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ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making

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Colorectal cancer (CRC) is the most common tumour type in both sexes combined in Western countries. Although screening programmes including the implementation of faecal occult blood test 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 CRC must be a multi-modal approach performed by an experienced multi-disciplinary 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 a 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 commonly diagnosed cancer in Europe and one of the leading causes of cancer death

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worldwide [1, 2]. 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 and a selected treatment approach based on tumour–node–metastasis (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 multi-modal 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 insights 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 on translating all data into a standard clinical practice guideline. The multi-disciplinary ESMO consensus conference, held in Lugano 23.09.2010 to 25.09.2010, assembled 37 experts from all the disciplines involved from most countries and regions worldwide. All the available literature (including abstracts and full papers) regarding diagnosis, staging and treatment was reviewed, 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 the consensus achieved by the panel. These were further developed after the meeting. Levels of evidence (Table 1) 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 [3]. 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.

2 Epidemiology

In 2008, 436,000 new cases of CRC were diagnosed in Europe, thus being the most common cancer with 13.6% of all diagnosed cancer [1]. Worldwide 1.23 million cases of CRC were responsible for 9.7% of the total cancer burden, after lung (1.61 million) and breast cancer (1.38 million) [4]. 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 [5, 6].

Table 1. Level of evidence and strength of recommendation given in square brackets in the text according to [3]

Level of evidence	
I	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
II	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
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports and experts opinions
Grade of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

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 at 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 on an altered molecular screening [microsatellite instability (MSI) and/or immunohistochemistry (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 the results of molecular screening (MSI and/or IHC of MMR). If a

Table 2. Management of hereditary colorectal cancer

Syndrome	Diagnosis of index case (with cancer)			Management of the affected individual (with cancer)		Management of individuals at high risk (healthy mutation carriers or individuals at 50% risk of being mutation carrier)		
	Clinical	Molecular screening (tumour tissue)	Germline genetic testing (blood)	Treatment	Follow-up	Cancer risk	Surveillance	Germline genetic testing (blood)
Lynch	Amsterdam, Bethesda	MSI and/or IHC for MMR proteins	MLH1, MSH2 MSH6, PMS2	• Tumour resection • Discuss colectomy, especially in young patients	Yearly endoscopy of the remnant colon or rectum	High	• Colonoscopy q 1–2 years, starting age 25 (30 years in case of MSH6 or PMS2 mutations) • Annual pelvic examinations, transvaginal ultrasound, ca125, endometrial biopsy in females, starting age 30–35 years	Direct genetic testing of the mutation identified in the family
Familial CRC X	Amsterdam, Bethesda	No MMR deficiency	Unknown	As average population	As average population	Moderate only CRC	• Colonoscopy 1 3–5 years, starting 5–10 years before youngest case in the family.	None
FAP	Colonoscopy: >100 adenomas	none	APC	• Total or subtotal colectomy when adenomas occur • Endoscopic removal of duodenal adenomas	• After subtotal colectomy: rectal examination q 6–12 m • After total colectomy: pouch exam. q 1–2 years • Duodenoscopy from 6 months to 5 years according to Spigelman stage • Thyroid examination yearly	100%	• Flexible sigmoidoscopy q 2 years, starting age 12–14 years until diagnosis of adenomas • If no mutation identified in the family: Flexible sigmoidoscopy q 2 years until 40 years, then q 3–5 years until 50, then general population screening	APC
Attenuated FAP (aFAP)	Colonoscopy: a) 2 relatives 10–99 adenomas (>30 years of age) b) 1 relative of CRC patient with 10–99 adenomas (>30 years of age)		APC	• Total or subtotal colectomy when adenomas occur. • Endoscopic removal of duodenal adenomas	As above	High	• Colonoscopy q 2 years, starting age 18–20 years, lifelong in mutation carriers.	APC
MAP	As aFAP		MUTYH	As aFAP	As aFAP	High	As aFAP	MUTYH

APC, adenomatous-polyposis-coli; MSI, microsatellite instability; MMR, mismatch repair proteins; CRC, colorectal cancer; FAP, familial adenomatous polyposis; aFAP, attenuated FAP; MAP, MUTYH-associated polyposis.

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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 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 of 20–25 years and should be repeated every 1–2 years [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 years. Again, no specific upper limit is established [II, A].

Endometrial and ovarian cancer screening may be performed on 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 on the basis of 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 [7] [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 for 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 gynecological cancer should also be discussed. Chemotherapy regimens are the same as those for sporadic CRC.

3.2 Familial colorectal cancer × 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 extra-colonic cancers is not recommended.

3.3 FAP

Clinical diagnosis of classical familial adenomatous polyposis (FAP) is based on the identification of >100 colorectal adenomas. Lifetime risk of 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 adenomatous-polyposis-coli (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 and 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 extra-colonic manifestations

It should start when colorectal polyposis is diagnosed or at the age of 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 desmoid tumours [V, C]. Screening for other extra-colonic 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

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.

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 focussing 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 (Tables 3–6), some of which 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 characteristics (performance status (PS), 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 7). The relevance of molecular and genetic markers emerge, with status of high-frequency microsatellite instability (MSI-H) or mismatch repair

Table 3. Established poor prognostic factors in early CRC

Group	Factors for poor prognosis
Clinical/ pathological	T4
	N+ after preoperative chemoradiation (rectal)
	CRM involvement (rectal)
	Obstruction/perforation
	Rupture during surgery
	Less than 12 analysed (retrieved) lymph nodes (and ratio)
	Vascular (venous/lymphatic) and perineural invasion (V1, L1, PN1)
	Poor differentiation (G3/4)
Molecular/genetic	MSI-H/dMMR

CRM, circumferential resection margins; MSI-H, high-frequency microsatellite instability; dMMR, mismatch repair deficiency.

Table 4. Potential prognostic factors in early CRC

Group	Factor
Patient-related	Age (>60 years)
	N2
	Appropriateness of the pathology report
	Lymphocytes infiltration
	Tumour budding
	Tumour type
	Sentinel lymph node
Center-related	Low volume/less experience
Molecular/genetic	KRAS mutation
	TS positivity (>25% of cells)
	18qLOH
	p53 (high)
	SMAD4 (any loss)
	Multi-gene signatures

TS, thymidylate synthase.

Table 5. Established poor prognostic factors in advanced CRC

Group	Factors for poor prognosis
Patient-related	Performance status ≥2
	(biologic) age ≥70 years
Biochemical	CEA >50 μg/l
	Alkaline phosphatase ≥300 U/l
	Platelets $\geq 400 \times 10^9$/l
	Haemoglobin <11 g/dl
	White blood cell count $\geq 10 \times 10^9$/l
	High LDH
	Low serum albumin
Molecular/genetic	BRAF mutation

CRC, colorectal cancer; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase.

Table 6. Potential prognostic factors in advanced CRC

Group	Factor
Patient-related	Presence of severe co-morbidities
	High socio-economic status
Tumour-related	Symptomatic disease
	Metastatic sites
	• Liver ± lung only versus multiple sites/organs
	• Peritoneal involvement
	Previous adjuvant treatment with oxaliplatin
	Early relapse after adjuvant therapy (<6 months)
	Previous lines of treatment
Center-related	Low volume/less experience
	Deviation from standard clinical practise
Molecular/genetic	MSI-H
	EGFR (IHC)
	KRAS mutation
Treatment-related	Skin rash during treatment with EGFR-mAB

CRC, colorectal cancer; MSI-H, high-frequency microsatellite instability; EGFR, epithelial growth factor receptor.

deficiency (dMMR) and KRAS-Codon 12 or G13D or BRAF mutation gaining importance in determination of prognosis for early and advanced CRC [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].

4.1 Early CRC

- 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 (OS) in PETACC 3 (particularly in patients with MSI-L 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 with wild-type (wt), but not in PETACC 3.
- MSI is caused by either (sporadic) somatic tumour MLH1 promoter methylation or germline MMR gene mutations. BRAF mutation (V600E) is associated with MLH1 promoter methylation status and might thus be useful for prediction of germline MMR mutations [21].
- BRAF status seems to influence the generally favourable prognosis of MSI-H/dMMR patients, dividing this group into a good [BRAF wild-type (wt)] and an intermediate (BRAF mutant) prognosis group [22].
- 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 frontline studies ongoing, none of these signatures is ready for routine clinical use, and further validation studies are needed [23–25].

Table 7. Predictive factors in advanced CRC

Group	Factor
Tumour-related	Symptomatic peritoneal carcinomatosis
	Multiple sites of metastases/ very extensive disease
Centre-related	Deviation from standard clinical practise
Biochemical	Efficacy after start of treatment
	• CEA flare and drop
	For toxicity of chemotherapy
	• Creatinine clearance <30 ml/min for capecitabine
	• Bilirubin >3 ULN for irinotecan
Molecular/genetic	For treatment with EGFR-mAB
	• KRAS mutation
	For chemotherapy toxicity
	• UGT1A1*28 genotype for irinotecan
	• DPD deficiency for fluoropyrimidines

DPD, dihydropyrimidine dehydrogenase.

