstaging errors occur in 30-40% for both ERUS and MRI. T3 is a heterogeneous group with different risks for local recurrence and metastatic disease.

The penetration of the tumour into the mesorectal fat should be given in millimetres to define the T3 subgroups.

MRI may help in defining T3 subgroups, and is superior to multidetector CT (MDCT) in distinguishing T3 from T4 in the rectum especially for lower rectal tumours. It is superior to CT for the assessment of invasion into the anal sphincter complex and the MRF [III, B].

For advanced, non-stenosing tumours (T3/4) MRI is equal to ERUS, but gives a better roadmap of the tumour extension.

For high stenosing tumours MRI is superior to ERUS [IV, A].

Therefore, MRI is the preferred method. If MRI is not available, MDCT is an alternative for the mid and high rectal tumours. Sphincter infiltration can be determined with ERUS or MRI with comparable accuracy. [III, A]

6.1.3 Mesorectal fascia (MRF) involvement/ potential circumferential resection margins (CRM)

Treatment strategy is dependent also on the relation of the tumour to the MRF. Although it has been the standard in the past, it is inappropriate to use the term (potential) CRM+ for initial clinical staging before surgery, since CRM can only be defined postoperatively by the surgical plane. The tumour growth on primary staging MRI should better be described in relation to an anatomical structure, like the MRF 49.

MRI is the method of choice for the prediction of positivity of MRFs [III, A]. MDCT seems to be equivalent to MRI only in tumours in the mid/high rectum.

The distance from the tumour and from the suspicious lymph nodes (if closer) to the MRF should be given in millimetres.

6.1.4 N-stage

Identification of nodal disease is still a diagnostic problem for radiologists. Prediction of nodal metastases is conventionally based on size: nodes >8mm were defined as malignant nodes. The number, size and location of the nodes should be reported (within and outside the mesorectum).

MRI or ERUS (or even MDCT) are equally well in performance for the detection of a N+ patient, but only when nodes are visualized that have specific imaging features such as large nodes with size >= 8mm/ round shape/ heterogeneous aspect / irregular border [III, A].

If nodes>= 8mm with the specific imaging features are absent and only smaller nodes are visible, imaging becomes less accurate, regardless of which method used, because the majority of rectal cancer lymph node metastases occur in nodes less than 6 mm in size and therefore size criteria are not sufficiently accurate. In a meta-analysis, sensitivity and specificity of ERUS, MDCT and MRI for the prediction of nodal metastases in rectal cancer have shown to be 67% and 78% for ERUS, 55% and 74% for CT, and 66% and 76% for MRI, respectively 50.
Whereas all imaging methods are not accurate enough to predict lymph node positivity only ERUS-guided fine needle aspiration has an accuracy up to 100% in single centre studies [IV, B]; however it is a rarely used technique that has not gained widespread acceptance.

FDG-PET is not helpful to substitute or improve the standard measures for N staging [IV, D].

Because of the importance to identify lymph node involvement within and outside the mesorectum, MRI is the method of choice as it has a larger field of view than ERUS [IV, B].

6.1.5 M-stage
- Abdominal contrast enhanced MDCT and chest X-ray or -CT (to be preferred) are the minimal requirements for staging of distant metastases [IV, A].
- MRI is helpful in further characterization of equivocal liver lesions diagnosed by CT scan [IV, A].
- FDG-PET should not be used routinely for initial staging [III, D], but might be used for patients with CT-detected synchronous liver metastases, who are scheduled for curative liver surgery or in the presence of nodes in the common iliac region [I, C]. FDG-PET is more sensitive than CT to rule out extrahepatic metastases.
- Bone scan and brain imaging should only be performed for patients with related symptoms [V, B].

6.1.6 Diagnosis of response after chemoradiation
None of the available imaging modalities (ERUS, MRI, CT) can reliably predict complete remission. Although downsizing can be assessed with these methods, accuracy for pT-stage and regression rate/histopathological response is low. [III, C]
- Only MRI can accurately distinguish ypT0-2 from ypT3 [III, B]. However, restaging-MRI is only useful if it alters treatment. It should not be performed before 4-6 weeks after chemoradiation.
- Diffusion Weighted MRI is more sensitive than MRI only for prediction of a pathological complete response 51-53
- The role of FDG-PET CT is under investigation. Combination of FDG-PET and MRI might be more reliably for predicting pathological response 54. However, this benefit must be weighed against higher cost.

6.1.7 Pathology
Guidelines are important and there should be national or preferably international guidelines for dissection and reporting. The Guidelines of the Royal College of Pathologists in the United Kingdom have gained widespread acceptance as the minimum standard for reporting this disease. They are available at http://www.rcpath.org/index.asp?pageID=1153. The macroscopic examination of the specimen is critical and of prognostic significance.

6.1.7.1 Preparation and assessment of specimen
- For local excision resection specimens, careful examination of all resection margins should be performed, including the examination of the basal resection margin. In order to adequately predict the presence of lymph node metastases and the subsequent need for radical resection, differentiation grade, lymphangioinvasion and invasion depth (using the Kikuchi classification, sm1-3) should be reported.
- **TME resection specimen**: The used categories for the quality of surgery evaluation are (according to the CRO7 classification)\textsuperscript{55}: Level of resection at the muscularis propria (formerly incomplete, poor) vs. at the mesorectal fat (formerly nearly complete, moderate) vs. at the mesorectal fascia (formerly complete, good).

- If abdominoperineal resection is performed and the anal region is included in the resection, the region can be assessed as follows: Level of resection in the submucosa/perforation vs. in the sphincter region vs. in the region beyond the sphincters.

- Careful macroscopic evaluation of the specimen is necessary. For recording of any perforation and the plane of surgical dissection anterior and posterior surfaces should be photographed.

- The specimen is opened anteriorly except for the area of the tumour, which is left intact to allow assessment of CRM involvement, without distortion introduced by opening the bowel. The surgically created margin surfaces are painted with ink.

- The specimen should be fixed in formalin for 72 h or longer. It should then be described and the tumour (including 2 cm below and above) should be thinly sliced (3-5 mm). Good fixation allows thinner slices to be taken and thus a better assessment of tumour spread. These slices should be photographed to document the plane of surgical dissection.

- The distance of direct tumour spread outside the muscularis propria should be recorded and the area in which tumour spreads closest to the CRM should be identified macroscopically.

- Blocks should be taken from the area closest to the CRM and any area where the tumour extends to within less than 3 mm from the margin. Other blocks should be taken to include at least 5 blocks of tumour to confirm the presence or absence of extramural venous invasion.

- In patients without preoperative treatment at least 12 lymph nodes (TNM/NICE guidelines) have to be assessed. Number of lymph nodes needed to accurately stage preoperatively treated cases is unknown. [IV, A]

### 6.1.7.2 Circumferential resection margin (CRM)

- The most important resection margin for rectal cancer is the CRM, which is created by the surgeon ideally along the mesorectal fascia unless the tumour involves or grows within 1 mm from the fascia. There is an increased risk for local recurrence, distant metastases, and poorer survival, when the CRM is involved or less than 1 mm. Patients with less than 2 mm could be considered at higher risk, therefore it is important to report the exact CRM in mm.

- CRM must be defined as involved if it is $\leq 1$ mm from tumour free margin in order to define risk for local recurrence and potentially adjuvant strategy. CRM should always be measured from the primary tumour and given in millimetres.

- If a positive lymph node or a tumour deposit is closer to the margin, a second CRM measurement should be made and reported.

- CRM is less confusing and should be used instead of the R classification in rectal cancer.

### 6.1.7.3 Classification of rectal primary tumour

Rectal cancer is classified according to the TNM system. Recent changes in the TNM definition of what constitutes a positive lymph node have been confusing and lead to
a highly subjective classification that is not reproducible. The 1997 definition states that tumour deposits should be counted as positive lymph nodes when they are larger than 3 mm in size is reproducible and standardized. The additional benefit of this definition is that comparisons with radiologic imaging can be performed. It is unclear which TNM version should be used in classification of colorectal cancer. Whereas several central and north-European national guidelines recommend version 5, others endorse the most recent version 7, which should preferably be used as long as no new official version is published. This is a matter of ongoing controversy and interdisciplinary discussion.

6.1.7.4 Tumour regression grading
Tumour regression grading after preoperative treatment (TRG) has not demonstrated any independent and reproducible prognostic value. Currently there is no indication for the routine reporting of TRG. However, it is important to report pathological complete response (pCR) for comparison within clinical trials – although a pCR has no or poor prognostic value regarding DFS or OS. This should be investigated in a standardized fashion; initially 5 tissue blocks should be taken from the suspect area. If there is no tumour in these blocks the whole area should be blocked and if there is still no tumour there, three levels should be cut to exclude the presence of viable tumour.

6.2 Management of localized rectal cancer
6.2.1 Patient classification for defining treatment strategy
• Patients with rectal cancer should be staged and treated in a centre of experience.
• Treatment strategy has to be decided by a multidisciplinary team – before treatment is started.
• Patients should be classified according to clinical stage TNM, involvement of mesorectal fascia, size, level, and localization. Other factors, such as cN-stage, and vascular and nerve invasion are also relevant.
• For treatment decision the following five groups based on clinical staging (if sufficient quality measures including ERUS and MRI available) can be helpful:
  o very early: cT1 sm1/2
  o early: >cT1 sm2-cT2, cT3a/b MRF- N0 in the upper/middle rectum
  o intermediate: >cT3b MRF-, cT4 with limited levator only in the upper/middle rectum or ≥ cT3a/b MRF- N0 in the lower rectum
  o locally advanced: cT3 MRF+, cT4, positive lateral lymph nodes
  o synchronous metastases
• All following guidelines are related to tumours of low and mid location up to 10cm distance of anal verge measured by rigid proctoscopy. Tumours above this line are generally treated as colosigmoid cancer (see chapter 7), except high seated tumours with extension into adjacent structures or peritoneal reflection (see chapter 6.2.2.7).

6.2.2 Preoperative treatment modalities
Aims of preoperative treatment are reduction of risk for local relapse, improvement of resectability to enable R0-resection in MRF+ or T4 disease, preservation of sphincter function in low located tumours and avoidance of stoma.
6.2.2.1 Preoperative Radiotherapy

There are two modalities of giving the radiotherapy, either as
• short course radiotherapy with 5x5 Gy followed by immediate surgery
• long course radiotherapy with 50.4 Gy in 25-28 fractions, with surgery after 4-8 weeks break.

For long-term radio(chemo)therapy the dose is 45-50.4 Gy [II, A]. A boost up to a total dose of 55.4 Gy can be administered (not mandatory) [II, C]. Brachytherapy or intraoperative radiation (IORT) is a special form of local boost, but still experimental.

Volumes to irradiate (clinical target volume, CTV)

- The entire mesorectum is at great risk of having tumour deposits, often in the mesorectal lymph nodes, in all tumours except the very earliest [T1 sm1 (–2?)] and should be included in the clinical target volume (CTV). Exceptions are high tumours, where it is sufficient to include the 4–5 cm distal to the tumour. This means that in these tumours the lower border of the beams can be 5–6 cm distal to the tumour.
- Besides the mesorectal nodes, the presacral nodes along aa rectalis superior up to the level of S2 could be included, if presacral nodes are radiologically involved. Nodes along the internal iliac arteries up to below the bifurcation or to the level of about S2 should be included.
- The lateral nodes along aa obturatorii should be irradiated in tumours below the peritoneal reflection with at least cT3 or N+ stage.
- External iliac nodes should only be included if an anterior organ like the urinary bladder, prostate or female sexual organs are involved to such an extent that there is a risk of involvement of these lymph node stations.
- Fossae ischiorectalis should only be included when the levator muscles and the internal and external sphincters are involved.
- The medial inguinal nodes should not be included prophylactically unless there is massive anal sphincter invasion.
- When lymph nodes are involved by metastatic disease so that this can be seen on imaging, there is always a risk of aberrant spread. Therefore the CTV can be enlarged to include other nodal stations than those described above.

