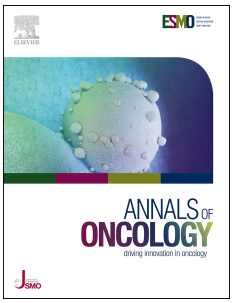

Localised Colon Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up

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Localised Colon Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up†

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Key words: localised colon, Clinical Practice Guidelines, diagnosis, treatment and follow-up

Highlights:

•This ESMO Clinical Practice Guideline provides key recommendations on the management of localised colon cancer

•Authorship includes a multidisciplinary group of experts from different institutions and countries in Europe and abroad

• Diagnostic work-up is reviewed

• Key treatment recommendations

• Follow up indications are provided

INTRODUCTION

Incidence and epidemiology

Colorectal cancer (CRC) is the third most common tumour in men and the second in women, accounting for 10% of all tumour types worldwide. Incidence is 25% higher in males and differs greatly between countries. With more than 600,000 deaths estimated each year, CRC is the 4th most common cancer-related cause of death globally [1-2]. The growing incidence in some countries reflects a modification in lifestyle and its consequences related with 'Westernisation' such as obesity, physical inactivity, alcohol consumption, high red meat intake and cigarette smoking [3]. Some data suggest a putative role in colon cancer carcinogenesis for factors that cause imbalances in gut microbiota [4, 5].

The mortality rate in the European Union is 15–20 out of 100 000 in males and 9–14 out of 100 000 in females and has decreased over time, particularly in females. In affected European individuals, 5-year survival ranges from 28.5% to 57% in men and from 30.9% to 60% in women, with a pooled estimation in 23 countries of 46.8% in men and 48.4% in women [6].

The risk of developing colon cancer depends on factors which can be classified into lifestyle or behavioural characteristics and genetically-determined factors. Screening tests are modulated according to the individual probability of developing CRC [7-9]. Age is considered the major unchangeable risk factor for sporadic colon cancer: nearly 70% of patients are >65 years of age and this disease is rare before the age of 40 years, even though data from Western registries show an increased incidence in the 40–44 year-age group [10].

Individuals with any of the following are considered at high risk of colon cancer and must be actively screened and in case of inherited syndromes, also referred for genetic counselling (see ESMO guidelines for hereditary gastrointestinal cancer [11]):

- a medical history of adenoma, colon cancer, inflammatory bowel disease (Crohn's disease and ulcerative colitis);
- significant family history of CRC or adenoma;

- an inherited cancer syndrome (2%–5% of all CRC), such as familial adenomatous polyposis coli and its variants (1%), Lynch-associated syndromes (hereditary non-polyposis colon cancer) (2%–4%), Turcot, Peutz-Jeghers and *MUTYH*-associated polyposis syndrome.

SCREENING PRINCIPLES

CRC arises following progression of normal mucosa to an invasive tumour, passing through different intermediate stages of premalignant and invasive malignant lesions; this stepwise process facilitates cancer prevention and early diagnosis when the tumour is still at an early stage and curable, through screening programmes. For average-risk populations, European and American evidence-based guidelines for quality assurance in CRC screening [12,13] should be followed.

Recommendations

Colonoscopic tests:

- Colonoscopic techniques, despite being invasive, have the advantage of being both diagnostic and therapeutic.
- A complete colonoscopy is the recommended method for CRC screening in average-risk men and women based on higher sensitivity and specificity when compared with other tests [14] [II, B]. The optimal age range for testing is 50–74 years [V, D] with an optimal repetition interval for a negative test of 10 years [III, C].
- Flexible sigmoidoscopy (FS) performed every 5–10 years may be an alternative for those who refuse colonoscopy [II, B]. The combination of this method with a yearly faecal occult blood test (FOBT) (see below) is recommended to reduce the risk of a right colon tumour [III, B].
- Other invasive tests including capsule colonoscopy are not recommended for screening [IV].

Non-invasive tests:

- Non-colonoscopic tests are recommended in average-risk men and women from the age of 50 not already taking part in colonoscopic screening programs. The optimal frequency of testing is every year and no later than every three years [I, B]. A colonoscopy must be performed at the earliest convenience when the test results are positive [I, A].