Table 8. Potential predictive factors in advanced CRC

Group	Factor
Patient-related	Performance status >1
	Efficacy after start of treatment
	Hand foot syndrome for capecitabine efficacy
	Hypertension for anti-VEGF-mAB efficacy
	For bevacizumab-related toxicity
	Cardiovascular disease/arterial thrombembolism
Molecular/ genetic	Predictive for chemoradiation in localized rectal cancer
	High TS
	Low EGFR
	TS polymorphism *3/*3 or *3/*4 (less benefit from CRT, than *2/*2, *2/*3, or *2/*4)
	For treatment with EGFR-mAB
	BRAF mutation
	Ligands: amphiregulin and epiregulin levels
	PI3K (exon 20 versus exon 9) mutation
	PTEN mutation
	NRAS mutation
	For treatment with bevacizumab
	VEGF >98 pg/ml
	bFGF, HGF, PlGF increase before progression under Bevacizumab (+chemotherapy)
	For chemotherapy toxicity or efficacy
	High ERCC1 for oxaliplatin
	High TOPO 1 for irinotecan ± oxaliplatin

VEGF, vascular endothelial growth factor; TS, thymidylate synthase; EGFR, epithelial growth factor receptor; CRT, chemoradiation.

4.2 Advanced CRC

- Elevated alkaline phosphatase (ALP) or leucocytes, low serum albumin, more than one tumour site, poor PS [8], high platelet count [26] and elevated lactate dehydrogenase (LDH) are indicators of poor prognosis.
- BRAF-mutation indicates worse prognosis. The prognostic value of KRAS mutations is not completely elucidated yet with conflicting results [27–30].

5 Predictive factors

Despite the numerous potential markers for prediction published (Tables 7–8), 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 7) 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 5-fluorouracil (5-FU) in patients with stage II MSI-H/dMMR tumours, what could not be confirmed by recent analyses from randomized trials (PETACC 3, QUASAR) [18, 31–33]. The discordance of the data might be due to insufficient analyses of the patients with respect to germline versus sporadic MMR defects [17]. Data on the predictive effect of MSI on efficacy of irinotecan are equivocal as well [31, 34].

5.2 Predictive factors for advanced CRC

Predictive markers for advanced CRC are summarized in Tables 7 and 8.

Epithelial growth factor receptor (EGFR) inhibitors

- *KRAS* mutation precludes efficacy of treatment with anti-epithelial growth factor receptor (EGFR) antibodies and KRAS status determination is therefore mandatory before treatment [35] [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 EGFR antibody treatment in KRAS mutant patients [36–38], although data are conflicting [39] [IV, C].
- *BRAF* mutation (8% of *KRAS* wt patients) seems to predict lack of benefit from treatment with EGFR antibodies [28, 39–41], whereas analyses of CRYSTAL/OPUS suggested some benefit [42].
- *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 inhibitors

- There is no predictive marker for bevacizumab yet [IV, C]. The efficacy of bevacizumab does not depend on the KRAS or BRAF mutational status, soluble vascular endothelial growth factor receptor (sVEGFR) or plasma VEGF levels [43, 44], whereas VEGF D in tumour tissue at baseline might be a potentially useful marker in the future [45]. 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, if reproduced, these are not predictive but only progression-associated markers [46, 47].

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 [48, 49] [IV, C].
- Excision repair cross-complementing gene 1 (*ERCC1*) polymorphisms, thymidine phosphorylase, or thymidylate synthase (TS) expression are associated with the efficacy of oxaliplatin or 5-FU; however, for clinical routine these factors are not used for treatment selection (trials ongoing) [48, 50, 51] [IV, C].

5.3 Predictive factors for toxicity

- *Dihydropyrimidine dehydrogenase (DPD) deficiency:* despite the risk of severe potential lethal toxicity under therapy with fluoropyrimidine (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 administration of 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/m^2) but of less importance when it is administered at lower doses (125–180 mg/m^2).

6 Rectal cancer

6.1 Diagnosis and staging of rectal cancer

Physical examination, family history of CRC, polyps and other cancers, and carcinoembryonic antigen (CEA) should be obtained. Full colonoscopy has to be performed either at diagnosis preoperatively or postoperatively in case of obstructing tumours 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)/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 15 cm (Table 9). According to the methodology used (rigid versus flexible endoscopy) the measurements are different. Definition for low versus mid/high with rigid

proctoscopy is accurate and more reliable than for 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 important only if it is relevant to the treatment strategy, in particular to low rectal tumours as well as high (separation from colosigmoid cancer) (Table 9).

MRI is the recommended modality for initial staging (III, A), because it is highly accurate for definition of localization, and for determining the total extension, and the relationship of the tumour to the peritoneal reflection (Table 10). However, the stage-specific management is always based on the best available staging method.

6.1.2 Definition of clinical T stage

- Sub-classification of T1 cancers is based upon depth of invasion into the sub-mucosal 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].
- ERUS 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].
- ERUS and MRI often fail in the differentiation between T2 and borderline T3, mainly because of 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 millimeters to define the T3 subgroups.
- MRI may help in defining T3 subgroups, and is superior to multi-detector 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].

Table 9. Measurement of rectal cancer with respect to reference level and method

Location	Rigid proctoscopy	Flexible endoscopy	MRI
Low	Up to 5 cm	Up to 5 cm	Up to 4 cm
Mid	From >5 to 10 cm	From >5 to 10 cm	From >4 to 8 cm
High	From >10 up to 15 cm	From >10 up to 15 cm	From >8 up to 12 cm
Reference level	Anal verge	Anal verge	Anorectal junction

6.1.3 Mesorectal fascia involvement/potential circumferential resection margins

- 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 be defined only 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 [52].
- 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.

Table 10. Diagnostic procedures for staging of the primary tumour in rectal cancer

Parameter		Method of choice		
		First choice	Equivalent (if first choice is not available)	Second choice
Location (distance from anal verge/anorectal junction)		MRI	Rigid proctoscopy	Flexible endoscopy
T stage	T1	ERUS		
	T2	MRI	ERUS	
	T3	MRI	ERUS	
	T4	MRI	(ERUS low rectum)	MDCT (high and mid rectum)
Sphincter infiltration		MRI	ERUS	
MRF involvement		MRI	MDCT (high and mid rectum)	
N stage		MRI	MDCT or ERUS	

Attention should be paid to recognize an adenocarcinoma of the anal canal when the infiltration is more towards the anal canal than towards the rectal wall. These are however very rare, and treated in the same way as a very low rectal cancer.
ERUS, endorectal ultrasound; MDCT, multidetector CT.

- 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 >8 mm 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 an N+ patient, but only when nodes are visualized that have specific imaging features such as large nodes with size ≥ 8 mm/ round shape/ heterogeneous aspect/irregular border [III, A].
- If nodes ≥ 8 mm with the specific imaging features are absent and only smaller nodes are visible, imaging becomes less accurate, regardless of the 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, the sensitivity and the specificity of ERUS, MDCT and MRI for the prediction of nodal metastases in rectal cancer have been shown to be 67% and 78% for ERUS, 55% and 74% for CT and 66% and 76% for MRI, respectively [53].
- Whereas all imaging methods are not accurate enough to predict lymph node positivity, only ERUS-guided fine needle aspiration has an accuracy of up to 100% in single centre studies [IV, B]; however it is a rarely used technique that has not gained widespread acceptance.
- [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG–PET) is not helpful in substituting or improving 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 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 be performed only 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 useful only if it alters treatment. It should not be performed before 4–6 weeks after chemoradiation therapy (CRT).
- Diffusion-weighted MRI is more sensitive than MRI only for prediction of a pathological complete response (pCR) [54–56].
- The role of FDG–PET CT is under investigation. Combination of FDG–PET and MRI might be more reliable for predicting pathological response [57]. 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) [58]: Level of resection at the muscularis propria (formerly incomplete, poor) versus at the mesorectal fat (formerly nearly complete, moderate) versus at the MRF (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 sub-mucosa/perforation versus in the sphincter region versus in the region beyond the sphincters.
- Careful macroscopic evaluation of the specimen is necessary. For recording 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 <3 mm from the margin. Other blocks should be taken to include at least five 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. The number of lymph nodes needed to accurately stage preoperatively treated cases is unknown [IV, A].

6.1.7.2 Circumferential resection margin.
- The most important resection margin for rectal cancer is the CRM, which is created by the surgeon ideally along the MRF unless the tumour involves or grows within 1 mm from the fascia. There is an increased risk of 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 ≤1 mm from the 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 expressed 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. 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 the classification of CRC. While 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 [59]. In the following text regarding rectal cancer the T classification according to the TNM version 5 is used.

6.1.7.4 Tumour regression grading. Tumour regression grading (TRG) after preoperative treatment 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 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 five 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 multi-disciplinary team (MDT)—before treatment is started.
- Patients should be classified according to clinical stage TNM, involvement of MRF, 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:
  - very early: cT1 sm1/2
  - early: >cT1 sm2-cT2, cT3a/b MRF− N0 in the upper/middle rectum
  - intermediate: >cT3b MRF−, cT4 with limited levator only in the upper/middle rectum or ≥cT3a/b MRF− N0 in the lower rectum
  - locally advanced: cT3 MRF+, cT4, positive lateral lymph nodes
  - synchronous metastases
- All the following guidelines are related to tumours of low and mid location up to a 10 cm 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 of 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 5 × 5 Gy followed by immediate surgery
- long course radiotherapy with 50.4 Gy in 25–28 fractions, with surgery after a 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 is a special form of local boost, but still experimental.