6.2.2.2 Chemoradiation (CRT)

Preoperative long-term radiotherapy should always be combined with fluoropyrimidine chemotherapy [I, A]. Standard preoperative CRT means a dose of 45–50.4 Gy [II, A], together with 5FU given preferably as prolonged continuous infusion (likely better than bolus) or oral 5FU prodrugs (capecitabine or uracil–tegafur (UFT)) [II, A]. Chemotherapy-options and doses for concomitant chemo are given in table 7.

<table>
<thead>
<tr>
<th>regimen</th>
<th>57, 58</th>
<th>59</th>
<th>60, 61</th>
<th>62</th>
<th>63, 64</th>
<th>65-68</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU 325-350 mg/m² + LV 20 mg/m² iv bolus, d1-5, week 1 and 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU 400 mg/m² + LV 100 mg iv bolus, d 1, 2, 11, 12, 21, 22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU 225 mg/m² iv continuous infusion, i.v. days per week, together with radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU 1000 mg/m² iv continuous infusion, d1-5, week 1 and 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>capecitabine 800-825 mg/m² bid po continuously, 5-7 days per week, together with radiotherapy</td>
<td></td>
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<tr>
<td>UFT (300-350 mg/m²/day) and LV (22.5-90 mg/day) po continuously, 5-7 days per week, together with radiotherapy</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>only preoperatively: 5FU 250 mg/m² iv continuous infusion on days 1-14 and 22-35</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
and oxaliplatin 50 mg/m² iv d1, 8, 22, 29

Table 7: chemotherapy-options and doses for concomitant chemotherapy during pre- or post-op radiation

- **Role of capecitabine vs. iv 5FU**: The NSABP R-04 trial and an AIO-trial showed that 5FU and capecitabine are equivalent (proven non-inferiority) \(^{63, 70}\). Therefore capecitabine can be considered as an alternative option to 5FU, especially in considering the avoidance of central venous access [I, B]. The optimal dose of capecitabine is not known.

- **Role of oxaliplatin**: Combination with oxaliplatin or irinotecan has been investigated in phase II and III trials with respect to local response. Despite early promising results for 5FU/oxaliplatin or capecitabine/oxaliplatin, local complete pathological response (pCR) was not increased compared to FU alone in the STAR-01, ACCORD 12/0405-Prodige 2, and NSABP R-04 \(^{64, 70, 71}\). Only in the German CAO/ARO/AIO-04 a significant increase in pCR rate of 4.5% was shown \(^{69}\). However, local control does not seem to be a surrogate for survival, as recently shown \(^{72}\). Therefore, survival data from these trials as well as from the ongoing PETACC 6 have to be awaited before final conclusion on the benefit of adding oxaliplatin can be made. Currently, CRT with FU alone remains the standard of care, whereas combination of FU together with oxaliplatin or other drugs remains experimental and should not routinely be used [I, B].

- **Role of targeted drugs**: Combination with targeted drugs (bevacizumab, cetuximab) produced interesting, but conflicting results and is still investigational. Out of clinical trials targeted drugs should not be used in combination with radiation.

### 6.2.2.3 Choice of preoperative treatment – 5x5Gy or chemoradiation

- Treatment options are radiotherapy alone, either short or long course, or chemoradiation. The advantage of short course radiation is the short preoperative treatment phase in comparison to long term radio(chemo)therapy; the disadvantage is, that downsizing of the primary cannot occur since surgery is performed 2-3 days after radiation. However, recently it has been shown that after short course radiotherapy downsizing can be expected if surgery is delayed until 6-8 weeks. This approach however is still experimental (ongoing trial in the Swedish Group).

- If long term radiation is used, concomitant chemotherapy with respect to only preoperative radiotherapy has the advantage of a higher chance for downsizing including more pathological complete remissions, improved resectability, potentially maintaining bowel/sphincter function in case of low located tumours, reduced risk for local relapse and improved long term survival \(^{73, 74}\) [II, A]. Therefore,
  - short course radiotherapy and chemoradiation are equivalent in those tumours were downsizing is not necessary and which are MRF-;
  - however, short course is much easier and more cost effective.
  - For locally advanced tumours (i.e. MRF+ or cT4), chemoradiation is mandatory.
6.2.2.4 Pre- vs. postoperative chemoradiation

It has been shown, that preoperative chemoradiation followed by adjuvant chemotherapy compared to postoperative adjuvant chemoradiation significantly reduces local recurrence rates, has less acute and long term toxicity and in addition enables a higher rate of sphincter saving surgery by down sizing and thus improves functional outcome in low located tumours \(^57, 62, 75\). However, distant relapse rate and overall survival are similar for both approaches. [I, A]

6.2.2.5 Intensive chemotherapy before definitive local treatment

Intensive and prolonged chemotherapy +/- followed by preoperative chemoradiation, before definitive surgery, is an investigational approach. In locally advanced tumours the value of upfront induction chemotherapy +/- targeted drugs (bevacizumab; cetuximab), followed by local treatment with chemoradiation and subsequent surgery is currently investigated \(^76-79\). Despite interesting results, in patients with R0-resectable primary tumour (after preoperative treatment) and no distant metastases, induction combination chemotherapy before definitive local treatment (radiotherapy and surgery) should not be given outside a clinical trial [II, C].

6.2.2.6 Intensive chemotherapy instead of local radiation

As a step further, for patients with limited tumours (T3 MRF-) combination chemotherapy with FOLFOX+bevacizumab, without chemoradiation, achieved in one trial a pCR of 27\% \(^80\). Despite these promising early results, induction chemotherapy as front line treatment and single modality before surgery, without additional local radio(chemo)therapy, should not be given out of a clinical trial [III, D].

6.2.2.7 Preoperative management of tumours of the upper third >10cm from the anal verge

Whereas tumour stage <=T4a in the upper third (>10cm measured from the anal verge) are treated like colosigmoid cancer, large tumours with extension to the adjacent structures or peritoneal reflection need preoperative chemoradiation. Intensive chemotherapy might be an option, which however is not systematically proven [III, B].

6.2.3 Definitive local treatment (surgery)

6.2.3.1 Procedures

In rectal cancer several surgical techniques according to extent of disease might be used [III, A]. A protective ileostomy should be the standard of care for all low colorectal or colo-anal anastomosis.

- For very early stages (cT1 sm1/2) a local excision can be performed. Local excision should go through the muscular layer. The transanal endoscopic mucosectomy (TEM) is the standard procedure, if local excision is chosen. TEM should be performed by special techniques. Local excision with loop via sigmoidoscopy is not an appropriate approach.

- Total mesorectal excision (TME) is the standard of care in rectal cancer surgery. The whole mesorectal fat, including all lymph nodes, should be excised. TME is recommended for patients with all rectal cancers localized in the middle and lower third of the rectum. Quality control of surgical specimen is crucial.

- Partial mesorectal excision (PME) is adequate for rectal cancer localized in the upper third of the rectum (>10 to 15 cm from anal verge) due to reduced morbidity. Rectum and mesorectum have to be divided 5 cm below tumour.
• **Abdomino perineal resection** (APR) is the preferred surgical approach in case of tumour involvement of the anorectal junction and anal sphincter or as salvage of local failures after local excision with or without prior (chemo) radiotherapy. APR should be performed starting with the dissection from above, stopping at the levator plane, continued dissection from below outside the sphincteric plane, finally dividing the levators from below.

• **Laparoscopic surgery** might reveal equivalent results in terms of function and relapse rate, compared to open surgery, in specialized centres, but should not be used as standard modality yet.

### 6.2.3.2 Timing of surgery

• **After preoperative short course radiation (5x5Gy)** standard timing is day 7-9 (after radiation from day 1-5), leaving a break of 2-3 days after termination of short course radiation [II, A].

• **Interval between** preoperative chemoradiation and surgery should be 4-8 weeks [III, B].

• **For elderly (>80 years) or frail patients**, who should receive short course radiation, surgery should be delayed to 8 weeks [V, A].

• **Short-course radiation with delayed surgery** in fit patients (6-8 weeks) is still experimental (trial on going).

### 6.2.3.3 Extent of surgery in case of clinical CR after preoperative radio(chemo)therapy

• If complete clinical response of the primary tumour occurs, the standard treatment is TME [III, A].

• If only a local excision (preferably TEM) of the scar is done and shows pCR, surveillance as sole “treatment” cannot be recommended as a standard of care at the moment. However, out of a clinical trial in an individual case e.g. young patient with low located tumour, who would receive permanent stoma in case of surgery, this approach can be discussed with the patient with an estimation of the risk of local relapse; according to initial stage of tumour and nodal status 81. This can be calculated from the nomograms by Valentini et al based on staging and treatment factors 74. [III, B]

### 6.2.3.4 Sphincter preservation

Whenever possible, sphincter preservation should be aimed at. The sphincter can generally be preserved, if the tumour can be resected with a 1cm distal margin. Chemoradiation or radiation with prolonged interval downsizes the tumour; the question whether by increasing the chance for sphincter preservation after good response to preoperative treatment is not increasing the risk of local relapse, cannot be answered presently. This approach is currently performed routinely in experienced centres in some countries 82.

### 6.2.3.5 Reversal of stoma

Stoma should be reversed, if feasible, after completion of adjuvant treatment (including radiation) in order to assure timely postoperative therapy. Interval between last chemotherapy and operation should be 5-6 weeks; in case of surgery during adjuvant treatment (e.g. urgent patient request) interval might be shortened to 3-4 weeks. However, treatment should be resumed after surgery.
6.2.4 Postoperative adjuvant treatment

6.2.4.1 Postoperative chemoradiation (CRT) and adjuvant chemotherapy

- Patients with indication to CRT (table 8) who received no preoperative treatment should receive postoperative CRT and chemotherapy in case of
  - involved circumferential margin (CRM+),
  - perforation in the tumour area or
  - in other cases with high risk of local recurrence (≥pT3b and/or N+) [I, A]

- **Postoperative treatment should be administered** for a total of 6 months containing chemotherapy with either capecitabine or 5FU (bolus or continuous infusion) and concomitant radiotherapy (e.g. 50 Gy, 1.8–2.0 Gy/fraction) either at the beginning or during 3rd and 4th cycle [I, B]. During radiotherapy either 5FU preferably as continuous infusion or capecitabine should be given [I, A]. Postoperative radiotherapy as single adjuvant modality without concomitant 5FU is obsolete [I, E].

- **The main advantage of the postoperative as compared to the preoperative approach** is the better selection of the patients based on pathologic staging; disadvantages include increased toxicity related to parts of the small bowel or the perineal scar after APR in the radiation field and potentially more radio-resistant tumour cells in a hypoxic postsurgical area.

- **Postoperative CRT** with concomitant FU-based chemotherapy instead of preoperative CRT is no longer recommended, since preoperative CRT is more efficient and has less acute and long-term toxicity.

- In a small randomised trial, patients who underwent abdominoperineal resection, the DFS rate at 10 years was significantly greater in the early RT arm than in the late RT arm (63% vs. 40%; p=0.043) suggesting that if neoadjuvant CRT was not given before surgery, early postoperative CRT should be considered for patients who had abdominoperineal resection [II, B].

- **After local excision of pT1 tumour with adverse factors (involved margins, poor differentiation, sm3 and lymphovascular invasion) or pT2 the risk for local recurrence is high.** In case of refusal or no susceptibility for required radical surgery after endorectal local excision, patients should receive postoperative chemoradiation [IV, B].

6.2.4.2 Postoperative (adjuvant) chemotherapy

In contrast to colon cancer, the available data from randomized trials for rectal cancer investigating the value of adjuvant chemotherapy after preoperative radio(chemo)therapy and surgery are limited by small numbers of patients and conflicting results [58, 87-89].

- **In case of upfront surgery** with or without postoperative radiation, adjuvant 5FU based chemotherapy reduced distant failure and improved survival [83, 85, 86] which is consistent with the results of the QUASAR trial rectal cancer subgroup, showing a significant superiority of about 50% reduction for any recurrence in the rectal cancer subgroup (stage III HR: (99%CI): 0.44 (0.18–1.06), stage II HR: 0.57 (0.34–0.97)) and a trend for overall survival (stage II HR: 0.80 (0.54–1.19)) [I, A].