- Among the available tests, faecal immunochemical testing (FIT) appears to be superior to high-resolution guaiac FOBT with respect to the detection rate and positive predictive value for adenomas and cancer [III]. Other novel methods including DNA-based or tests using other markers (e.g. M2-PK) lack formal comparisons of their performance, and integration with other assays needs to be monitored.

Screening for high-risk populations is covered in the ESMO guidelines for hereditary gastrointestinal cancer [11].

DIAGNOSIS

Symptoms and signs

Colon cancer arises from the mucosa of the bowel, growing both into the lumen and the bowel wall, and/or spreading to adjacent organs. Symptoms are associated with relatively large tumours and/or advanced disease stages and may not be specific for colon cancer. Alterations in bowel habit, general or localised abdominal pain, weight loss without other specific causes, weakness, iron deficiency and anaemia are the most common symptoms and depend on the location and stage of the primary tumour [15, 16]. Colon cancer can occur with multiple or synchronous lesions (3.6%) [17] with identical or different histological patterns and stages of development. Metachronous primary tumours arise in up to 3% of cases during the 5 years after surgery, and the incidence increases up to 9% after several decades in long-term survivors, justifying long-term surveillance of the colon in patients that have already experienced colon cancer [18].

Diagnostic work-up

A complete work-up should be carried out to achieve an accurate histological diagnosis of the primary tumour, assess the baseline characteristics of the patient and determine the extent of the disease (see Table 1).

Diagnosis of the primary tumour

In the absence of a bowel obstruction or massive haemorrhage, which may constitute indications of an urgent tumour resection, a total colonoscopy is recommended for diagnostic confirmation of colon cancer [I, A]. There are many advantages of endoscopy including determination and marking of the exact tumour location and biopsy of the lesion, detection and removal of (further) synchronous precancerous or cancerous lesions. Combining the limited left-sided colonoscopy with computed tomography (CT) colonoscopy is an alternative if full colonoscopy is not feasible [I, A] [19]. In cases where complete colonic exploration cannot be carried out before surgery, a complete colonoscopy should be carried out within 3–6 months [IV, B].

Assessment of patient baseline status and characteristics

After colonic tumour diagnosis, clinical examination and laboratory tests must be carried out to provide a correct assessment of patient status and characteristics before deciding the definitive treatment approach [II, A].

Besides a comprehensive physical examination [20] [IV], blood tests including complete blood count, coagulation, liver and kidney functions tests as well as albumin can provide relevant clinical information regarding the patient's baseline conditions and the existence of cancer-related complications [II, A].

In addition, serum levels of carcinoembryonic antigen (CEA), although not sufficient for colon cancer diagnosis themselves in the absence of a confirmatory tumour biopsy (because of low specificity and sensitivity), should be evaluated before surgery and monitored during the follow-up period to help the early detection of metastatic disease [III, A] [21-23]. In addition, CEA

determination after colon cancer diagnosis is of particular importance since baseline levels add information in defining prognosis; a preoperative serum CEA level >5 ng/ml (or even >2.35) suggests a worse outcome [21].

Assessment of distant tumour extension

Preoperative assessment of tumour extension should be done to determine whether the patient should be referred for primary tumour resection or, in the presence of unresectable distant metastases, systemic therapy. Approximately 20% of newly diagnosed colon cancers have synchronous metastasis, the most frequently involved organ being the liver (17%), followed by peritoneum (5%), lung (5%) and lymph nodes (3%) [24].

CT of the thoracic, abdominal and pelvic cavities with intravenous contrast administration is the preferred radiological method for the evaluation of the presence of distant metastases of CRC [II, B]. This test allows evaluation of locoregional tumour extension and its complications (e.g. obstruction, perforation, fistula, abscess) [25]. However, CT scanning may fail to detect peritoneal metastases, where sensitivity is relatively poor and depends on implant localisation and size [26,27].