Volumes to irradiate (clinical target volume)
- 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

Table 11. Chemotherapy options and doses for concomitant chemotherapy during pre- or postoperative radiation

Regimen	References
5-FU 325–350 mg/m^2 + LV 20 mg/m^2 i.v. bolus, day 1–5, weeks 1 and 5	[69, 84]
5-FU 400 mg/m^2 + LV 100 mg i.v. bolus, d 1, 2, 11, 12, 21, 22	[237]
5-FU 225 mg/m^2 i.v. continuous infusion, 5 days per week	[61, 79]
5-FU 1000 mg/m^2 i.v. continuous infusion, day 1–5, weeks 1 and 5	[68]
Capecitabine 800–825 mg/m^2 bid po, day 1–5, together with radiation or continously until end of radiation	[60–62]
UFT (300–350 mg/m^2/day) and LV (22.5–90 mg/day) po continuously, 5(−7) days per week, together with radiotherapy	[238–241]
Only preoperatively (no standard): 5-FU 250 mg/m^2 i.v. continuous infusion on days 1–14 and 22–35 and oxaliplatin 50 mg/m^2 i.v. day 1, 8, 22 and 29	[64]

UFT, uracil–tegafur.

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 be included only 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 be included only 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 other than those described earlier.

6.2.2.2 Chemoradiation. 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 5-FU given preferably as prolonged continuous infusion (likely better than bolus) or oral 5-FU prodrugs [capecitabine or uracil–tegafur (UFT)] [II, A]. Chemotherapy options and doses for concomitant chemo are given in Table 11.
- Role of capecitabine versus i.v. 5-FU: The NSABP R-04 trial and an Arbeitsgemeinschaft Internistische Onkologie-(AIO) trial showed that 5-FU and capecitabine are equivalent (proven non-inferiority) [60, 61]. Therefore, capecitabine can be considered an alternative option to 5-FU, 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 5-FU/oxaliplatin or capecitabine/oxaliplatin, local complete pathological response (pCR) was not increased compared with FU alone in the STAR-01, ACCORD 12/0405-Prodige 2, and NSABP R-04 [61–63]. Only in the German CAO/ARO/AIO-04 a significant increase in pCR rate of 4.5% was shown [64]. However, local control does not seem to be a surrogate for survival, as recently shown [65]. 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) has produced interesting, but conflicting results and is still being investigated. Out of clinical trials targeted drugs should not be used in combination with radiation.

6.2.2.3 Choice of preoperative treatment - 5×5 Gy or chemoradiation.
- Treatment options are radiotherapy alone, either short or long course, and CRT. The advantage of short-course radiation is the short preoperative treatment phase in comparison with 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 of downsizing including more pathological complete remissions, improved resectability, potentially maintaining bowel/-sphincter function in case of low located tumours, reduced risk of local relapse and improved long-term survival [66, 67] [II, A]. Therefore,
  - short-course radiotherapy and CRT are equivalent in those tumours where 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), CRT is mandatory.

6.2.2.4 Pre- versus postoperative chemoradiation. It has been shown, that preoperative CRT followed by adjuvant chemotherapy compared with postoperative adjuvant CRT significantly reduces local recurrence rates, has less acute

and long-term toxicity and in addition enables a higher rate of sphincter saving surgery by downsizing and thus improves functional outcome in low located tumours [68–70]. However, distant relapse rate and OS are similar for both approaches [I, A].

6.2.2.5 Intensive chemotherapy before definitive local treatment. Intensive and prolonged chemotherapy ± followed by preoperative CRT, 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 CRT and subsequent surgery is currently investigated [71–74]. 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 CRT, achieved in one trial a pCR of 27% [75]. 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 >10 cm from the anal verge. Whereas tumour stage ≤T4a in the upper third (>10 cm measured from the anal verge) is treated like colosigmoid cancer, large tumours with extension to the adjacent structures or peritoneal reflection need preoperative CRT. Intensive chemotherapy might be an option, which however has not yet systematically been proved [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 colo-rectal or colo-anal anastomoses.

- For very early stages (cT1 sm1/2) a local excision can be performed. Local excision should go through the muscular layer. The transanal endoscopic microsurgery (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 is adequate for rectal cancer localized in the upper third of the rectum (>10–15 cm from anal verge) because of 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, continuing 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 with 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 (5 × 5 Gy) 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 CRT 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 complete response (cCR) after preoperative radio(chemo)therapy.

- If cCR 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 [76]. This can be calculated from the nomograms by Valentini et al. on the basis of staging and treatment factors [67] [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. CRT or radiation with prolonged interval downsizes the tumour; currently, the question whether by increasing the chance of sphincter preservation after good response to preoperative treatment does not increases the risk of local relapse, cannot be answered presently. This approach is currently performed routinely in experienced centres in some countries [77].

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. The interval between the last chemotherapy and operation should be 5–6 weeks; in case of surgery during adjuvant treatment (e.g. urgent patient request), the 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 plus adjuvant chemotherapy.

- Patients with indication to CRT (Table 14) 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+) [78–82] [I, A]
- Postoperative treatment should be administered for a total of 6 months containing chemotherapy with either capecitabine or 5-FU (bolus or continuous infusion) and concomitant radiotherapy (e.g. 50 Gy, 1.8–2.0 Gy/fraction) either at the beginning or during the third and fourth cycle [I, B]. During radiotherapy either 5-FU preferably as continuous infusion or capecitabine should be given [I, A]. Postoperative radiotherapy as single adjuvant modality without concomitant 5-FU is obsolete [I, E].
- The main advantage of the postoperative as compared with the preoperative approach is the better selection of the patients on the basis of pathologic staging; the 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% versus 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 [80] [II, B].
- After local excision of pT1 tumour with adverse factors (involved margins, poor differentiation, sm3 and lymphovascular invasion) or pT2 the risk of local recurrence is high. In case of refusal or no susceptibility for required radical surgery after endorectal local excision, patients should receive postoperative CRT [IV, B].

6.2.4.2 Postoperative (adjuvant) chemotherapy (Table 12).
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 [83–86].

- In case of upfront surgery with or without postoperative radiation, adjuvant 5-FU-based chemotherapy reduced distant failure and improved survival [79, 81, 82] which is consistent with the results of the QUASAR trial rectal cancer subgroup, showing a significant superiority of ~50% reduction for any recurrence in rectal cancer patients in the first 2 years after randomization for adjuvant 5-FU (stage III hazard ratio (HR): 0.44 (99% confidence interval (CI) (0.18–1.06), stage II HR: 0.57 (0.34–0.97)) and a trend for OS (stage II HR: 0.80 (0.54–1.19) [85]) [I, A]. Further subgroup analyses indicated that the benefit was independent of administration of pre- or postoperative radiotherapy, although significance level was not reached because of the small number of patients [87].
- In case of upfront CRT or radiotherapy (in the more recent trials), no significant benefit for adjuvant chemotherapy was demonstrated in the European Organisation for Research and Treatment of Cancer (EORTC) or Italian trial [86, 88]. Current pooled analysis of 2795 treated patients (EORTC, Fédération Francophone de la Cancérologie Digestive (FFCD), Chirurgische Arbeitsgemeinschaft für Onkologie (CAO), Arbeitsgemeinschaft Radiologische Onkologie (ARO), Polish, and Italian trials) with 1572 patients receiving adjuvant treatment indicated significantly increased OS with adjuvant 5-FU ($P < 0.001$) [67]. This is in contrast to the lack of benefit shown in a systematic review of all trials, using published study results [89]. The older trials, although confounded by additional postoperative radiotherapy, indicated significant survival improvement for adjuvant chemotherapy. Whether this effect will be influenced by improved locoregional control is questionable [90]. Although the role of adjuvant chemotherapy after preoperative radiotherapy with or without chemotherapy is controversial and formally not proven, the available data from the postoperative CRT era and the perioperative management era together lead to the overall conclusion that postoperative chemotherapy should be administered if adjuvant treatment is indicated (stage II/III).
- A definite answer from a phase III trial as in colon cancer will not be achieved, since all ongoing or closed trials use single-agent 5-FU 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 CRT 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 5-FU/LV or capecitabine or FOLFOX. The ongoing Intergroup trial which compares

Table 12. Standard adjuvant chemotherapy regimens in rectal cancer (number of cycles without chemoradiation are given in brackets)

Regimen	Cycles	
5-FU 350–370 mg/m^2 + LV 20–25 mg/m^2 i.v. bolus, day 1–5, q 4 weeks	4 (−6)	[84, 85]
5-FU 500 mg/m^2 i.v. continuous infusion, day 1–5, q 4 weeks	4	[68]
5-FU 500 mg/m^2 + LV 100 mg, i.v. Bolus day 1 and 2, q 2 weeks	8	[237]
Capecitabine 2000–2500 mg/m^2 po day 1–14, q 3 weeks	5–6 (−8)	[60, 102]

5-FU/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) vs adjuvant SFU. 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, i.v. or orally, with or without oxaliplatin (based on data from colon cancer) for stage III and stage II (preoperative clinical staging) [V, C]. Standard treatment options are given in Table 12.
- Exceptions from adjuvant treatment: Retrospective subgroup analyses suggest that certain patients might not require adjuvant treatment, because of 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 contrast to responders in a subgroup analysis of the EORTC trial [88].
- 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 [67].

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 after 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

The total duration of perioperative treatment should be 5.5–6 months. If preoperative CRT was given, adjuvant chemotherapy for 4–4.5 months should be administered. If no preoperative treatment was performed, adjuvant chemotherapy with or without radiation should be administered for 5.5–6 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 aforementioned clinical groups could be used. The treatment is summarized in the algorithm depicted in Figure 1 and Table 13 for localized and Figures 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 endoscopic microsurgery (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. Alternative 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 CRT 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 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
  - 5 × 5 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 i.v. FU has to be administered, followed by surgery. In case of concomitant morbidity prohibiting CRT, short-course radiotherapy with delayed surgery might be considered, although this approach is still under clinical investigation.