- **In case of upfront CRT or radiotherapy** (in the more recent trials), a pooled analysis of 2795 treated patients (EORTC, FFCD, CAO/ARO, Polish, and Italian trials) with 1572 patients receiving adjuvant treatment, adjuvant 5FU
significantly increased overall survival (p<0.001) \[74\] [II, B]. This is in contrast to the lack of benefit shown in a systematic review of all trials, using only published study results \[90\]. The overall body of data leads to the conclusion that postoperative single agent fluoropyrimidine should be the current standard if adjuvant therapy is indicated.

A definite answer from a phase III trial like in colon cancer will not be achieved, since all ongoing or closed trials use single agent 5FU or capecitabine as control and have no arm without adjuvant chemotherapy anymore - with the exception of the SCRIPT trial, comparing no adjuvant chemotherapy with single agent capecitabine after short course radiation or chemoradiation and TME. Sample size in the SCRIPT trial may be too small to detect a significant difference (data not before 2013).

In the US, standard adjuvant treatment for locally advanced rectal cancer is 5FU/LV or capecitabine or FOLFOX. The ongoing Intergroup trial which compares 5FU/LV with FOLFOX or FOLFIRI is not recruiting. PETACC 6 and the German ARO/CAO/AIO trial will be able to give clear information about the value of postoperative FOLFOX (ARO/CAO/AIO) or XELOX (PETACC 6). However, definitive data will not be available before 2013.

- **Role of oxaliplatin:** Regarding the choice of treatment there is no direct evidence from randomized trial yet, that fluoropyrimidine/oxaliplatin combination should be given in the adjuvant situation.

- **Current standard:** The majority of consensus participants recommend adjuvant FU, iv or orally [II, B], with or without oxaliplatin (based on data from colon cancer) [V, B] for stage III and stage II (preoperative clinical staging). Standard treatment options are given in table 8 and 10.

- **Exceptions from adjuvant treatment:** Retrospective subgroup-analyses suggest that certain patients might not require adjuvant treatment, due to only minimal improvement of local recurrence rate, without currently being clinical standard [IV, D]:
  - low risk stage II patients, e.g. with upper rectal pT3 N0 tumours after TME with 12 lymph-nodes examined and an adequate radial resection
  - patients without response to preoperative CRT at surgery, who had no benefit of adjuvant treatment in contrary to responders in a subgroup analysis of the EORTC trial \[91\].

- **Nomograms developed in the current pooled analysis might be helpful for decisions about postoperative adjuvant chemotherapy predicting risk of distant metastases, local recurrences, and survival for an individual patient \[74\].

<table>
<thead>
<tr>
<th>regimen</th>
<th>cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU 350-370 mg/m² + LV 20-25 mg/m² iv bolus, d1-5, q 4 weeks</td>
<td>4 (-6)</td>
</tr>
<tr>
<td>5FU 500 mg/m² iv continuous infusion, d1-5, q 4 weeks</td>
<td>4</td>
</tr>
<tr>
<td>5FU 500 mg/m² + LV 100 mg, iv Bolus d 1,2, q 2 weeks</td>
<td>8</td>
</tr>
<tr>
<td>Capecitabine 2000-2500 mg/m² po d1-14, q 3 weeks</td>
<td>5-6 (-8)</td>
</tr>
</tbody>
</table>

table 8: standard adjuvant chemotherapy regimens in rectal cancer (number of cycles without chemoradiation are given in brackets)

**Older age patients**
In principle there is no age limit as long as co-morbidity allows treatment. However, initial dose reduction for chemotherapy should be considered for elderly or frail patients [IV, B].

**Timing**

Adjuvant chemotherapy should be started as early as possible starting from the fourth week up to a maximum of 8-12 weeks since surgery [IV, B] (refer to colon cancer chapter 7.3.2.5). Adjuvant treatment should not be started in the presence of inadequate postoperative recovery or pelvic septic complications.

**Duration**

Total duration of perioperative treatment should be 5.5 to 6 months. If preoperative chemoradiation was given, adjuvant chemotherapy for 4 to 4.5 months should be administered. If no preoperative treatment was performed, adjuvant chemotherapy with or without radiation should be administered for 5.5 to 6 months. [IV, B]

### 6.2.5 Treatment standard according to clinical stage at diagnosis

Treatment is based on the clinical stage at diagnosis and modified by pathological examination of the excised or resected specimen. For the choice of treatment strategy the above-mentioned clinical groups could be used. Treatment is summarized in the algorithm depicted in figure 1 and table 9 for localized and figure 2 and 3 for synchronous metastatic disease.

#### 6.2.5.1 Very early stage: cT1 sm1/2

- **cT1 sm1 with good/moderate differentiation**: transanal excision, if possible by transanal microscopic excision (TEM) is the method of choice.
- **cT1 sm2 with good/moderate differentiation**: TEM or TME can be performed and should be discussed with the patient. Alternatively to local surgery, local radiotherapy (e.g. brachytherapy or contact therapy) could be used. Experience however, is limited to very specialized centres.

If the tumour appears to be of higher stage (>pT1sm2) or shows worse prognostic factors (differentiation, venous invasion, perineural invasion) after local excision the patient should receive TME, as postoperative chemoradiation after TEM is not as good as TME.

#### 6.2.5.2 Early stage: >cT1 sm2-cT2, cT3a/b MRF- N0 upper/middle rectum

- **>cT1 sm2-cT2**: Transabdominal resection, including total mesorectal excision (TME) without preoperative treatment is recommended.
- **cT3a/b MRF- N0 upper/middle rectum** can be managed in two ways:
  - either upfront resection followed by surveillance only or
  - 5x5 radiation followed by surgery, which reduces the risk of local relapse, however is associated with more long term sequelae.

**Of note**: Postoperative CRT should be administered in patients with positive CRMs, perforation in the tumour area or in other cases with high risk of local recurrence, if preoperative (C)RT has not been given.

#### 6.2.5.3 Intermediate stage: >cT3b MRF-, cT4 with limited levator only in the upper/middle rectum or ≥ cT3a/b MRF- N0 in the lower rectum

In these cases (>cT3b without threatened and without involved MRF (MRF-) according to MRI) preoperative treatment followed by surgery (TME) is recommended.
CRT and short course radiotherapy seem to have equivalent outcome in terms of local relapse rate and long-term toxicity. Short course radiotherapy has the advantage of less acute toxicity and less cost.

6.2.5.4 Locally advanced: cT3 MRF+ and cT4 and positivity of “lateral lymph nodes”

- **Lateral lymph nodes** are defined to be in the drainage of the arteria rectalis media (if present) or along the obturator and internal iliac vessels.
- In >cT3 MRF+ tumours preoperative CRT with single agent oral or iv FU has to be administered, followed by surgery. In case of concomitant morbidity prohibiting chemoradiation, short course radiotherapy with delayed surgery might be considered, although this approach is still under clinical investigation.

6.3 Management of primary tumour in synchronous metastatic rectal cancer

Treatment strategy for synchronous oligometastatic rectal cancer should be based on the possibility to achieve R0-resection, either initially or after induction treatment for systemic disease and primary tumour. Treatment algorithms are summarized in figure 2 and 3.

R0 resectable liver+/−lung metastases (group 0, see table 13)

- For initially R0 resectable metastatic disease, irrespective of primary tumour, perioperative chemotherapy (3 months pre- and postoperative FOLFOX) should be applied analogue to the EORTC 40983 trial 93 [II, B]. In case of a metachronic relapse less than 12 months after adjuvant oxaliplatin-containing chemotherapy, FOLFIRI might be considered.
- In locally advanced primary tumours (≥T3 or N+): upfront chemotherapy with FOLFOX for 3 months and local treatment according to stage (or reverse sequence) followed by resection of the primary (staged or synchronous) followed by postoperative FOLFOX for 3 months should be applied [V, B].
- In early primary tumours (<T3 N0): resection of primary and metastases followed by postoperative treatment with FOLFOX for a total of 6 months could be considered, and if necessary (e.g. CRM+ etc) postoperative local treatment according to stage [V, B].

Potentially resectable metastatic disease after chemotherapy (group 1, see table 13)

- For initially unresectable metastatic disease, most active available induction treatment should be chosen [IV, A]. If metastases become resectable, local treatment according to stage for primary followed by resection of primary and metastases should be performed, followed by postoperative continuation of the same regimen for a total of 6 months (including preoperative) [IV, A]. If metastases remain unresectable, treatment should be continued or switched, depending on quality of response [V, B].

Never resectable metastatic disease (group 2/3, see table 13) and group 1 not becoming resectable

- Treatment aim is palliation and chemotherapy should be chosen accordingly (paragraph 9). Radical and mutilating surgery of the primary should be avoided, unless necessary due to emergency situation. Chemoradiation or 5x5 RT should be restricted to otherwise uncontrollable local tumour [V, B].
In case of symptomatic primary of the rectum:

- Local measures (e.g. insertion of a stent, stoma) should be performed initially, and only in specific circumstances palliative surgical resection [V, B].
<table>
<thead>
<tr>
<th>independent of localisation</th>
<th>diagnosis</th>
<th>preoperative</th>
<th>surgery</th>
<th>pathology report</th>
<th>postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>very early cT1 sm1</td>
<td>ERUS</td>
<td>TEM</td>
<td>&gt;pT1sm2, &gt;G1, V1, P1</td>
<td>TME</td>
<td>CRT</td>
</tr>
<tr>
<td>cT1 sm2</td>
<td></td>
<td></td>
<td>(TEM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>low (up to 5cm) and APR necessary</td>
<td>MRI</td>
<td>ERUS</td>
<td>CRT or RT (5x5) or nothing</td>
<td>APR (TME, if feasible)</td>
<td>CRT (if not preop.) or FU +/- oxaliplatin (4-6 months)</td>
</tr>
<tr>
<td>mid (&gt;5-10cm) and low without APR</td>
<td>MRI</td>
<td>ERUS</td>
<td>nothing or RT (5x5) or CRT</td>
<td>TME</td>
<td>CRT (if not preop.) or FU +/- oxaliplatin (4-6 months)</td>
</tr>
<tr>
<td>cT3a/b N0</td>
<td>MRI</td>
<td>ERUS</td>
<td>nothing or RT (5x5) or CRT</td>
<td>TME</td>
<td>CRT (if not preop.) or FU +/- oxaliplatin (5.5-6 months)</td>
</tr>
<tr>
<td>intermediate cT3 MRF-, cT4 with limited levator only</td>
<td>MRI</td>
<td>MDCT</td>
<td>CRT or RT (5x5)</td>
<td>TME</td>
<td>FU +/- oxaliplatin (4-6 months)</td>
</tr>
<tr>
<td>advanced (cT3 MRF+, cT4, positive lateral lymphnodes</td>
<td>MRI</td>
<td>MDCT</td>
<td>CRT</td>
<td>TME</td>
<td>FU +/- oxaliplatin (4-6 months)</td>
</tr>
<tr>
<td>high (&gt;10-15cm)</td>
<td>early</td>
<td>MDCT</td>
<td>nothing</td>
<td>T(P)ME</td>
<td>stage I or II (low risk) (FU)</td>
</tr>
<tr>
<td>intermediate</td>
<td>MRI</td>
<td>MDCT</td>
<td>nothing exceptional RT (5x5)</td>
<td>II (high risk: &lt;12 LN examined, L1, V1, P1, &gt;G2, pT4, obstruction, perforation)</td>
<td>FU +/- oxaliplatin (6 months)</td>
</tr>
<tr>
<td>very advanced (tight to lateral wall, T4b)</td>
<td>MRI</td>
<td>CRT</td>
<td>III</td>
<td></td>
<td>FU +/- oxaliplatin (4-6 months)</td>
</tr>
</tbody>
</table>

Table 9: Treatment algorithm for localized rectal cancer
(Note: Stage specific management is always based on the best available staging method.)
Figure 1: Treatment algorithm for localized rectal cancer
(Lateral LN: drainage of the a rectalis media (if present) or along the obturatorius or internal iliac vessels)
figure 2: treatment algorithm for resectable synchronous metastatic rectal cancer

figure 3: treatment algorithm for unresectable synchronous metastatic rectal cancer


7 Colon cancer

7.1 Diagnostics and Staging

- CT of the abdomen is recommended as primary local staging tool to assess growth of the colon tumour into the surrounding structures.
- Minimal requirements for distant staging are CT of the chest (if not available, X-ray of chest is acceptable) and abdomen, and complete colonoscopy (either pre- or postoperatively).
- FDG-PET is not recommended for initial staging.
- Physical examination and medical and family history of colorectal cancer, polyps and other cancers should be obtained.
- CEA should be determined before treatment.
- Bone scan and brain imaging should only be performed for patients with related symptoms.
- Additional investigations like virtual colonoscopy or CT colonography, even though they are not yet standard procedures, could be valuable to precisely locate the tumour, which is particularly useful for the surgical approach especially in patients who are candidates for a laparoscopic resection; they could also help to detect other synchronous colonic lesions or polyps if colonoscopy is incomplete (for example in obstructing tumours).