Contrast-enhanced magnetic resonance imaging (MRI) permits better definition of the soft tissues. It constitutes the reference test when it is necessary to evaluate the relationship of locally advanced tumours with surrounding structures or in defining ambiguous liver lesions previously detected by CT scan [II, A] [28]. Likewise, MRI can substitute for CT scanning in patients with iodine contrast allergies or chronic renal insufficiency where glomerular filtration rate is <30 ml/min [II, A] [29-31].

Positron emission tomography (PET) with the glucose analogue 18-fluoro-2-deoxy-D-glucose (FDG-PET), with or without integrated CT (PET/CT), does not add significant information to the CT scans on preoperative staging of CRC and is not recommended for routine use in staging of localised CRC beyond assisting in interpretation of ambiguous findings [II, A] [32, 33].

Recommendations

- In the absence of indications for urgent tumour resection, a total colonoscopy is recommended for diagnostic confirmation of colon cancer and to rule out synchronous tumours. Combining the limited left-sided colonoscopy with CT colonoscopy is an alternative if full colonoscopy is not possible [I, A].
- When not carried out before or during the surgical procedure, a complete colonoscopy should be carried out within 3–6 months following tumour resection [IV, B].
- Comprehensive physical examination and laboratory tests including full blood counts, biochemistry, serum CEA must be carried out prior to decisions on the definitive treatment approach [III, A].
- CT of the thoracic, abdominal and pelvic cavities with intravenous contrast administration is the preferred radiological method for the evaluation of the extent of CRC [II, B].
- Contrast-enhanced MRI constitutes the reference test for evaluation of the relationship of locally advanced tumours with surrounding structures or in defining ambiguous liver lesions [II, A].

MANAGEMENT OF LOCALISED COLONIC TUMOURS

Treatment of adenocarcinomas presenting in adenomas

Complete *en bloc* endoscopic resection should be carried out whenever the morphological structure of the polyp permits [34]. Endoscopic resection is sufficient for hyperplastic or adenomatous polyps, and non-invasive (pTis, i.e. intraepithelial or intramucosal) adenocarcinomas [35] (see Figure 1). For (pT1) invasive carcinomas, the management is determined by the polyp morphology and the presence of histological features associated with adverse outcome [36]:

- lymphatic or venous invasion;
- grade 3 differentiation;
- significant (grade >1) tumour budding [37]

For a pedunculated polyp with a pT1 carcinoma confined to the head, neck and stalk (Haggitt 1–3) endoscopic resection with proper follow-up is enough even

with the presence of submucosal invasion provided that no other unfavourable factors are present [IV, B] [38]. However, the presence of any unfavourable factor in a sessile or flat polyp (Paris classification) with a pT1 carcinoma, mandates surgical resection in patients with average operative risk [IV, B] [39]. The role of the surgical resection will be to complete lesion resection and to include lymph node removal for optimal risk assessment [IV, B]. In contrast finding positive resection margins (<1 mm) constitutes only a risk for local recurrence and can be managed by excision repetition or local surveillance [39]. When surgery is not possible due to significant comorbidities, surveillance colonoscopy within 6 months after polyp removal is recommended, as well as close oncological follow-up including CT scan to detect lymph node recurrences [IV, B] [38, 39].

Management of locally infiltrative colon cancers

Infiltrative colon cancers cannot be resected by colonoscopy and necessitate surgery, with the goal of wide resection of the involved bowel segment and its lymphatic drainage [I, A]. The extent of the colonic resection is determined by the blood supply and distribution of regional lymph nodes. The resection should include a segment of colon of at least 5 cm on either side of the tumour, but wider margins are often included due to the mandatory ligation of the arterial blood supply [IV, B]. *En bloc* colonic and mesentery resection is recommended in order to clearly define stage II versus stage III and to identify and eradicate potential lymph node metastases, at least 12 lymph nodes should be resected when feasible [IV, B] [40]. Likewise, *en bloc* resection of adjacent organ invaded portions must be carried out in case of pT4b [41] [I, B].

During the procedure a complete assessment of the peritoneal cavity and ovaries should be carried out to investigate for possible metastasis [41] [I, C]. (See ESMO guidelines for metastatic colorectal cancer for the management patients with removed metastasis [42]).