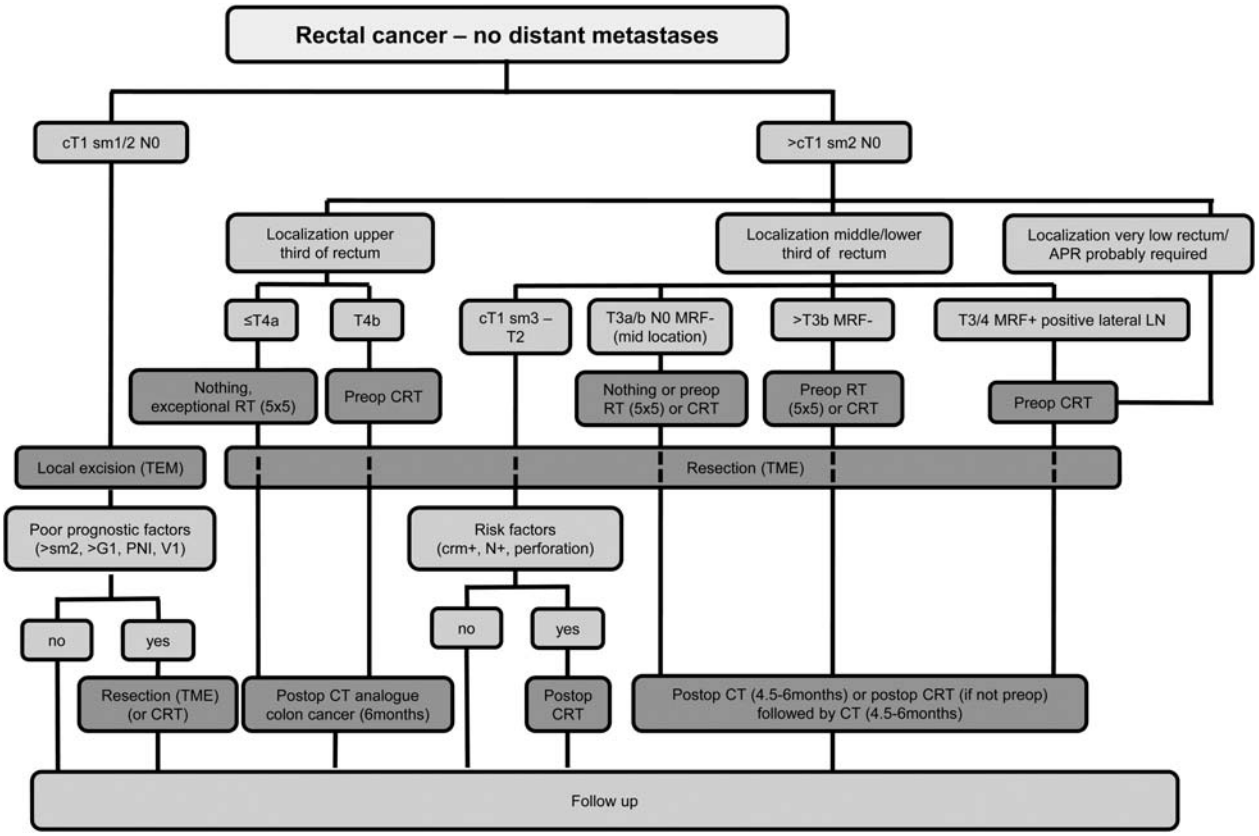

Figure 1. Treatment algorithm for localized rectal cancer. (Lateral LN: drainage of the a rectalis media (if present) or along the obturatorius or internal iliac vessels).

6.3 Management of primary tumour in synchronous metastatic rectal cancer

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

R0 resectable liver ± lung metastases (group 0, see Table 17)

- *For initially R0 resectable metastatic disease*, irrespective of primary tumour, perioperative chemotherapy (3 months pre- and postoperative FOLFOX) should be applied analogous to the EORTC 40983 trial [91] [II, B].
- *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 17)

- *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 the quality of response [V, B].

Never resectable metastatic disease (group 2/3, see Table 17) 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 necessitated by an emergency situation. CRT or 5 × 5 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 or stoma) should be performed initially, and palliative surgical resection only in specific circumstances [V, B].

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.

Table 13. Treatment algorithm for localized rectal cancer

		Diagnosis		Preoperative	Surgery	Pathology report	Postoperative	
		First choice	Second choice				First choice	Second choice
Independent of localization	Very early cT1 sm1	ERUS			TEM	>pT1sm2, >G1, V1, PN1	TME	CRT
	cT1 sm2				(TEM)			
Low (up to 5 cm) and APR necessary		MRI	ERUS	CRT or RT (5 × 5) or nothing	APR (TME, if feasible)	CRM+, N+, perforation	CRT (if not preoperatively) or FU ± oxaliplatin (4–6 months)	
Mid (>5–10 cm) and low without APR	Early cT1 sm2/3, T2	MRI	ERUS		TME	CRM+, N+, perforation	CRT (if not preoperatively) or FU ± oxaliplatin (4–6 months)	
	cT3a/b N0	MRI	ERUS	Nothing or RT (5 × 5) or CRT	TME	CRM+, N+, perforation	CRT (if not preoperatively) or FU ± oxaliplatin (5.5–6 months)	
	Intermediate cT3 MRF−, cT4 with limited levator only	MRI	MDCT	CRT or RT (5 × 5)	TME		FU ± oxaliplatin (4–6 months)	
	Advanced cT3 MRF+, cT4, positive lateral lymphnodes	MRI	MDCT	CRT	TME		FU ± oxaliplatin (4–6 months)	
High (>10–15 cm)	Early	MRI	MDCT	Nothing	T(P)ME	stage I or II low risk	(FU)	
	Intermediate	MRI	MDCT	Nothing, exceptional RT (5 × 5)		II high risk: <12 LN examined, L1, V1, PN1, >G2, pT4, obstruction, perforation	FU ± oxaliplatin (6 months)	
	Very advanced tight to lateral wall, T4b			CRT		III	FU ± oxaliplatin (6 months)	

Stage-specific management is always based on the best available staging method.

ERUS, endorectal ultrasound; FU, fluoropyrimidine; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; CRT, chemoradiation; APR, abdomino perineal resection; CRM, circumferential resection margins; MDCT, multidetector CT.

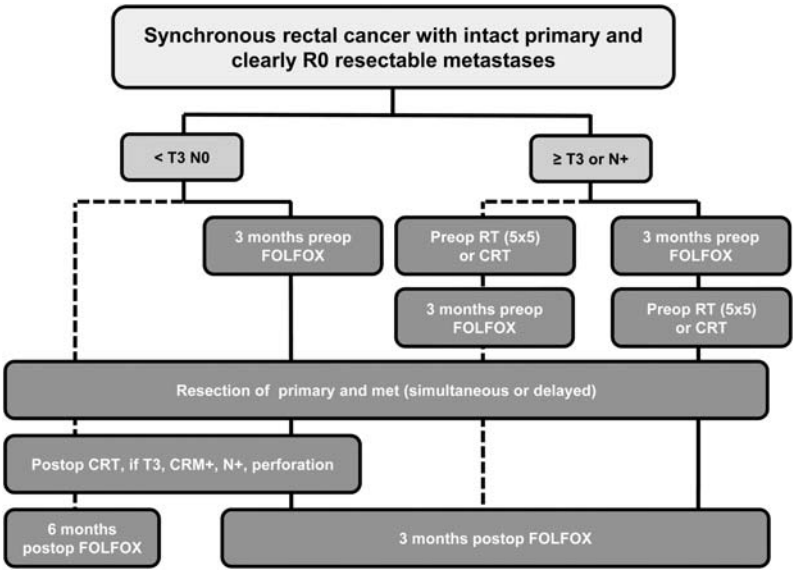

Figure 2. Treatment algorithm for resectable synchronous metastatic rectal cancer.

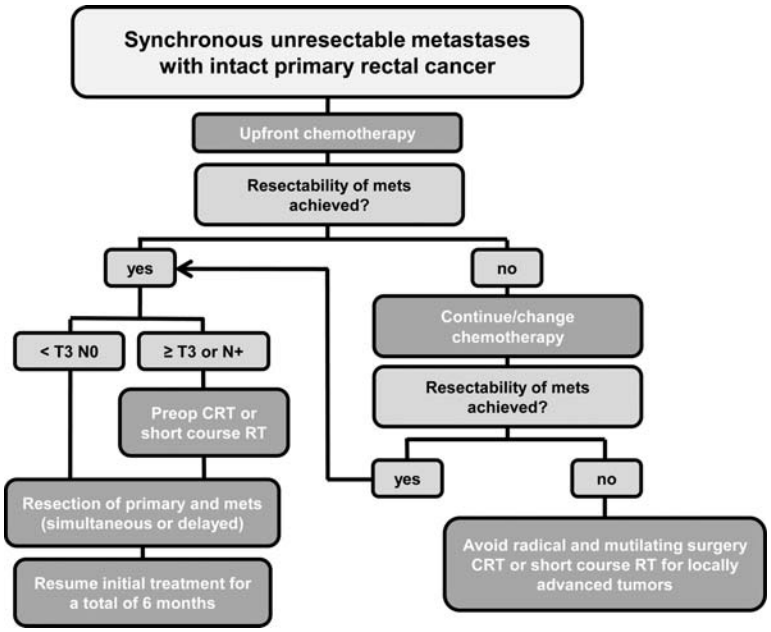

Figure 3. Treatment algorithm for unresectable synchronous metastatic rectal cancer.