7.2 Pathology

Pathological assessment must include nodal spread of disease, extension of tumour to the peritoneum or to the bowel wall and into adjacent structures, grading and status of proximal, distal, and radial margins.

- Pathologic assessment should include staging for depth of penetration (T), lymph node status (N, minimum 12 nodes examined), resection margin status, grading (G), tumour type, tumour deposits, perineural growth, extramural invasion, lymphovascular invasion. Standardized reporting is required.
- For adequate pN-staging, at least 12 nodes must be removed: this is particularly important for stage II patients to reduce the risk for understaging [IV, B].
- Patients with stage II disease are classified as clinically high risk, if they have at least one of the following factors [IV, B]:
  - lymph nodes sampling <12,
  - poorly differentiated tumour,
  - vascular or lymphatic or perineural invasion,
  - pT4 stage,
  - clinical presentation with intestinal occlusion or perforation

7.3 Perioperative management of Stage 0 - III colon cancer

Colon cancer is classified according to the current TNM classification (UICC 2010). The same controversy about the appropriate TNM version as in rectal cancer is present in colon cancer. Primary treatment is based on upfront surgery, followed by adjuvant chemotherapy according to stage. Treatment algorithm is shown in figure 4 and table 11.

7.3.1 Surgical treatment of the primary tumour in resectable colon cancer

7.3.1.1 Treatment of malignant polyps

The extent of surgical treatment of the primary tumour in colon cancer is based on
For early cancer stage 0 (Tis N0 M0) or partly stage I (T1 N0 M0) local excision could be considered. The group of T1 carcinomas has a lymph node metastasis rate of 0% to 20%. In case of G1 or G2 and no lymphatic invasion (low risk), the rate of metastasis is less than 4%. Therefore, wide surgical resection after R0 polypectomy is not necessary [IV, B].

- In case of a higher risk situation (e.g. grading>2, invasion of submucosa, lymphatic or venous invasion, resection margins less than 1 mm, or tumour budding) or invasive carcinoma in a sessile polyp, standard resection should follow, even after definite R0 removal [IV, B].

- Tumours >T1 N0 should be treated with a wide surgical resection [IV, B].

- Pedunculated polyps with invasive carcinoma confined to the head and no further risk factors have only minimal risk for relapse and are therefore amenable for endoscopic polypectomy. Pedunculated polypoid carcinomas can be treated using the same criteria as other pedunculated polyps with invasive carcinoma.

### 7.3.1.2 Treatment of localized disease

#### Primary tumour

For stage $\geq$T2 N0 M0 wide surgical resection and anastomosis is the surgical treatment of choice. The goal of surgery is a wide resection of the involved segment of bowel together with removal of its lymphatic drainage. The resection should include a segment of colon of at least 5 cm on either side of the tumour, although wider margins are often included because of obligatory ligation of the arterial blood supply [IV, B].

#### Lymph nodes

To clearly define stage II vs. III and to eradicate potential lymph node metastases, at least 12 lymph nodes must be resected; otherwise the risk of understaging (false determination of stage II) is high, which might have negative impact on survival, if otherwise necessary adjuvant treatment is not administered [IV, B].

#### Minimal invasive surgery

Laparoscopic assisted open surgery or laparoscopic colectomy are potential alternatives to laparotomy [II, B]. Laparoscopic approach might be considered particularly for left-sided cancer but should only be performed based upon the following criteria:

- surgeons experienced with laparoscopic colectomy
- no prohibitive abdominal adhesion (prior major abdominal surgery)
- no locally advanced disease/acute bowel obstruction or perforation.

#### Experimental approach in locally advanced tumours

In locally advanced tumours and/or with bulky lymph node involvement, preoperative chemotherapy has shown to be feasible and effective in inducing local regression and thus improving surgery. However, this is still an experimental approach, which should be applied within clinical trials 94.

#### 7.3.2 Postoperative treatment

Adjuvant chemotherapy after resection of the primary tumour reduces the risk of death, by absolute 3-5% in stage II with single agent FU and 15-20% in stage III with
FU + oxaliplatin combination [I, A]. Due to the different clinical situations given in stage II, with about 80% of patients being cured by surgery alone, compared to stage III with only 60% cured by surgery alone, both stages will be discussed separately. Decision on adjuvant treatment must be based on thorough discussion with the patient on an individual basis taking into account patient characteristics (performance status, age, co-morbidity and patient preference) and cancer features (pathological stage, grading, and overall risk of relapse).

Prognostic and predictive factors (see chapter 4 and 5)
With respect to indication for adjuvant treatment beyond clinicopathological factors only MSI/MMR status has shown not only prognostic but also some predictive value. However, with availability of more retrospective analyses for more cumulated patients the predictive value of MSI/MMR was challenged:

- **Stage II:**
  In contrast to the clear prognostic role of MSI/MMR status, it does not appear that MMR status can be used to predict response to fluoropyrimidine therapy, however there is category one evidence to suggest that it is a useful prognostic marker which can be used to identify a subset of stage II colon cancer patients (10-15%) who have a very low likelihood of recurrence and who are unlikely to have a clinically significant absolute benefit from chemotherapy (1-2%) [I, B]. It may be possible to reassure these patients that the benefits of chemotherapy are not sufficiently high to warrant further treatment.

- **Stage III:**
  Early data with small number of patients (n=63) have shown no benefit of adjuvant 5FU in stage III dMMR patients. In contrast, the recent updated data showed a benefit for adjuvant 5FU in stage III MSI-H/dMMR, however this benefit was limited to germline (n=99) and not seen in sporadic (n=245) MSI-H/dMMR tumours [17, 29]. For the role of oxaliplatin in adjuvant chemotherapy for stage III no conclusive data are available with respect to the role of MSI/MMR status. Therefore, MSI/MMR is not relevant for treatment decision and does not need to be determined, if oxaliplatin combination is scheduled [IV, D].

### 7.3.2.1 Stage II disease

Adjuvant therapy should not be routinely recommended for unselected stage II colon cancer patients. However, stage II patients must be separated into high and low risk, according to the presence of at least one of the following tumour-related risk factors [IV, B]:

- lymph nodes sampling <12,
- poorly differentiated tumour,
- vascular or lymphatic or perineural invasion,
- pT4 stage,
- clinical presentation with intestinal occlusion or perforation

  - **Low risk stage II patients** according to this definition should not generally receive adjuvant treatment, although it might be considered in individual patients.
  - **High-risk stage II patients** may be treated with postoperative chemotherapy with FU with or without oxaliplatin because of a small absolute benefit. The addition
of oxaliplatin in the MOSAIC trial in high risk stage II patients produced a non-
significant trend for improved DFS compared to FU alone which did not
translate into improved OS, due to an excess of non-tumour-related deaths.97
However, recent analyses of the NSABP protocol C05-C08 demonstrated a 2-
3% benefit in 5 year OS rate for the addition of oxaliplatin to FU based adjuvant
chemotherapy in stage II.98 Thus, high-risk stage II patients should receive
adjuvant chemotherapy at least with single agent FU. However, combination
with oxaliplatin may be considered, particularly in case of multiple risk factors or
younger age.

- **Beyond prognostic information** MSI/MMR status is not useful for guidance of
treatment decision.

### 7.3.2.2 Stage III disease

Adjuvant chemotherapy should be offered to all eligible patients with stage III disease
[I, A]. FU and oxaliplatin combinations (FLOX, FOLFOX, XELOX) are superior to
single agent 5FU in terms of DFS and OS.99-101 Therefore, stage III patients should
receive adjuvant chemotherapy with FU and oxaliplatin [I, A], with a preference for
infused (FOLFOX) or oral FU (XELOX) combinations over the bolus FLOX regimen
(see below)102,103 [IV, A]. In case of clinical relevant neurotoxicity oxaliplatin should
be stopped, and FU continued, as the fluoropyrimidine contributes with about 2/3 to
the effect of adjuvant FOLFOX/XELOX.

### 7.3.2.3 Choice of treatment

- **Infusional 5FU** should be preferred to bolus 5FU due to better tolerability, which
  is even more relevant for elderly. However, this implies the use of a (central)
  venous device, potentially associated with complications (thrombosis, pulmatory embolism, infection) [II, B].
- **Since oral FU** does not require central venous access, this treatment modality
  should be preferred, whenever applicable102,104 [IV, B].
- In general the **FLOX regimen should not be used** because of its associated
toxicity and a lack of survival benefit [IV, D].
- Recommended treatment options for adjuvant chemotherapy are displayed in
  table 10.

### Table 10: Recommended treatment options for adjuvant treatment

<table>
<thead>
<tr>
<th>regimen</th>
<th>drug/ dosage/ schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>single agent</td>
<td></td>
</tr>
<tr>
<td>capecitabine</td>
<td>capecitabine 1250 mg/m² po twice daily d1-15</td>
</tr>
<tr>
<td>LV5FU2 de Gramont</td>
<td>5FU 400 mg/m² iv bolus and LV 200 mg/m² iv followed by 5FU 600mg/m² iv 22 h-infusion d1+2</td>
</tr>
<tr>
<td>combination</td>
<td></td>
</tr>
<tr>
<td>XELOX</td>
<td>capecitabine 1000 mg/m² po twice daily d1-15 oxaliplatin 130 mg/m² d1</td>
</tr>
<tr>
<td>mFOLFOX6</td>
<td>5FU 400 mg/m² iv bolus and LV 400 mg/m² iv followed by 5FU 2400 mg/m² iv 46 h-infusion oxaliplatin 85 mg/m³ d1</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>5FU 400 mg/m² iv bolus and LV 200 mg/m² iv followed by 5FU 600mg/m² iv 22 h-infusion d1+2 oxaliplatin 85 mg/m³ d1</td>
</tr>
</tbody>
</table>

### 7.3.2.4 Adjuvant treatment in elderly (>70 years) patients stage II and III

- Combined analyses of **MOSAIC and NSABP C07** within the ACCENT database
showed a decreased to absent survival benefit for patients aged ≥70 compared to <70 years for oxaliplatin-based combinations in stage II and III (OS HR: 1.18; 95% CI: 0.90-1.57 vs. HR: 0.81; 95% CI: 0.71-0.93, respectively) \(^\text{105}\).

- However, in the XELOXA trial with only stage III patients, the survival benefit over FU alone was maintained in elderly patients treated with XELOX, although the DFS-benefit was reduced and became non-significant in patients ≥70 years (HR: 0.87; 95% CI: 0.63-1.18) compared to <70 years (HR: 0.79; 95% CI: 0.66-0.94). No interaction between age and treatment was observed with XELOX for DFS (p=0.6222) or OS (p=0.7065) \(^\text{106}\).

- Recent SEER analysis in stage II patient (70% at least 75 years of age) showed no survival benefit for adjuvant treatment, mostly single agent 5FU \(^\text{107}\).

- If capecitabine is used, upfront dose reduction of 80% for both combination and single agent is recommended (albeit not investigated in a randomized fashion).