- 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 CRC, polyps and other cancers should be obtained.
- CEA should be determined before treatment.
- Bone scan and brain imaging should be performed only for patients with related symptoms.
- Additional investigations such as 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

Table 14. Treatment algorithm for early colon cancer

Stage	TNM	Treatment Surgery	Pathology report	Clinical risk	Additional surgery	Age (years)	Postoperative (6 months)
0/I	Tis/T1 N0	Local excision	<G3, L0, R0 >G2, L1, V1, invasion of sub-mucosa	• Low (LN mets in 4%) • High	– Wide resection		– –
I	>T1	Wide surgical resection and anastomosis		–	–		–
II	T3/4 N0	Hemicolectomy and lymph node resection		• Low • High: at least one of <12 LN examined, L1, V1, PN1, >G2, pT4, occlusion, perforation	– – –	 <70 >70	(FU) FU(+oxaliplatin) FU (+ oxaliplatin for younger biological age)
III	N+				–	<70 >70	FU + oxaliplatin FU (+ oxaliplatin for younger biological age)

TNM, tumour–node–metastasis.

invasion and 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 of under-staging [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 (Table 14, Fig. 4)

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 the stage. The treatment algorithm is shown in Figure 4 and Table 14.

7.3.1 Surgical treatment of primary tumour in resectable colon cancer

7.3.1.1 Treatment of malignant polyps. The extent of surgical treatment of primary tumour in colon cancer is based on the clinical stage.
- 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%–20%. In case of G1 or G2 and no lymphatic invasion (low risk), the rate of metastasis is <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 sub-mucosa, lymphatic or venous invasion, resection margins <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 of relapse and are therefore amenable to 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 ≥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 versus III and to eradicate potential lymph node metastases, at least 12 lymph nodes must be resected; otherwise the risk of under-staging (false determination of stage II) is high, which might have a 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 be performed only on the basis of the following criteria:

- surgeons experienced in 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, thus improving surgery. However, this is still an experimental approach, which should be applied within clinical trials [92].

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]. Owing to the different clinical situations given in stage II, with ~80% of patients being cured by surgery alone, compared with 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 (PS, age, co-morbidity and patient preference) and cancer features (pathological stage, grading, and overall risk of relapse).

Prognostic and predictive factors (see chapters 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 [85].
- Stage III:
  Early data with small number of patients ($n = 63$) have shown no benefit of adjuvant 5-FU in stage III dMMR patients. In contrast, the recent updated data showed a benefit for adjuvant 5-FU 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, 32].

Table 15. Recommended treatment options for adjuvant treatment of stage II/III rectal and colon cancer

Regimen	Drug/dosage/schedule	q day
Single agent		
Capecitabine	Capecitabine 1250 mg/m^2 po twice daily day 1–15	22
LV5-FU2, de Gramont	5-FU 400 mg/m^2 i.v. bolus and LV 200 mg/m^2 i.v. followed by 5-FU 600 mg/m^2 i.v. 22 h-infusion day 1 + 2	15
Combination		
XELOX	Capecitabine 1000 mg/m^2 po twice daily day 1–15, oxaliplatin 130 mg/m^2 day 1	22
mFOLFOX6	5-FU 400 mg/m^2 i.v. bolus and LV 400 mg/m^2 i.v. followed by 5-FU 2400 mg/m^2 i.v. 46 h-infusion, oxaliplatin 85 mg/m^2 day 1	15
FOLFOX4	5-FU 400 mg/m^2 i.v. bolus and LV 200 mg/m^2 i.v. followed by 5-FU 600 mg/m^2 i.v. 22 h-infusion day 1 + 2, oxaliplatin 85 mg/m^2 day 1	15

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 to 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 [93, 94] [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 with FU alone which did not translate into improved OS, because of an excess of non-tumour-related deaths [95]. However, recent analyses of the NSABP protocol C05-C08 demonstrated a 2%–3% benefit in the 5-year OS rate for the addition of oxaliplatin to FU-based adjuvant chemotherapy in stage II [96]. 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.

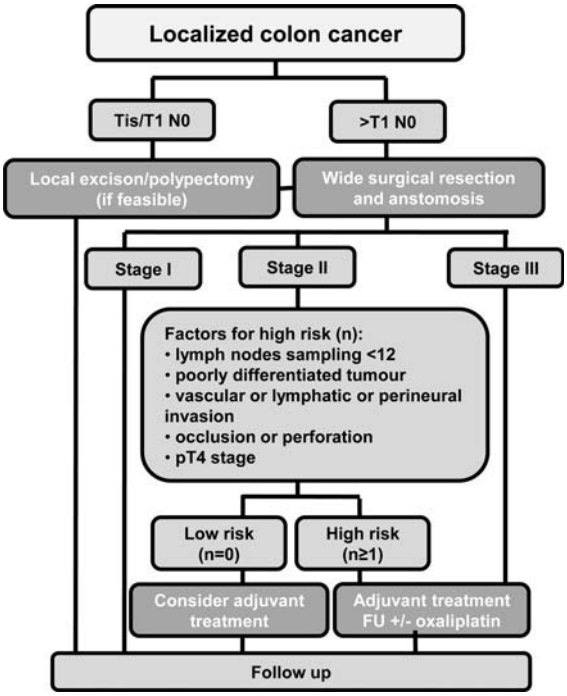

Figure 4. Treatment algorithm for early colon cancer.

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 5-FU in terms of DFS and OS [97–99]. Therefore, stage III patients should receive adjuvant chemotherapy with FU and oxaliplatin [I, A], with a clear preference for infused (FOLFOX) or oral FU (XELOX) combinations over the bolus FLOX regimen (see below) [100, 101] [IV, A]. In case of clinically relevant neurotoxicity oxaliplatin should be stopped, and FU continued, as the fluoropyrimidine contributes with about two-third to the effect of adjuvant FOLFOX/XELOX.

7.3.2.3 Choice of treatment.

- Infusional 5-FU should be preferred to bolus 5-FU because of better tolerability, which is even more relevant to the elderly. However, this implies the use of a (central) venous device, potentially associated with complications (thrombosis, pulmonary embolism, infection) [II, B].
- Since oral FU does not require central venous access, this treatment modality should be preferred whenever applicable [102, 103] [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 15.

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 with <70 years for oxaliplatin-based combinations in stage II and III (OS HR: 1.18; 95% CI 0.90–1.57 versus HR: 0.81; 95% CI 0.71–0.93, respectively) [104].
- 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 with <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 ($P = 0.7065$) [105], as well as in a recent metananalysis of XELOXA, AVANT, NSABP C-08 and X-ACT trial [238].
- In stage III disease observational data from five US registries demonstrated a maintained survival benefit for the addition of oxaliplatin to 5-FU-based adjuvant treatment in patients up to 75 years of age [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 5-FU [107].
- If capecitabine is used, an upfront dose reduction of 80% for both combination and single agent is recommended (albeit not investigated in a randomized fashion).
- Based on the available retrospective data decision to treat elderly patients with oxaliplatin combination-therapy should be considered with caution [III, D].
- Therefore, single-agent FU is the treatment of choice. However, oxaliplatin combination-therapy might be applicable to patients with 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 after surgery. If the start of treatment is delayed for more than 12 weeks, chemotherapy should be given on the basis of an individual decision taking into account relatively limited likelihood of benefit against the potential toxicity [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 [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).

7.4 Management of primary tumour in synchronous metastatic colon cancer

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

R0 resectable liver±lung metastases (group 0, see Table 17)

- For initially R0 resectable metastatic disease, irrespective of primary tumour, perioperative chemotherapy (3 months pre-

and postoperative FOLFOX) should be applied analogous to the EORTC 40983 trial [91] [II, B].
- Alternatively, resection of the primary tumour and metastases, followed by postoperative adjuvant FOLFOX for 6 months could be considered. However, adjuvant 5-FU 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 supported only by the indirect evidence in regard to the potential value of FOLFOX in the perioperative situation [V, C].

Potentially resectable metastatic disease after chemotherapy (group 1, see Table 17)
- 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 17) 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]. Prophylactic resection of the primary tumour for asymptomatic primary in case of unresectable systemic disease is still a matter of debate. Current retrospective analyses demonstrated both the beneficial prognostic impact of upfront resection and the feasibility of an upfront chemotherapy approach, which was further supported by the preliminary results of the NSABP C-10 trial [113, 114]. Since these retrospective data are subject to selection bias, this question is currently being prospectively addressed in several phase III trials (UK, Netherlands, Germany, Sweden). However, consensus participants agreed on upfront chemotherapy in case of asymptomatic primary and metastatic disease [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].

8 Management of resectable liver and/or lung metastases

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

8.1 Definition of resectability

The criteria for R0-resectability of liver metastases are not standardized and are varying, depending on technical aspects (and herein they are related to the experience of the surgeon and the multi-disciplinary team) and the question of prognostic information for a chance of cure. Resectability is not limited by number (e.g. <4), size (>5 cm), 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 because of location. Other considerations must include the presence of questionably resectable extrahepatic disease and eligibility of the patient for surgery in terms of comorbidity. 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. The algorithm for resectable/borderline resectable liver/lung metastases is shown in Figure 6.

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 5-FU or FOLFIRI—or hepatic arterial infusion of floxuridin—indicate some benefit, although no single study or meta-analysis has shown a statistically significant survival benefit [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 [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 have not shown a significant benefit due to insufficient number of patients (OS was not the primary endpoint)—a current standard [91]. Both concepts of pre- and postoperative versus postoperative alone as well as the addition of bevacizumab or 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 months* of previous adjuvant oxaliplatin-based treatment should not receive perioperative FOLFOX, or rather another active protocol (e.g. FOLFIRI), in the same manner of pre-/postoperative treatment, or immediate surgery if feasible [IV, C].

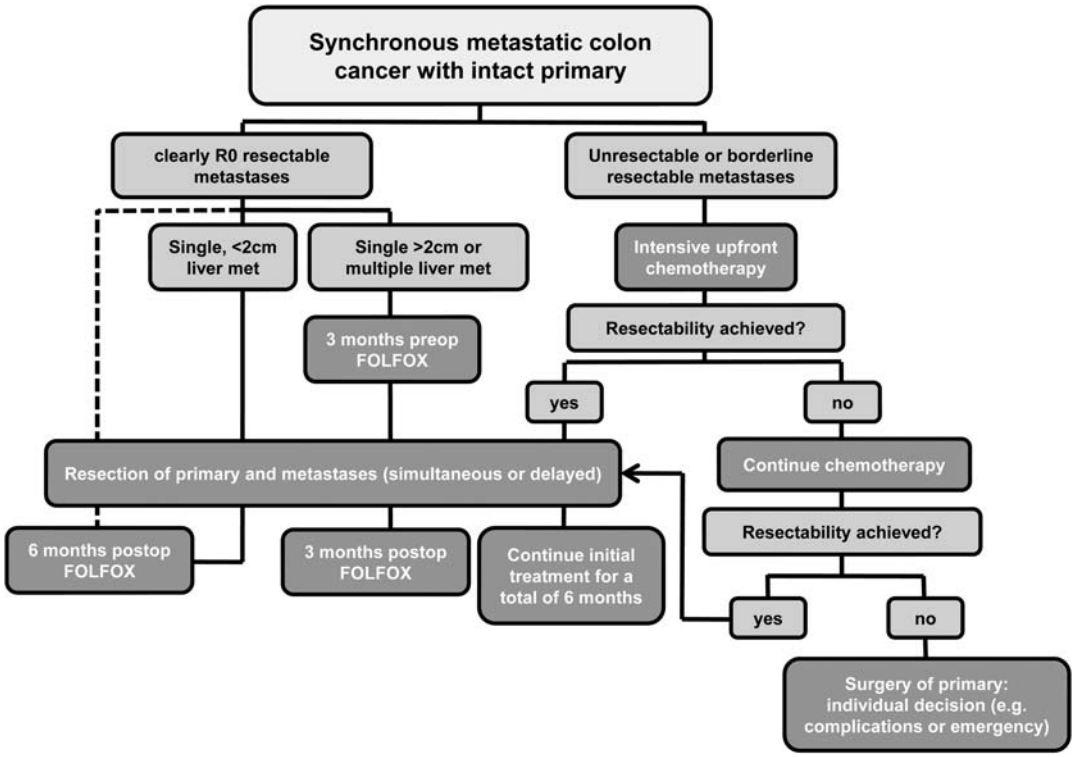

Figure 5. Treatment algorithm for synchronous metastatic colon cancer.

- *Good prognosis patients, with a single small (<2 cm) 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].
- *Achieving complete response* (CR) to chemotherapy is of major prognostic importance for liver metastases but should be avoided in order to enable resection (before complete disappearance) [126, 127]. Therefore, close follow-up with imaging and multi-disciplinary discussion is mandatory. If an anatomical resection can be performed, CR is not a major problem, because resection will be based on initial sites of liver metastases. In case of CR 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 [128, 129], but progression during neoadjuvant treatment represents aggressive tumour biology, and likely predicts a worse outcome even in case of resection. Therefore, the 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 [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 [131] [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 to curative approach treatment may be resumed [IV, C].
- *In case of contraindications against surgery or unresectable oligometastases* (size up to 3–4 cm for RFA and 4–5 cm for SBRT, if properly located) local ablative measures (RFA, SBRT) should be considered [132–134] [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].

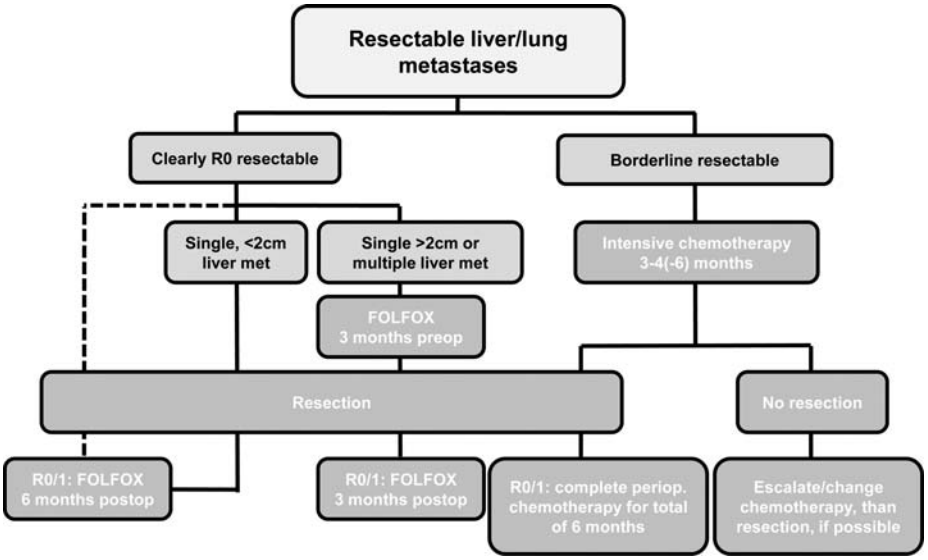

Figure 6. Treatment algorithm for management of resectable liver/lung metastases.

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

Relevant for the choice of first-line treatment is the treatment aim, which 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; prognostic molecular or biochemical markers, like BRAF mutation), 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) (Table 16). In case of major response of liver and 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. By 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 17.

- **Age/PS:** Neither age (less and more than 70 years) nor PS (0,1 versus 2) seems 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 [136–139]. 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 EGFR-antibodies is available [II, A]. No further predictive molecular marker is relevant to decision on routine first-line treatment out of clinical trials, in particular not for the decision on the use of bevacizumab [IV, D]. The potential of BRAF mutation to be involved in the decision in the future needs further validation and is not ready for the routine use yet [IV, C].

Stratification of patients for first-line treatment

Using the factors in Table 16 and Fig. 7, patients can be individually divided into the four clinical groups (Table 17), 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 [IV, B].

- **Group 0: liver or lung metastases, R0 resectable:** This group comprises those patients in whom metastases are limited to liver/lung metastases, which 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 $\geq$ 1 resection.
- **Group 1: liver or lung metastases, not R0 (R1) resectable:** 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 means of giving the potential of long-term survival or

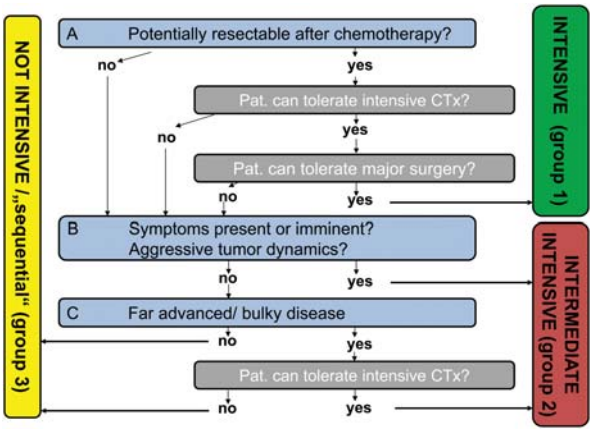

Figure 7. Hierarchy of factors for definition of treatment aim/group

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.

- **Group 2: Intermediate intensive treatment** for the intermediate group, where the treatment aim is palliative rather 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 first-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 OS are also relevant.
- **Group 3: Not intensive/sequential treatment** 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 disappearance 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 (5-FU/FA)], preferably given as 24–48 h infusion biweekly, or oral prodrugs (e.g. capecitabine, UFT, S1), irinotecan and oxaliplatin. Capecitabine can safely substitute i.v. 5-FU/FA in combination with oxaliplatin without impairment in terms of progression-free survival (PFS) and OS [140–144]. There are less data for the combination of oral fluoropyrimidines with irinotecan because of 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, apparently without loss of efficacy (cross-trial comparison) [149, 150]. S1 can safely be combined with irinotecan with comparable efficacy versus FOLFIRI [151]. However, no data in a non-Asian population with respect to efficacy and toxicity are available yet.

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 [152–155]. Whereas the Greek FOLFOXIRI showed a non-significant improvement in overall reponse rate (ORR), PFS, and OS compared with FOLFIRI, the Italian trial proved the superior efficacy of the triplet in terms of response and OS. Different schedules with

Table 16. Factors influencing choice of first-line treatment

Tumour biology-related factors

• Localization
  ○ Liver- or lung-only metastases versus
  ○ Multiple sites
  ○ Potentially R0-resectable lesions after induction chemotherapy and sufficient downsizing versus massive disease extension

• Growth dynamics   ○ Aggressive versus indolent growth
• Asymptomatic versus symptomatic disease
• Imminent relevant tumour symptoms if low active or inactive treatment
• Second-line treatment after ineffective first-line single-agent treatment may not be possible anymore
• Chemosensitivity (not detectable before start of chemotherapy)
• Prognostic molecular or biochemical markers (e.g. BRAF mutation)
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

PFS, progression-free survival; OS, overall survival.