- The decision to treat elderly patients with oxaliplatin combination-therapy should therefore be considered with caution [III, D].

- Therefore, single agent FU is the treatment of choice. However, oxaliplatin combination-therapy might be applicable for patients with very good general health status and younger biological features.

### 7.3.2.5 Timing and duration

- Adjuvant chemotherapy should be started as early as possible, starting from the third week up to a maximum of 8-12 weeks since surgery. If the start of treatment is delayed for more than 12 weeks, chemotherapy should be given based on an individual decision taking into account relatively limited likelihood of benefit against the potential toxicity \(^\text{108-111}\) [II, B].

- In case of laparoscopic surgery an even earlier start of adjuvant chemotherapy may be possible.

- Adjuvant chemotherapy should be given for 6 months \(^\text{112}\) [I, A].

- Shorter adjuvant treatment duration (3 months) is currently under prospective evaluation (International Duration Evaluation of Adjuvant chemotherapy – IDEA meta-analysis project), collecting data of 12.000 patients from 6 ongoing trials (data available 2014).

<table>
<thead>
<tr>
<th>stage</th>
<th>TNM</th>
<th>treatment</th>
<th>pathology report</th>
<th>clinical risk</th>
<th>additional surgery</th>
<th>age</th>
<th>post-operative (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/I</td>
<td>Tis/T1 N0</td>
<td>local excision</td>
<td>&lt;G3, L0, R0</td>
<td>low (LN mets in 4%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;G2, L1, V1, invasion of submucosa</td>
<td>high</td>
<td>wide resection</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>&gt;T1</td>
<td>wide surgical resection and anastomosis</td>
<td>-</td>
<td>-</td>
<td>(FU)</td>
<td>&lt;70 y</td>
<td>FU (+oxaliplatin)</td>
</tr>
<tr>
<td>II</td>
<td>T3/4 N0</td>
<td>low</td>
<td>high: at least one of &lt;12 LN examined, L1, V1, PN1, &gt;G2, pT4, occlusion, perforation</td>
<td>-</td>
<td>&lt;70 y</td>
<td>&lt;70 y</td>
<td>FU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>N+</td>
<td>-</td>
<td>&lt;70 y</td>
<td>FU+oxaliplatin</td>
<td>&gt;70 y</td>
<td>FU</td>
<td></td>
</tr>
</tbody>
</table>
7.4 Management of primary tumour in synchronous metastatic colon cancer

Treatment strategy for synchronous oligometastatic colon cancer should be based on the possibility to achieve R0-resection, either initially or after induction treatment for systemic disease and primary tumour. Treatment algorithm is displayed in figure 5.

R0 resectable liver+/−lunge metastases (group 0, see table 13)
- For initially R0 resectable metastatic disease, irrespective of primary tumour, perioperative chemotherapy (3 months pre- and postoperative FOLFOX) should be applied analogue to the EORTC 40983 trial [II, B]. In case of a metachronic relapse less than 12 months after adjuvant oxaliplatin-containing chemotherapy, FOLFIRI might be considered.
- Alternatively, resection of the primary tumour and metastases, followed by postoperative adjuvant FOLFOX for 6 months could be considered. However, adjuvant 5FU has not shown significant benefit in two small randomized trials and no data are available for FOLFOX. The use of FOLFOX in this situation is only supported by the indirect evidence in regard of the potential value of FOLFOX in the perioperative situation [V, C].

Potentially resectable metastatic disease after chemotherapy (group 1, see table 13)
- For initially unresectable metastatic disease, most active available induction treatment should be chosen [V, C]. If metastases become resectable surgery for primary and metastases should be performed, followed by postoperative continuation of the same regimen for a total of 6 months (including preoperative) [V, C]. If metastases remain unresectable treatment should be continued or switched, depending on quality of response.

Never resectable metastatic disease (group 2/3, see table 13) and group 1 not becoming resectable
- Palliative surgery, stenting, laser ablation, or (chemo)radiation in case of unresectable disease, even after systemic treatment should be confined to bleeding or obstruction and as minimal invasive as possible and non invasive measures applied first [V, C]. Upfront surgery of the primary tumour for asymptomatic primary in case of unresectable systemic disease may not be performed. However, upfront chemotherapy should be started [113, 114] [V, C].

In case of symptomatic primary of the colon, local measures (e.g. insertion of a stent, stoma) or resection could be performed initially; however upfront chemotherapy is mostly active in eliminating tumour related local symptoms [V, C].
Figure 4: treatment algorithm for early colon cancer

Figure 5: treatment algorithm for synchronous metastatic colon cancer
8 Management of resectable liver and/or lung metastases

Surgical resection of R0 resectable colorectal liver metastases (CLM) is a potentially curative treatment, with reported 5-year survival rates of 20% to 45% from both, controlled trials and large observational series.\footnote{115-118}[III, A].

8.1 Definition of resectability

The criteria for R0-resectability of liver metastases are not standardized and are varying, dependent from technical aspects (and herein they are related to the experience of the surgeon and the multidisciplinary team) and the question of prognostic information for a chance of cure. Resectability is not limited by number (e.g. <4), size (>5cm), and bilobar involvement. Regarding technical aspects, multiple resections can also be performed, provided there is sufficient remnant liver (>30%) and surgery is not too risky due to location. Other considerations must include the presence of questionably resectable extrahepatic disease and eligibility of the patient for surgery with respect of co-morbidity. However, the main determinant of the outcome is beyond surgery itself – the biology of the disease, which is an essential component of the definition of resectability. Algorithm for resectable/ borderline resectable liver/lung metastases is shown in figure 6.

![Figure 6: Treatment algorithm for management of resectable liver/lung metastases](image)

8.2 Management of resectable liver metastases

Postoperative adjuvant chemotherapy

The role of postoperative adjuvant chemotherapy for 6 months is still unclear, in particular those incorporating modern chemotherapy. Underpowered trials with single agent 5FU or FOLFIRI - or hepatic arterial infusion of floxuridine - indicate some benefit, although no single study or meta-analysis has shown a statistically significant survival benefit.\footnote{119-124} However, postoperative adjuvant chemotherapy with FOLFOX (Europe) or FOLFOX+bevacizumab (US) is often administered, despite lack of data favouring this approach. The recently presented Dutch HEPATICA trial has indicated...
that there might be an option in intensifying combination chemotherapy with bevacizumab, but this approach is still experimental.\textsuperscript{125}

**Perioperative chemotherapy**

For perioperative chemotherapy with FOLFOX (3 months pre- and postoperatively) superior DFS was demonstrated in patients undergoing resection plus chemotherapy versus resection alone, and this approach represents - although final survival data are still lacking - a current standard.\textsuperscript{93} Both concepts of pre- and postoperative vs. postoperative alone as well as the addition of bevacizumab or anti-EGFR antibodies to perioperative chemotherapy (CRUK06/031, EORTC BOS-2) are investigated in ongoing trials.

**Standard procedure**

- As current standard, primary resectable patients should receive perioperative treatment for 3 months preoperatively followed by resection and 3 months postoperatively. This approach is proven for FOLFOX and for the group of patients being defined in the EORTC 40983 trial (up to four liver metastases, no extrahepatic disease, no previous oxaliplatin) \[II, B\].

- **Patients failing within 12 month of previous adjuvant oxaliplatin** based treatment should not receive perioperative FOLFOX, rather another active protocol, in the same manner of pre-/postoperative treatment, or immediate surgery if feasible [IV, C].

- **Good prognosis patients, with a single small (<2cm) liver metastasis** may be considered for upfront surgery since this lesion may not remain visible during surgery if responding well to chemotherapy. However, in this case postoperative chemotherapy with FOLFOX for 6 months is recommended [III, B].

- **If preoperative chemotherapy was not applied, in case of primary R0-resection:**
  - adjuvant chemotherapy with FU + oxaliplatin for 6 months should be administered (expert opinion) [V, B].
  - Single agent FU is also an option, mainly for patients with contraindication to oxaliplatin [V, B].

- **To achieve complete response to chemotherapy** is of major prognostic importance for liver metastases but should be avoided in order to enable resection (before complete disappearance)\textsuperscript{126, 127}. Therefore, close follow up with imaging and multidisciplinary discussion is mandatory. If an anatomical resection can be performed, complete response is not a major problem, because resection will be based on initial sites of liver metastases. In case of complete response on CT and no option for anatomical resection, different imaging methods might be used (MRI, PET scan, contrast enhanced ultrasound) or resection might be delayed until relapse occurs [IV, B].

- **Progression during neoadjuvant treatment**

  In the EORTC 40983 trial 7% of patients had primary progression during preoperative chemotherapy leading to unresectability in 8 of 12 patients, half of them presenting with new lesions. However, data on survival after surgery at progression under preoperative chemotherapy are controversial \textsuperscript{128, 129}, but progression during neoadjuvant treatment represents aggressive tumour biology, and likely predicts a worse outcome even in case of resection. Therefore, best available salvage treatment may be preferred, instead of straight resection [V, D].

- **In case of R1-resection** postoperative treatment should be continued as planned.\textsuperscript{130} Notably, surgical techniques using ablation techniques will lead to a
broader thermal destruction zone on the remnant liver front, and therefore, local R1 situations are very uncommon [IV, C].

- **Cryo- or radiofrequency ablation techniques** of positive margins could be considered to reduce local recurrence [IV, C].
- **In case of R2-resection** the intention of further treatment should be re-evaluated. In patients who might still be candidates for curative approach, chemotherapy should be modified and/or intensified. In addition or alternatively, other measures of treatment should be considered (expert opinion). In patients who are not amenable for curative approach treatment may be resumed [IV, C].
- **In case of contraindications against surgery or unresectable oligometastases** (size up to 3-4cm for RFA and 4-5cm for SBRT, if properly located) local ablative measures (RFA, SBRT) could be considered [IV, C].

### 8.3 Resectable lung metastases

The prognosis of patients with limited lung metastases is similar to those with liver metastases, with a 5 year survival rate of 25-35% after resection [135]. Despite the lack of data from prospective trials regarding perioperative treatment, an approach similar to management of resectable liver metastases should be considered [IV, B]. Alternatively, an initial resection followed by postoperative adjuvant treatment with FU with or without oxaliplatin for 6 months can be performed, however, this has the disadvantage of lack of information about treatment efficacy, albeit the potential benefit of postoperatively given adjuvant chemotherapy [121] [IV, B].

### 9 First line treatment of advanced disease

#### 9.1 Selection criteria for first-line treatment in advanced colorectal cancer

**Factors influencing choice of first-line treatment**

- **Clinical factors:** Relevant for the choice of first line treatment is the treatment aim. This aim depends on the clinical presentation and patterns of tumour-biology (e.g. metastases limited to liver and/or lung, or peritoneum; dynamic of progression; present or imminent symptoms), as well as patient related factors (e.g. co-morbidity, and related potential to undergo secondary resection), and drug related factors (availability of targeted drugs; predictive markers, e.g. KRAS). In case of major response of liver, lung (or even peritoneal) metastases to induction chemotherapy R0/R1 resection can result in long-term survival and potential cure in some patients - although this is confined only to a minority of patients; such a situation deserves most active chemotherapy in terms of induction of major regression. In contrast, if the treatment aim is not resection of metastases, but rather prolongation of survival, initially low toxic chemotherapy might be preferred. These factors, which should be considered before choosing first line treatment, are summarized in table 12.
table 12: factors influencing choice of first line treatment

- **tumour biology related factors**
  - localisation
    - o liver- or lung-only metastases versus
    - o multiple sites
    - o potentially R0-resectable lesions after induction chemotherapy and sufficient downsizing versus massive disease extension
  - growth dynamics
    - o aggressive versus indolent growth
    - o asymptomatic versus symptomatic disease
    - o imminent relevant tumour symptoms if low active or inactive treatment
    - o second-line treatment after ineffective first-line single-agent treatment may not be possible anymore
  - chemosensitivity (not detectable before start of chemotherapy)

- **patient-related factors**
  - biological age
  - co-morbidity
  - physical capacity to tolerate more intensive treatment
  - eligibility for potential secondary resection of liver/lung
  - psychological capacity/willingness to undergo more intensive treatment

- **drug efficacy/toxicity profile of chemotherapy**
  - potential to induce maximal regression of metastases size/number
  - potential to prolong PFS or OS
  - toxicity profile
  - drug sensitivity/predictive biomarkers

- **drug availability and cost**
  - availability (depending on region)
  - reimbursement
  - cost/economic reasons

**table 12: factors influencing choice of first line treatment**

- **Age/performance status (PS):** Neither age (less and more than 70 years) nor PS (0,1 vs. 2) seem to have an influence on the relative benefit from treatment with oxaliplatin or irinotecan based chemotherapy as well as bevacizumab, although the survival of those patient groups is shorter than younger and better PS patients. However, selection of patients with younger age or better PS for clinical trials makes extrapolation to daily clinical practice difficult.