Table 17. Clinical groups for first-line treatment stratification

Group	Clinical presentation	Treatment aim	Treatment intensity
0	Clearly R0-resectable liver and/or lung metastases	• Cure, decrease risk of relapse	Nothing or moderate (FOLFOX)
1	Not R0-resectable liver and/or lung metastases only which • Might become resectable after response to induction chemotherapy • ±Limited/localized metastases to other sites, e.g. locoregional lymphnodes • Patient is physically able to undergo major surgery (biological age, heart/lung condition) and more intensive chemotherapy	• Maximum tumour shrinkage	Upfront most active combination regimen
2	Multiple metastases/sites, with • Rapid progression and/or • Tumour-related symptoms and/or risk of rapid deterioration • Co-morbidity allows intensive treatment	• Clinically relevant tumour shrinkage as soon as possible • At least achieve control of progressive disease	Upfront active combination: at least doublet

3	Multiple metastases/sites, with
	• Never option for resection
	• and/or no major symptoms or risk of rapid deterioration
	• and/or severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1 + 2)
		• Abrogation of further progression
		• Tumour shrinkage less relevant
		• Low toxicity most relevant
			Treatment selection according to disease characteristics and patients preference re toxicity and efficacy:
			• "Watchful waiting" (exceptional)
			• Sequential approach: start with
			  • Single agent, or
			  • Doublet with low toxicity
			• Exceptional triplets

Modified from Schmoll et al. [242, 243].

capecitabine, irinotecan and oxaliplatin were evaluated in small non-randomized phase II trials displaying similar efficacy and, as expected, decreased tolerability due to diarrhoea [156–159]. However, on the basis of 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 5-FU/FA or capecitabine, and all fluoropyrimidine and oxaliplatin or irinotecan combinations [146, 149, 160–163]. Whereas, bevacizumab increased ORR by 10% when added to the IFL regimen (bolus 5-FU, leucovorin and irinotecan), with significantly improved PFS and OS, the addition of bevacizumab to fluoropyrimidine and oxaliplatin did not increase response rates [164]. 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 preferably be used in patients requiring tumour shrinkage [I, C]. 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 [160].
- **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 [165–170]. Both drugs are active only in KRAS wt tumours. EGFR antibodies-based triplets have therefore an advantage, if a high intensity, and likely induction of a remission is required [II, A], as for downsizing of unresectable liver metastases or for a rapid induction of a tumour 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 [171, 172].

  If cetuximab/panitumumab for KRAS wt tumours is chosen, chemotherapy combination should be carefully selected. Combinations of oxaliplatin plus capecitabine or bolus 5-FU and cetuximab seem to have no additional benefit and must be avoided [39, 173]. Therefore, either cetuximab or panitumumab should be combined only with FOLFIRI or FOLFOX [165, 168, 174] [I, A]. However, outside the US, panitumumab is licensed only with FOLFOX for first-line treatment.

Table 18. Options for first-line treatment according to the clinical groups and grading (defined by the treatment aim, available data and expert recommendation)

Group	KRAS wild-type	Recommendation[a]	KRAS mutant	Recommendation[a]
1	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan/Cet	+++	FOLFOXIRI	++(+)[b]
	FOLFOX/XELOX + Bev	++(+)	FOLFIRI/XELIRI + Bev	++(+)[c]
	FOLFOXIRI	++(+)[b]	FOLFOX/XELOX	+
	FOLFIRI/XELIRI + Bev	++(+)[c]	FOLFIRI/XELIRI	+
	FOLFOX/XELOX	+	IRIS	+
	FOLFIRI/XELIRI	+		
	IRIS	+		
2	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan	+++	FOLFIRI/XELIRI + Bev	++(+)[c]
	FOLFOX/XELOX + Bev	+++	FOLFOX/XELOX	++
	FOLFIRI/XELIRI + Bev	++(+)[c]	FOLFIRI/XELIRI	++
	FOLFOXIRI	+(+)[b]	FOLFOXIRI	++[b]
	FOLFOX + Cet	+(+)	IRIS	+
	FOLFOX/XELOX	+		
	FOLFIRI/XELIRI	+		
	IRIS	+		
3	FUFOL/Cape (mono)	+++	FUFOL/Cape (mono)	+++
	FUFOL/Cape + Bev	+++	FUFOL/Cape + Bev	+++
	XELOX/FOLFOX	++	XELOX/FOLFOX	++
	FOLFIRI/XELIRI	++	FOLFIRI/XELIRI	++
	IRIS	+	IRIS	+
	Cet/Pan (mono)	(+)	watchful waiting	+ selected pts.[d]
	Watchful waiting	+ selected pts.[d]	triplets (±Bev)	+ option for spec. situations[e]
	Triplets (+/−Bev or Cet/Pan)	+ option for spec. situations[e]		

[a]Consented recommendation, however decision might be modified based on individual objective and subjective parameters.
[b]FOLFOXIRI: only two (small) phase III trials with contradictory results.
[c]No randomized data for FOL(XEL)IRI + Bev.
[d]Option in case of low tumour burden, asymptomatic, indolent disease: close control until definitive progression (not until symptoms!).
[e]Patients who are group 3 but deserve (and tolerate) more intensive treatment due to specific reasons.
XELIRI, capecitabine + irinotecan; IRIS, irinotecan + S1.

- **Bevacizumab and 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 [175, 176].
- **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 [177–179]. 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 [180, 181].

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, efficacy in first-line setting is rather poor (AFFIRM-trial) [182, 183].
- **Regorafenib** is a dual targeted VEGFR2-TIE2 tyrosine kinase inhibitor, which has shown significant improvement of PFS and OS in third/last line as single agent compared with placebo [184].
- **BIBF 1120** is a pan VEGFR, PDGF and FGF tyrosine kinase inhibitor, which has shown comparative efficacy and toxicity in combination with FOLFOX versus FOLFOX + bevacizumab in first-line treatment [185].
- **Cediranib** is a pan VEGFR TK inhibitor, which showed in a large phase III trial with FOLFOX in first-line comparable efficacy versus FOLFOX/bevacizumab; however, quality of life measurements favoured bevacizumab [186].

9.4 Selection of first-line regimen

The selection of the first-line regimen depends on the chosen treatment strategy (see Table 18). In the absence of conclusive comparative data, options in Table 18 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 groups 1 and 2 and cetuximab-based triplets in group 3 could be achieved. However, the proposal (Table 18) 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 to 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 is a low-toxic valid option for patients who are not eligible for secondary resection and have no symptoms or risk of rapid deterioration of their disease (group 3).

Induction chemotherapy for group 1

- **Chemodoublets:** Combination chemotherapy regimens comprising 5-FU/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 [187–189]. 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 EGFR-antibody) to a doublet or even to a triplet might be more effective in liver limited disease [190–193], but also FOLFOXIRI resulted in a comparable high R0-resection rate of 36% in liver only patients. The combination of a chemodoublet with 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 [167, 168, 171, 174]. 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 [194].

  There are no data available from randomized studies comparing a chemodoublet plus bevacizumab with a chemodoublet plus EGFR-antibodies yet, although in KRAS wt tumours, induction treatment with FOLFIRI/FOLFOX with 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 EGFR-antibodies, and is the preferred option if targeted drugs, in particular 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]. Chemotriplet plus bevacizumab (FOLFOXIRI/Beva) are in general even more active, positive results from the GONO-group in 450 patients-phase-III-trial will be presented soon (personal communication, Falcone).

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 call 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].

Initial treatment for 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 5-FU/LV, oxaliplatin and irinotecan at some point during the course of the disease [195].
- Several large trials evaluated different sequential approaches, comparing either single-agent FU, followed by single-agent irinotecan and afterwards FU/oxaliplatin with upfront FU/irinotecan combination, followed by FU/oxaliplatin (CAIRO, FOCUS), or 5-FU/LV/capecitabine with or without oxaliplatin (FOCUS 2) followed by irinotecan (LIFE) [148, 196, 197]. Although ORR and PFS were improved with upfront combination treatment, OS was similar for both approaches with a non-significant median difference of 1 month. Comparable results could be shown in an elderly and/or frail population in the FOCUS 2 trial [13].
- 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 (i.v. or orally) plus bevacizumab is an active and well-tolerated therapy, also for the elderly population (AGIT-trial) [160] [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.

Table 19. Options for maintenance after induction chemotherapy for 3–4.5–6 months not valid for group 1 or aggressive disease

Continuously	Stop and go approach			
	Maintenance and reinduction		Complete stop and reinduction	
Continue until progression or unacceptable toxicity (standard)	Stop and restart at progression	Stop for pre-planned intervals	Stop and restart at progression	Stop for pre-planned intervals
	• Stop most toxic drug (oxaliplatin, irinotecan, EGFR inhibitor) • Continue only FU or FU + bevacizumab (or bevacizumab or cetuximab) until progression • Restart drug at progression (OPTIMOX 2, MACRO, COIN-B)	• Stop/restart toxic drugs in pre-planned intervals (3/4 months on/off) (OPTIMOX 1, CONcePT)	• Stop all drugs • Restart at progression • Stop after further 3 months (COIN, OPTIMOX 2)	• Stop/restart all drugs in pre-planned intervals (GISCAD)

EGFR, epithelial growth factor receptor; FU, fluoropyrimidine.

A full sequential design with chemodoublet + molecular targeted agent (EGFR and VEGF inhibitors) in first and further lines is not available; however, in very selected patients, a triplet with EFGR inhibitors might be indicated.

- Owing 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 because of 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 5-FU only era have conflicting outcomes [198, 199] [II, B].