- **Predictive markers:** Despite the tremendously important issue of availability and reimbursement, predictive markers for efficacy are highly relevant, to avoid unnecessary treatment, toxicity, and expenses. However, currently only KRAS mutation excluding patients from treatment with anti-EGFR-antibodies is available. No further predictive molecular marker is relevant for decision on routine first line treatment out of clinical trials, in particularly not for the decision on the use of bevacizumab. The probable potential of BRAF mutation and KRAS mutation codon G13D to be involved in the decision in the future needs further validation and is not ready for the routine use yet.

**Stratification of patients for first line treatment**

Using the factors in table 12, patients can be individually divided into the 4 clinical groups (table 13), by parameters describing localization, extent, and resectability of the disease, tumour dynamics, co-morbidity, potential of the patient to tolerate chemotherapy and secondary surgical treatment.
• **Group 0:** This group comprise those patients were metastases are limited to liver/lung metastases and are clearly R0 resectable even without preoperative chemotherapy. This group is different from group 1, where upfront resection has a high likelihood for a R≥1 resection.

• **Group 1:** Although never prospectively proven, it seems evident, that the achievement of a disease-free status after downsizing by induction chemotherapy, enabling secondary surgery, is the only mean to give the potential of long-term survival or cure in an otherwise incurable/palliative situation. For this aim, the most active induction chemotherapy should be selected upfront, which is able to induce downsizing as much as possible in as many patients as possible. Due to the higher response rate achievable with EGFR antibodies in KRAS wt tumors this treatment option along with the use of FOLFOXIRI should be considered.

• **Group 2:** For the intermediate group, where the treatment aim is rather palliative than curative, (with individual exception e.g. in case of high chemosensitivity and extensive response) most reliable and rapid regression of metastases is important; in particular in case of imminent or present symptoms or tumour associated complications. An escalation strategy (single agent followed by combination) might have the risk that the first line treatment is not effective and switch to more effective second line treatment either will or cannot be performed or might be established too late. Therefore, very active 1° line treatment with a high likelihood to induce metastases regression in short time, seems to be appropriate for most of these patients. However, since for the majority of these patients secondary surgery is not an issue (otherwise they would belong to group 1) maximum downsizing is not aimed at but rather a high likelihood that regression of any dimension will be achieved as soon as possible. Further, the duration of any response, time to progression and overall survival are also relevant.

• **Group 3:** For these patients maximal shrinkage of metastases is not the primary treatment aim. Without present or imminent symptom and limited risk for rapid deterioration, the aim is rather prevention of tumour progression with symptom appearance and prolongation of life with minimal treatment burden. Therefore, an escalation strategy seems to be appropriate, starting with single agent or well tolerated two-drug combination.

### 9.2 Definition of treatment strategy

The optimal strategy should be developed according to the characteristics of the patient and be discussed in the multidisciplinary team and should incorporate the (potential) view of the patient as well.

### 9.3 Selection of drugs

**Chemodoublets:** Available chemotherapeutic agents in the first line treatment are fluoropyrimidines (5-fluorouracil/folinic acid (5FU/FA), preferably given as 24-48 hours infusion biweekly, or oral prodrugs e.g. capecitabine, UFT, S1), irinotecan and oxaliplatin. Capecitabine can safely substitute iv 5FU/FA in combination with oxaliplatin without impairment in terms of progression free survival (PFS) and overall survival (OS) \(^{140-144}\). There are less data for the combination of oral fluoropyrimidines with irinotecan due to early termination of comparative trials \(^{145-147}\). CAPIRI was associated with a high rate (27%) of grade 3/4 diarrhoea in the CAIRO study \(^{148}\). Tolerability of capecitabine and irinotecan improves, if doses are reduced,
without loss of efficacy (cross trial comparison)\textsuperscript{149, 150}. S1 can safely be combined with irinotecan with comparable efficacy vs. FOLFIRI\textsuperscript{151}. However, no data in a non-Asian population with respect to efficacy and toxicity are available yet.

<table>
<thead>
<tr>
<th>group</th>
<th>clinical presentation</th>
<th>treatment aim</th>
<th>treatment intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>clearly R0-resectable liver and/or lung metastases</td>
<td>• cure, decrease risk of relapse</td>
<td>nothing or moderate (FOLFOX)</td>
</tr>
<tr>
<td>1</td>
<td>liver and/or lung metastases only</td>
<td>• maximum tumour shrinkage</td>
<td>upfront most active combination regimen</td>
</tr>
<tr>
<td></td>
<td>which</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• might become resectable after induction chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• limited/localized metastases to other sites, e.g. locoregional lymphnodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• physically able to undergo major surgery (biological age, heart/lung condition)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>multiple metastases/sites, with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• rapid progression and/or</td>
<td>• clinically relevant tumour shrinkage as soon as possible</td>
<td>upfront active combination: at least doublet</td>
</tr>
<tr>
<td></td>
<td>• tumour-related symptoms/risk of rapid deterioration</td>
<td>• at least achieve control of progressive disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• co-morbidity allows intensive treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>multiple metastases/sites, with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• never option for resection</td>
<td>• abrogation of further progression</td>
<td>treatment selection according to disease characteristics and patients preference re toxicity and efficacy:</td>
</tr>
<tr>
<td></td>
<td>• and/or no major symptoms or risk of rapid deterioration</td>
<td>• tumour shrinkage less relevant</td>
<td>• “watchful waiting”</td>
</tr>
<tr>
<td></td>
<td>• and/or severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1+2)</td>
<td>• low toxicity most relevant</td>
<td>• sequential approach: start with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o single agent, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o doublet with low toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• exceptional triplets</td>
</tr>
</tbody>
</table>

**Chemotriplets:** Combining FU, irinotecan and oxaliplatin is a feasible first line option. Several regimens are available e.g. Italian or Greek FOLFOXIRI, French FOLFIRINOX and the Italian alternating POKER regimen\textsuperscript{154-157}. Whereas the Greek FOLFOXIRI showed a non-significant improvement in ORR, PFS, and OS compared to FOLFIRI, the Italian trial proved superior efficacy of the triplet in terms of response and overall survival. Different schedules with capecitabine, irinotecan and oxaliplatin were evaluated in small non-randomized phase II trials displaying similar efficacy and, as expected, decreased tolerability due to diarrhoea\textsuperscript{158-161}. However, based on the current data the Italian FOLFOXIRI-schedule should be the preferred chemotriplet [II, B].

**Combinations with targeted drugs**
- **Bevacizumab:**
Bevacizumab can be combined with single agent 5FU/FA or capecitabine, and all fluoropyrimidine and oxaliplatin or irinotecan combinations. Wherever, bevacizumab increased ORR by 10% when added to the bolus 5FU regimen IFL, with significantly improved PFS and OS, the addition of bevacizumab to fluoropyrimidine and oxaliplatin did not increase response rates. No randomized phase III data are available for FOLFIRI+bevacizumab; thus, the influence of bevacizumab on RR, as well as on PFS and OS in this regimen is not known. Bevacizumab showed different effects with XELOX and FOLFOX, being more effective with XELOX regarding PFS, without difference observed on OS. A bevacizumab-based triplet might therefore not be used in patients requiring tumour shrinkage. Definite information about comparative efficacy of bevacizumab or anti-EGFR combination with chemotherapy will be available from the US Intergroup trial (CALGB/SWOG 80405) and the AIO study KRK-0306. Bevacizumab combinations seem to be equally effective and toxic with bolus, infusional, or oral fluoropyrimidines and no preferred schedule or combination partner can be identified in the absence of comparative trials. Mitomycin did not increase efficacy of capecitabine if given in combination with bevacizumab.

- Cetuximab/Panitumumab:
  Cetuximab in combination with either FOLFIRI or FOLFOX and panitumumab with FOLFOX, increased response rate, particularly in liver limited disease, PFS and OS. Both drugs are active only in KRAS wildtype (wt) tumours. Anti-EGFR antibodies based triplets have therefore an advantage, if a high intensity, and likely induction of a remission is required, as for downsizing of unresectable liver metastases or for a rapid induction of a tumor response. Currently, more data are available in favour of cetuximab in the perioperative setting based on the CRYSTAL subgroup analysis and the CELIM study, but it is likely that both antibodies have similar efficacy.

If cetuximab/panitumumab for KRAS wt tumours is chosen, chemotherapy combination should be carefully selected. Combinations of oxaliplatin with capecitabine or bolus 5FU and cetuximab seem to have no additional benefit and must be avoided. Therefore, either cetuximab or panitumumab should be combined only with FOLFIRI or FOLFOX. However, outside the US, panitumumab is licensed only with FOLFOX for first line treatment.

- Bevacizumab and anti-EGFR antibodies: The double targeting of EGFR and VEGF combined with a chemodoublet showed no benefit but increased toxicity and decreased survival, especially in the KRAS mt population.

- Comparative toxicity of targeted drugs
  Bevacizumab induces moderate but treatable hypertension, increased risk of thrombembolic events and a rare risk of intestinal perforation, but is in general well tolerated and does not add tremendous clinical significant toxicity. Anti-EGFR antibodies induce skin toxicity in various degrees in the majority of patients or rarely acute infusion reactions (cetuximab) and moderate increase of risk of diarrhoea.

New targeted drugs
- Aflibercept: Recent data with aflibercept showed significantly increased response rates, PFS and OS in combination with FOLFIRI in second line, including previous bevacizumab failures; however, data on the response inducing capacity in first line setting are still lacking.
- **Regorafenib** is a dual targeted VEGFR2-TIE2 tyrosine kinase inhibitor, which has shown significant improvement of PFS and OS in third line as single agent compared to placebo.\(^\text{185}\)
- **BIBF 1120** is a pan VEGFR, PDGF and FGF tyrosine kinase inhibitor, which has shown comparative efficacy and toxicity in combination with FOLFOX vs. FOLFOX+bevacizumab in first line treatment.\(^\text{186}\)
- **Cediranib** is a pan VEGFR TK inhibitor, which showed in a large phase III trial with FOLFOX in first line comparable efficacy vs. FOLFOX and bevacizumab; however, quality of life measurements favoured bevacizumab.\(^\text{187}\)

### 9.4 Selection of first line regimen

The selection of the first line regimen depends on the chosen treatment strategy (see table 14). In the absence of conclusive comparative data, options in table 14 should be regarded as proposals rather than as strong recommendations, reflecting the available options and the likelihood of efficacy with respect to the specific treatment aim in the different disease groups. They can be modified according to individual patients situation and experience. The majority of the proposals are not supported by sufficient randomized data but rather by small trials and retrospective subgroup analyses. Reflecting this uncertainty, not 100% consensus regarding strength of bevacizumab based triplet in group 1 and 2 and cetuximab based triplets in group 3 could be achieved. However, the proposal (table 14) was agreed by the majority of participants.

In general; for potentially resectable (group 1) and/or symptomatic disease (group 2) first line treatment should be a triplet, either a chemotherapy doublet with monoclonal antibody or chemotherapy triplet. In group 1, cetuximab/panitumumab based combinations might be preferred over bevacizumab combinations for KRAS wt tumours since response rate seems to be higher [III, B]. If triplets, including chemotriplets, are not available, at least a chemodoublet should be chosen. First line treatment with a fluoropyrimidine alone or with bevacizumab are low toxic valid options for patients, who are not eligible for secondary resection and have no symptoms or risk for rapid deterioration of their disease (group 3).