9.5 Treatment duration/timing for assessment of response

Response assessment 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 palliation, the timing of first control investigation is of less importance; an interval of 8–12 weeks might be appropriate, unless clinically indicated [III, B].

Treatment duration

The treatment duration is dependent of the treatment aim.

- *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 (>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 months (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 [200–202]. However, the potential toxicity of the treatment should be balanced with the potential benefits of achieving a resectable status.
- *If secondary resection cannot be achieved*, as well as in all other patients 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 aforementioned potentially resectable group response is the main treatment aim [203], 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**
  - 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].
  - If metastases are not resectable because of their location additional measures such as radiofrequency ablation or stereotactic body radiotherapy (in specialized institutions) should be considered, although the benefit is not formally proven [III, B].
  - 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]; instead, most active salvage chemotherapy should be started (Figure 8).

9.7 Maintenance/intermittent treatment (Table 19)

- 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 6 months indicating that in many patients (~60%–70%) treatment is stopped not because of progression but because of 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 [26]. Therefore, it is mandatory to restart induction (reinduction), if induction was stopped without tumour progression [III, A].
- Survival will be impaired by ~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 [26]. However, patients with liver-limited disease as well as aggressive disease, and poor prognostic features, e.g. high platelet count or LDH and more than two 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 [26, 204, 205]. 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 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 pre-planned treatment intervals and break duration ("intermittent treatment") of one or all drugs resulting in comparable overall outcome in comparison to treatment until progression [26, 206–208]. 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 [209]. 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 with 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 with full stop of treatment and reinduction of FOLFOX + cetuximab in case of progression [210]. However, the control arm of standard 5FU+/− Oxaliplatin was not included, which very likely would have shown the same result without skin toxicity.

An overview of these options for maintenance is given in Table 19.

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 5-FU and bevacizumab, which seem to act as chemosensitizers. 5-FU has single-agent activity on its own but improves efficacy of oxaliplatin even resistance to IFL occurred; this might be vice versa with FOLFIRI after FOLFOX [211].
- Continuation of bevacizumab with changed chemotherapy backbone in second-line increases OS after progression with first-line bevacizumab and chemotherapy [212]. Therefore,

5-FU 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 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 [182, 212].
  - 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 with FOLFOX after failure of FU/irinotecan [214].
  - Second-line treatment with aflibercept plus FOLFIRI is superior in terms of RR, PFS and OS compared with FOLFIRI after failure of FOLFOX [182].
  - 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 [184].

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-HT_3-receptor antagonist (palonosetron is preferred) + dexamethasone 8 mg
  - delayed phase (day 2–3): single-agent dexamethasone 8 mg, alternatively 5-HT_3-RA
  - The role of the NK-1-receptor antagonist aprepitant 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, 5-FU):

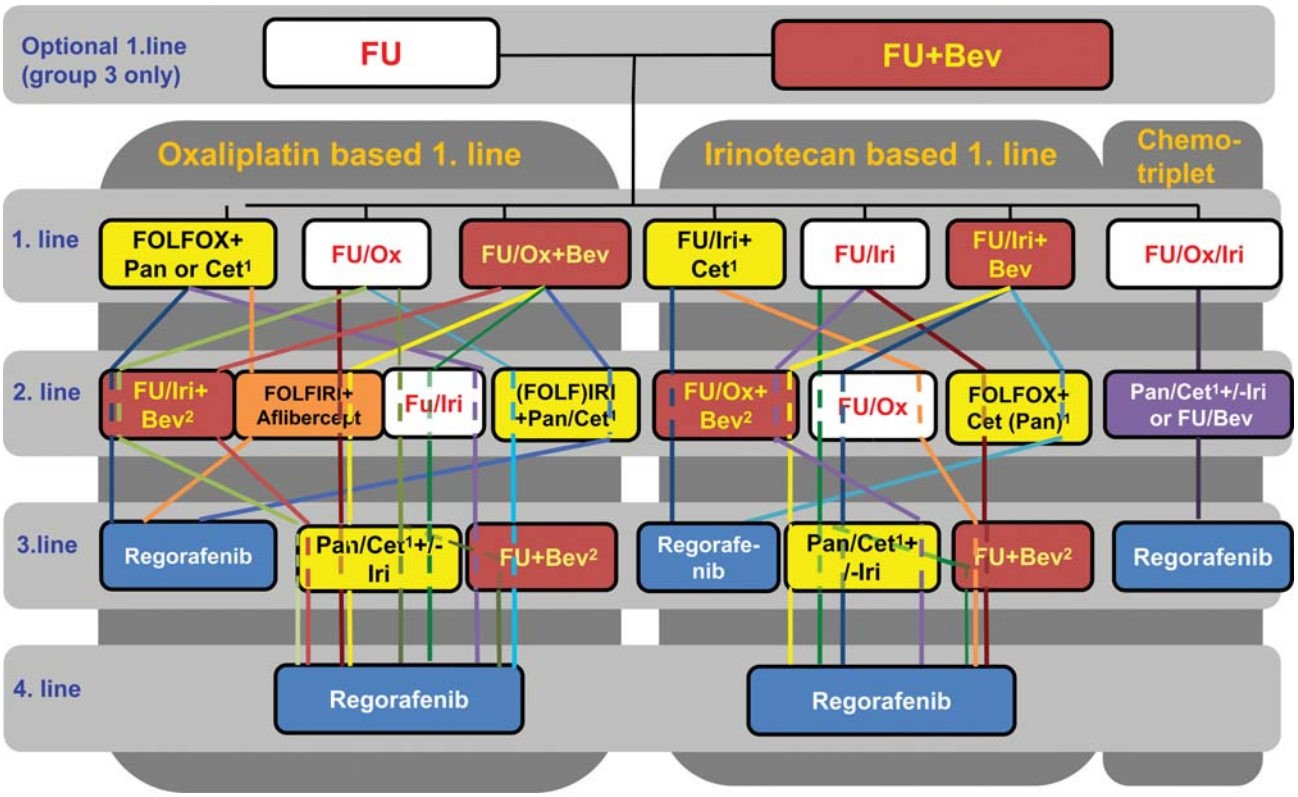

Figure 8. Proposal for sequence of salvage-chemotherapy. (1) only KRAS wt; (2) continuation of Bev not beyond second line, in case of optional first line and first line both with Bev; FU, fluoropyridmidines; Iri, irinotecan; Ox, oxaliplatin; Bev, bevacizumab; Afli, aflibercept; Cet, cetuximab; Pan, panitumumab.

- 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-HT_3-RA given prophylactically for the total treatment time depending on toxicity 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-HT_3-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 (tetracyclines) lowers the incidence of severe skin reactions and might thus strongly 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, erythromycine 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/m^2, 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, gluthatione, 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 [208, 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, although not very likely from the current data.

9.9.4 Chemotherapy-induced diarrhoea

Chemotherapy-induced diarrhoea (CID) is a common problem with a frequency of 50%–80% (≥30% common toxicity criteria grade 3–5), especially with 5-FU bolus or combination of irinotecan and FU [IFL, capecitabine + irinotecan (XELIRI), irinotecan + S1 (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 CRC 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 multi-modal 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 extra-abdominal 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].

Table 20. Surveillance schedule for colorectal cancer (months after surgery/adjuvant treatment)

		3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
	CEA	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Colonoscopy				x								x				
High risk	Abdominal/chest CT scan		(x)		x		(x)		x		(x)		x				

CEA, carcinoembryonic antigen.

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 controversy. Importantly, patients should be motivated for optimization of life style (maintain healthy weight, physical activity, cessation of smoking, moderate alcohol use, healthy diet adoption).
- Accepted are 3-monthly clinical visits for the first 3 years, followed by every 6 month for further 2 years, with clinical examination, evaluation of long-term toxic effects (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 5 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 20 based on ASCO and European guidelines [234–236], noting that the 12 monthly scanning would be more typical in stage II and III surveillance. Six 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 OS. 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].
- Patients receiving local excision of rectal cancer should be closely monitored for local recurrence with digital rectal examination and sigmoidoscopy every 3–6 months for the first 3 years, afterwards every 6–12 months for 2 years. Surveillance for multi-modal-treated rectal cancers should continue beyond 5 years, as perioperative treatment might delay recurrence beyond this point in time [III, B].

conflict of interest

HJS: consultant or advisory role, honoraria and research support: Roche, Merck Serono, and Sanofi-Aventis. DA: consultancy/honoraria: Roche, Merck Serono. Research grants: Roche, Sanofi Aventis; G: Advisory Boards: Amgen, Roche; ACR: Speakers' Bureau: Merck Serono, Roche; FC: Research funded by Roche, Merck Serono; RG-J: Consultancy/honoraria: Roche, Merck Serono, Sanofi, Pfizer, Nucletron; Research Funding: Merck Serono and Roche; Funding from Roche to attend international GI cancer meetings; PMH: Consultancy/honoraria: Roche, Astra Zeneca, Merck, Pfizer; DJK: Research grants: Merck, Roche, AstraZeneca, Genomic Health; C-HK: Research grants: Merck, BMS; WS: Conducting research, medical consultant and invited speaker: Amgen, Merck, Roche; H-JS is advisor with honorarium of Roche and Merck; AS: Advisor and speaker for: Merck-Serono, Roche, Sanofi-Aventis, Pfizer, Amgen, Bayer, AstraZeneca; JT: Advisory boards: Merck Serono, Amgen, Roche, Pfizer, Sanofi-Aventis, Agendia, Genomic Health; EJDvC: Research funding to University of Leuven: Amgen, Bayer, Merckserono, Novartis, Roche, Sanofi. All other authors have reported no conflicts of interest.

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