**Induction chemotherapy for group 1**

- **Chemodoublets**: Combination chemotherapy regimens comprising 5FU/LV in combination with irinotecan, or oxaliplatin or both have been reported to facilitate resection of liver metastases in up to 40% of patients with initially unresectable disease depending upon the initial selection of patients.\(^\text{188-190}\) However, 75%–80% of these patients experience relapse within 2 years.

- **Triplets**: Data emerging from randomized and single arm trials suggest that the addition of a targeted agent (bevacizumab or anti-EGFR-antibody) to a doublet or even to a triplet, might be more effective in liver limited disease,\(^\text{191-194}\) but also FOLFOXIRI resulted in a comparable high R0-resection rate of 36% in liver only patients. The combination of a chemodoublet with anti-EGFR-antibodies has led to high ORR of 75-80% of liver metastasis and higher resection rates accordingly (although still low in absolute numbers) in patients with liver limited unresectable metastatic KRAS wt CRC.\(^\text{169, 170, 172, 175}\) In contrast, the combination of a FU with oxaliplatin and bevacizumab has led to a non-significant trend in an increased resection rate compared with the chemo-backbone alone, although no increase in response rate was shown.\(^\text{195}\)
There are no data available from randomized studies comparing a chemodoublet plus bevacizumab with a chemodoublet plus anti-EGFR-antibodies yet, although in KRAS wt tumours, induction treatment with FOLFIRI/FOLFOX with anti-EGFR-antibodies appears to be more effective in terms of major tumour shrinkage and secondary resectability, than bevacizumab based combinations. FOLFOXIRI could be an alternative to FOLFIRI/FOLFOX combined with anti-EGFR-antibodies, and is the preferred option if targeted drugs, in particular anti-EGFR-antibodies, are not available, and in particular for KRAS mutant tumours [II, B]. Although, very limited data are available and in the absence of prospective randomized comparison, chemotriplet or FOLFIRI/FOLFOX with cetuximab/panitumumab might be the preferred option for KRAS wt tumours [II, B].

**Initial treatment for group 2:**
- Since the treatment aim is not maximal tumour shrinkage, but rather rapid regression and at least improvement of tumour size and therefore symptoms in as much patients as possible, triplets or at least chemodoublets are the first choice, which guarantee the chance of fast and major response. Although the sequential approach with initial single agent FU might be an option for some patients in this group, the factors defining group 2 ask for more active treatment. There is no clear preference for triplets or doublets, which have to be decided individually (depending on tumour symptoms and dynamics, and patient factors), in relation to toxicity [II, B].

**Group 3:**
- An important issue is the choice of an upfront combination versus single agent. A retrospective pooled analysis revealed a correlation between improved survival and the availability of 5FU/LV, oxaliplatin and irinotecan at some point during the course of disease.  
- Several large trials evaluated different sequential approaches, comparing either single agent FU, followed by single agent irinotecan and afterwards FU/oxaliplatin to upfront FU/irinotecan combination, followed by FU/oxaliplatin (CAIRO, FOCUS), or 5FU/LV/capecitabine with or without oxaliplatin (FOCUS 2) followed by irinotecan (LIFE). Although ORR and PFS were improved with upfront combination treatment, OS was similar for both approaches with a non-significant median difference of one month. Comparable results could be shown in an elderly and/or frail population in the FOCUS 2 trial. These data show that upfront single agent fluoropyrimidine does not have a significant negative impact on final outcome, although these studies reported a lower OS (<20 months), as would nowadays be expected (>20 months) at least in a patient population mainly from group 2 and 3. Patient selection may well explain these differences. The combination of FU (iv or orally) plus bevacizumab is an active and well-tolerated therapy, also for the elderly population (AGIT-trial) [II, B], with significant improvement of PFS, but not survival.
- A few participants would recommend FOLFIRI/FOLFOX+EGFR antibody for first line treatment in group 3. However, despite the survival benefit shown with FOLFIRI+cetuximab (CRYSTAL) and supported by the PRIME trial, which was demonstrable in all groups, including group 3, this regimen does not qualify for first line in all group 3 patients since the cross over rate to EGFR inhibitors in
the control arms is far too low (<30%) to draw any conclusions. A full sequential
design with chemodoublet+molecular targeted agent (EGFR and VEGF
inhibitors) in first and further lines is not available, however in selected patients
a triplet with EFGR inhibitors might be indicated.

- Due to the relatively high efficacy seen in a very small trial upfront treatment
with single agent EGFR antibody in KRAS wt patients is an alternative option to
a fluoropyrimidine (NCCN guidelines), however this is more expensive and less
subjectively tolerated due to skin toxicity. It may be an option in patients where
cardiac morbidity contraindicates FU, as an alternative to the standard option
raltitrexed.

- Watchful waiting can be recommended in patients with the following criteria: low
tumour burden, but not eligible for secondary resection; indolent disease,
asymptomatic; patient is fully informed and agrees to this approach; and that
the patient is monitored frequently, noting that the three pivotal trials from the
5FU only era have conflicting outcomes[199,200][II, B].

9.5 Timing for assessment of response

The selected induction chemotherapy for potentially resectable patients should be
evaluated after not more than 6-8 weeks to avoid unnecessary chemotherapy
application in case of early progression. However, if the treatment aim is pure
growth control, the timing of first control investigation is of less importance; an interval of
8-12 weeks might be appropriate, unless clinically indicated [III, B].

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<tr>
<th>group</th>
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<th>Recommend</th>
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<td>1</td>
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<td>• FOLFOX/XELOX+Bev</td>
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<td>+ selected pts. 4)</td>
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<td>+ option for spec. situations 5)</td>
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<td></td>
<td>• triplets (+/-Bev or Cet/Pan)</td>
<td>(+)</td>
<td>• triplets (+/-Bev)</td>
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<td>• selected pts. 4)</td>
<td>(+)</td>
<td>• selected pts. 4)</td>
<td>+ option for spec. situations 5)</td>
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Table 14 Options for first line treatment according to the clinical groups and grading
(defined by the treatment aim, available data and expert recommendation)
1) Rec: consented recommendation, however decision might be modified based on individual objective and subjective parameters
2) FOLFOXIRI: only 2 (small) phase III trials with contradictory results
3) no randomized data for FOL(XEL)IRI + Bev
4) option in case of low tumor burden, asymptomatic, indolent disease: close control until definitive progression (not until symptoms!)
5) Patients who are group 3 but deserve (and tolerate) more intensive treatment due to specific reasons

Treatment duration
The treatment duration is dependent of the treatment aim (table 15).

- **If secondary surgery is attempted:**
  - Induction chemotherapy should be continued until potential resectability might be achieved, ideally at least for 3-4 months, with first evaluation after 6-8 weeks, to evaluate whether the chosen regimen is active at all, if resectability still not achieved, for up to 6 and 8 months. Further treatment (more than 8 months) with the same regimen is not recommended, since it is unlikely that by continuation of the same treatment resectability will be achieved. At this point and, in case of insufficient response within 3-4 month (again judged by the MDT), a switch to alternative chemotherapy could be considered [V, B].
  - **Cumulative liver toxicity** with the risk of perioperative morbidity/mortality and delayed recovery after liver resection will be increased by prolonged treatment duration. However, the potential toxicity of the treatment should be balanced to the potential benefits of achieving a resectable status.

- **If secondary resection cannot be achieved**, as well as in all other pts where resection is not the treatment aim, treatment should be continued according to the individual situation, pts needs, cumulative toxicity (in particular oxaliplatin) and aggressiveness of the disease (for maintenance see 9.7). Whereas in the above mentioned potentially resectable group response is the main treatment aim, PFS, OS, time to failure of strategy, and toxicity are the important outcome measures.

9.6 Surgery after induction treatment

- **Timing of surgery**
  - Surgery can be performed safely when the patient has recovered from chemotherapy, which can be expected 4 weeks after the last cycle of chemotherapy plus or minus cetuximab, and at least 5 weeks following bevacizumab [III, B].
  - Resection of the metastases should be performed as soon as the metastases are resectable, since unnecessary prolonged administration of chemotherapy may lead to higher perioperative morbidity [III, A]. However, perioperative morbidity is more related to the duration of the chemotherapy than to the type of chemotherapy that is administered, although oxaliplatin and irinotecan may cause different histological changes in liver parenchyma: oxaliplatin is related to sinusoidal liver lesions and irinotecan to steatohepatitis.
  - Usually, in chemo-sensitive disease, 50% of surgery is done after 4 months and 80% after 6 months of induction chemotherapy.
• Extent of surgery/additional measures
  o If possible, all tumour lesions should be resected. Additional measures like in situ split, prior portal vein embolization or ligation to enable resection of otherwise non resectable lesions might be used [III, B].
  o If metastases are not resectable due to their location additional measures like radiofrequency ablation or stereotactic body radiotherapy (in specialized institutions) should be considered, although the benefit is not formally proven [III, B].
  o Lesions with complete regression mostly contain residual vital tumour cells. The basic principle is therefore to remove, if possible, all initially involved sites [III, B].

• Role of surgery in disease still unresectable after induction chemotherapy
  In case of insufficient response to induction chemotherapy of liver metastases in dominant liver disease surgical resection should not be performed, since tumour debulking is an inappropriate method to improve survival [IV, E].

9.7 Maintenance / intermittent treatment
• Despite all past and present protocols (as long as maintenance is not the major question of the trial) prescribing treatment until progression, the median treatment duration is only six months indicating that in many patients (about 60-70%) treatment is stopped not due to progression but due to other reasons. This is acceptable as long as the full induction protocol is given again for reinduction (oxaliplatin depending on neurotoxicity level), with an ORR of 27% and further stable disease of 32% at least for oxaliplatin based combination within the COIN trial 24. Therefore, it is mandatory to restart induction (reinduction), if induction was stopped without tumour progression [III, A].
• Survival will be impaired by about 6 weeks if first line combination treatment with all drugs is not given continuously until progression but stopped after 3 months and restarted at progression 24. However, patients with liver limited disease as well as aggressive disease, and poor prognostic features e.g. high platelet count or LDH, more than 2 metastatic sites after 3 months of oxaliplatin containing induction, might have a more substantial loss; for these patients maintenance chemotherapy seems to be definitive preferable 24, 205, 206. In all other patients, induction chemotherapy (without oxaliplatin) might be stopped after 3-4 months until progression; in case of progression the same treatment should be reinstituted if feasible (“stop and go”) [I, B]. However, if complete stop of induction chemotherapy is chosen, accurate selection of patients and close monitoring for progression (not waiting until clinically evident by symptoms) is strongly recommended [II, A].
• An alternative to “stop and go” is the preplanned treatment intervals and break duration (“intermittent treatment”) of one or all drugs resulting in comparable overall outcome in comparison to treatment until progression 24,207-209. However, the two approaches, intermittent and “stop and go”, have not been prospectively compared yet.
• Treatment with oxaliplatin should be stopped before intolerable toxicity occurs, although individual duration of oxaliplatin including repeated applications is solely dependent on the degree of cumulative neurotoxicity and recovery from it. In case of oxaliplatin limiting toxicity, the drug should be stopped; at progression during maintenance with fluoropyrimidine +/- second drug, second
line treatment must be started since oxaliplatin might not be applicable any more.

- **In case of bevacizumab containing first line chemotherapy** for 4-6 months continuation of full induction treatment or maintenance with bevacizumab alone seems to be borderline equivalent in terms of PFS and potentially also survival. However, the outcome of two large randomized trails (AIO0207/CAIRO3) should be awaited before definite conclusions can be drawn. In particular, these data will show the outcome of maintenance with initial combination compared to single agent or no maintenance, all arms including reinduction in case of progression.

- **In case of EGFR inhibitors as part of induction chemotherapy** the best approach is unclear. Standard procedure according to the data from clinical trials is based on continued treatment until progression/toxicity; however median treatment time was 5-6 months. In a recent randomized phase II trial (COIN-B) maintenance with cetuximab after 12 weeks induction with FOLFOX+cetuximab and reinduction of FOLFOX in case of progression showed a favourable trend in terms of failure free survival (defined as stop of strategy due to progressive disease during combination therapy, cumulative toxicity or patients choice) and PFS compared to full stop of treatment and reinduction of FOLFOX+cetuximab in case of progression.

An overview of these options for maintenance is given in table 15.

<table>
<thead>
<tr>
<th><strong>continuously</strong></th>
<th><strong>stop and go approach</strong></th>
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<tbody>
<tr>
<td>maintenance and reinduction</td>
<td>complete stop and reinduction</td>
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<tr>
<td><strong>continue until progression or unacceptable toxicity (standard)</strong></td>
<td><strong>stop at progression</strong></td>
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<td></td>
<td><strong>preplanned intervals</strong></td>
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<td><strong>stop/restart toxic drugs in preplanned intervals (3/4 months on/off) (OPTIMOX 1, CONCePT)</strong></td>
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<td></td>
<td><strong>restart drug at progression (OPTIMOX 2, MACRO, COIN-B)</strong></td>
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<tr>
<td></td>
<td><strong>stop/restart all drugs in preplanned intervals (GISCAD)</strong></td>
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</tbody>
</table>

Table 15: Options for maintenance after induction chemotherapy for 3-4.5-6 months not valid for group 1 or aggressive disease

### 9.8 Second and further line treatment

- In first line treatment patients should be treated as long as possible by restart of the former first line regimen (reinduction), when the toxicity (especially neurotoxicity) allows such reinduction. Second line is defined when the first line chemotherapy backbone has to be changed.

- Second line treatment is dependent on the choice of the first line treatment. However, several agents can and should be used again in second and further lines, despite proven resistance to first line combination (depending on the national registration label). This applies for 5FU and bevacizumab, which seem to act as chemo-sensitizers. 5FU has single agent activity on its own but improves efficacy of oxaliplatin even resistance to 5FU and irinotecan (IFL) occurred; this might be vice versa with FOLFIRI after FOLFOX. Continuation of bevacizumab with changed chemotherapy backbone in second line increase
OS after progression with first line bevacizumab and chemotherapy (press release 01/2012). Therefore, 5FU and bevacizumab could be continued throughout first and second line treatment, and solely irinotecan and oxaliplatin will be exchanged by each other. For EGFR antibodies the situation is unclear, as no trials are available investigating their potential to improve efficacy of the alternative chemo-backbone maintaining EGFR antibody.

- The sequence of salvage treatment figure 7 and 8 is based on the following facts (trial results and registration labels), but the individual situation of the patient including toxicity of last regimen and second line regimen might require individual treatment decisions.
  - After bevacizumab combination chemotherapy, aflibercept and bevacizumab in combination with second line chemotherapy are active with increase in PFS and OS (press release 01/2012) \(^{184}\).
  - Sequence is either FU/oxaliplatin followed by FU/irinotecan or the reverse sequence, which yields similar results in terms of OS \(^{213}\).
  - Second line FOLFOX and bevacizumab is superior in terms of ORR, PFS and OS compared to FOLFOX after failure of FU/irinotecan \(^{214}\).
  - Second line treatment with aflibercept plus FOLFIRI is superior in terms of RR, PFS and OS compared to FOLFIRI after failure of FOLFOX \(^{183,184}\).
  - For KRAS wt patients not previously treated with anti EGFR antibodies, cetuximab with or without irinotecan, panitumumab with or without FOLFIRI are possible options (combination preferred) \(^{215-220}\).
  - In patients being refractory to FU, oxaliplatin, irinotecan, anti EGFR antibodies (only KRAS wt), bevacizumab, and regorafenib, treatment with fluoropyrimidines and mitomycin or reintroduction of oxaliplatin (and irinotecan) results in very limited improvement in some patients treated last line. However, despite poor data this might be justified in some patients [III, B].
  - Last line salvage treatment with regorafenib is superior to placebo in terms of OS \(^{185}\).

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**Figure 7** Course of treatment for upfront single agent or FU and bevacizumab (* only KRAS wt; FU: fluoropyridimines, Iri: irinotecan, Ox: oxaliplatin, Bev: bevacizumab, Afli: aflibercept, Cet: cetuximab, Pan: panitumumab)
figure 8 Course of treatment in case of upfront combination (* only KRAS wt; FU: fluoropyrimidines, Iri: irinotecan, Ox: oxaliplatin, Bev: bevacizumab, Afli: afibbercept, Cet: cetuximab, Pan: panitumumab)
9.9 Supportive measures

9.9.1 Prophylactic antiemetic treatment
In accordance to MASCC/ESMO antiemetic guidelines the following antiemetic prophylaxis is recommended [221].

- **Moderate emetogenic chemotherapy** (e.g. FOLFOX, FOLFIRI, CAPOX, CAPIRI based regimens):
  - acute phase (day 1): 5-HT₃-receptor antagonist (palonosetron is preferred) + dexamethasone 8 mg
  - delayed phase (day 2-3): single agent dexamethasone 8 mg, alternatively 5-HT₃-RA
  - The role of the NK-1-receptor antagonist aprepitan in moderate emetogenic chemotherapy is still controversial and not recommended. However, a NK-1-RA might be beneficial in selected patients [222], in particular if the standard prophylaxis is ineffective.

- **Low emetogenic chemotherapy** (e.g. cetuximab, panitumumab, 5FU):
  - acute phase (day 1): single agent dexamethasone 4-8 mg
  - delayed phase (day 2-3): no prophylaxis

- **Minimal emetogenic chemotherapy** (e.g. bevacizumab):
  - no prophylaxis

With regard to the oral agents (e.g. capecitabine) the antiemetic prophylaxis needs to be individualized, as no randomized study investigated an antiemetic prophylaxis in this setting. However, as capecitabine is low emetogenic, a low dose steroid or a 5-HT₃-RA given prophylactically for 3-4 days might be appropriate. Metoclopramide is not recommended in the current guidelines as a first line agent and should be reserved for patients intolerant of or refractory to a 5-HT₃-RA, dexamethasone or aprepitant.

9.9.2 Dermatotoxicity

- **Hand foot syndrome (HFS)**: HFS is a common toxicity of capecitabine containing chemotherapy. Pyridoxin or urea/lactic acid-based topical keratolytic agents have not shown any activity in preventing HFS [223, 224] [II, E]. Celecoxib was superior to placebo for the prevention of HFS in a phase II study but it cannot be recommended as standard prophylaxis yet [225] [II, C]. However, prophylactic basic skin care should be applied.

EGFR-inhibitor induced skin reactions: Dermatologic toxic effects are the subjective and objective most relevant and common side effects of EGFR inhibitor therapy (> 80%). Prophylactic basic skin care (skin moisturizer, sun protection) combined with a specific therapy adapted to the grade of skin reaction is recommended [II, B]. Prophylactic treatment with systemic antibiotics (e.g. tetracyclines) lowers the incidence of severe skin reactions and might thus be considered [226] [II, B]. If not prophylactically given, systemic antibiotics (tetracyclines doxycycline or minocycline) is recommended when grade ≥ 2 skin reactions occur. Topical antibiotics such as metronidazole, erythromycin or nadifloxacin are helpful if given at the early onset of skin reactions [227] [II, B]. The use of topical steroids is still controversial [III, C].
9.9.3 Oxaliplatin induced neurotoxicity

Chronic peripheral sensory neuropathy is cumulative and grade 3 toxicity occurs in 10-20% of patients receiving oxaliplatin doses of 750-850 mg/m², increasing with higher cumulative doses.228

Prophylactic measures: In a recent Cochrane Review none of the potential chemoprotective agents (acetylcysteine, amifostine, calcium and magnesium CaMg, glutathione, Org 2766, oxycarbazepine, diethyldithiocarbamate or Vitamin E) prevent or limit the neurotoxicity.229 However, recent trials have shown a protective effect without loss of efficacy of oxaliplatin-combination by CaMg infusion.209, 230 These data favour the use of CaMg as neuroprotectant, although being not very effective [II, B]. In addition, a tumour protective effect cannot be ruled out, also not very likely from the current data.

9.9.4 Chemotherapy induced Diarrhoea (CID)

CID is a common problem with a frequency of 50-80% (≥ 30% CTC grade 3-5), especially with 5FU bolus or combination of irinotecan and FU (IFL, XELIRI, IRIS). So far, only loperamide, octreotide and tinctura opii are recommended in the guidelines by the consensus conference on the management of CID.231 [II, B].

9.9.5 Prophylaxis of febrile neutropenia

The risk of febrile neutropenia for oxaliplatin and irinotecan based chemotherapy is < 20%, unless additional risk factors as defined in the actual EORTC guideline are present.232 A routine prophylaxis with G-CSF and antibiotics is therefore not indicated, only in patients with high risk of severe infection in case of (prolonged) neutropenia [III, A].

9.10 Management of peritoneal disease / ascites

Peritoneal carcinomatosis/ascites as single lesion in advanced colorectal cancer represents a special biologic entity with poor prognosis under systemic chemotherapy alone. Published data including one randomized controlled trial and numerous prospective and retrospective studies suggest a role of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) within the multimodal treatment regimen and may improve PFS as well as OS for selected patients with peritoneal carcinomatosis.233 The procedure can be performed with acceptable morbidity and low mortality in specialized centres. Nevertheless, preoperative patient selection is crucial for the success of the combined treatment concept. Main selection criteria are good general health status, limited intraperitoneal tumour dissemination (Peritoneal Cancer Index, PCI < 20), limited small bowel disease, and no extraabdominal metastasis. Localization and histology of the primary tumour, lymph node status and response to systemic chemotherapy should be taken into account.

CRS and HIPEC in patients with exclusive peritoneal carcinomatosis without ascites is effective, particular in patients with limited peritoneal disease. Phase III trials are ongoing and treatment within these trials is mandatory. Out of, and before having the results of these trials this treatment modality is still experimental and should only be considered for selected patients (low PCI, complete resection achievable) [III, B].

10 Follow up

- Patients’ follow up depends on stage, perioperative treatment, and amenability for resection of recurrent disease. The intensity of follow-up is subject to great
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Importantly, patients should be motivated for optimization of lifestyle (maintain healthy weight, physical activity, cessation of smoking, moderate alcohol use, healthy diet adoption).

- Accepted are 3-monthly clinical visits for the first three years, followed by every six month for further two years, with clinical examination, evaluation of long term toxicities (neuropathy after oxaliplatin), and CEA testing (in patients possibly amenable to resection at locoregional, hepatic or pulmonary recurrence).
- Complete colonoscopy must be performed at initial diagnosis, then every five years, providing there are no findings.
- In patients with high-risk disease, CT scan of the chest and abdomen every 6-12 months could be considered, although such close follow up should be confined to patients possibly amenable to resection of hepatic or pulmonary recurrence.
- CEUS could substitute for abdominal CT scan regarding diagnosis of liver metastases.
- As 80% of all metastases occur in the liver 3-6 monthly ultrasound might be applied.
- A potential surveillance schedule is shown in table 16 based on ASCO and European guidelines, noting that the 12 monthly scanning would be more typical in stage II and III surveillance. 6 monthly scanning for resected stage IV disease is a more pragmatic approach based on higher risk of recurrence. However, this intensive follow-up does not have any support in the literature to improve overall survival. A valid approach, used in some European countries is to assess the patient after 1 and 3 years with imaging of the lungs and liver together with CEA [IV, B].

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Table 16 surveillance schedule for colorectal cancer (months after surgery/adjuvant treatment)

- Patients receiving local excision of rectal cancer should be closely monitored for local recurrence with digital rectal examination and sigmoidoscopy every three/six months for the first three years, afterwards every six/twelve months for two years. Surveillance for multimodal treated rectal cancers should continue beyond five years, as perioperative treatment might delay recurrence beyond this point in time [III, B].
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Conflict of Interest:

HJ Schmoll declares no conflict of interest. He is advisor with honorarium of Roche and Merck.
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