Laparoscopic colectomy can be safely carried out for colon cancer when technical expertise is available in the absence of contraindications in view of reduced morbidity, improved tolerance and similar oncological outcomes [I, C]

[43, 44].

Obstructive CRCs can be treated in one or two stages. Two-stage procedures can include colostomy followed by colonic resection or, in the case of bowel perforation, Hartmann's procedure followed by colostomy closure and anastomosis. One-stage procedures are preferred when carried out by experienced teams; subtotal colectomy and ileorectal anastomosis or segmental resection after intraoperative colonic lavage are alternatives in selected cases [III]. Colonic stenting [45, 46] can be used in expert centres as a bridge to elective surgery, especially in patients with higher rates of postoperative complication after emergency surgery [>70 years old and/or American Society of Anesthesiologists (ASA) >II] [II].

Recommendations

- *En bloc* endoscopic resection of the polyp is sufficient for non-invasive (pTis, i.e. intraepithelial or intramucosal) adenocarcinomas [IV, B].
- The presence of invasive carcinoma (pT1) in a polyp requires a thorough review with the pathologist and surgeon. High-risk features mandating surgical resection with lymphadenectomy include lymphatic or venous invasion, grade 3 differentiation, significant (grade >1) and tumour budding [IV, B].
- Laparoscopic colectomy can be safely carried out for colon cancer when technical expertise is available in the absence of contraindications, in view of reduced morbidity, improved tolerance and similar oncological outcomes [I, C].
- Obstructive CRCs can be treated in one- or two-stage procedures, as indicated [III, B].

PATHOLOGICAL REPORT

Pathological reporting should be carried out at the time of surgery to precisely define nodal spread of disease and extension of the tumour through the bowel wall and onto adjacent structures, as well as to assess biopsies when a suspicion of liver or peritoneal metastases has been identified by the surgeon.

The standard assessment should include [47]:

- morphological description of the specimen;
- surgical procedure carried out;
- definition of tumour site and size;
- presence or absence of macroscopic tumour perforation;
- histological type and grade;
- extension of tumour into the bowel wall and adjacent organs (T stage);
- distance of cancer from resected margins (proximal, distal and radial);
- presence or absence of tumour deposits;
- lymphovascular and/or perineural invasion;
- presence of tumour budding [37];
- site and number of removed regional lymph nodes and their possible infiltration by cancer cells (N stage);
- involvement of other organs (e.g. peritoneum) if submitted either removed or biopsied (M stage)
- Mismatch repair (MMR)/microsatellite instability (MSI) status of the tumour

The pathological stage must be reported according to the Union for International Cancer Control (UICC) tumour, node, metastasis (TNM) classification, 8th edition [48] (see **Supplementary Table S1**, available at *Annals of Oncology* online).

Recommendation:

- A standard surgical/pathological report should include specimen description, and surgical procedure, tumour site and size, macroscopic tumour perforation, histological type and grade, extension into the bowel wall and adjacent organs, distance of cancer from resected margins (proximal, distal and radial), presence or absence of tumour deposits, lymphovascular and/or perineural invasion, tumour budding, site and number of removed and involved regional lymph nodes, MMR/MSI status and involvement of other organs [IV, A].

RISK ASSESSMENT

Definitive decisions regarding adjuvant treatment indication can only be made after discussing in detail the risk/benefit ratios of available options with the patient. To this end, the risk of tumour recurrence must be integrated with expected benefits and complications from the given adjuvant treatment (see Figure 2).

Assessment of recurrence risk and expected benefits from adjuvant therapy

The assessment of risk of recurrence is important in deciding when to recommend systemic adjuvant treatment with the aim of reducing risk of relapse and death. The risk of relapse after colon cancer resection is estimated by integrating the clinicopathological features of the tumour with the molecular marker MMR/MSI status [49].

TNM staging remains the most relevant histological criteria for risk assessment after surgery of colon cancer. Reported 5-year survival rates after surgical resection alone are 99% for stage I, 68%–83% for stage II and 45%–65% for stage III disease [48].

In addition, for intermediate stage II, further parameters need consideration to fine-tune the evaluation of risk given the observed variability on prognosis [II] [49]:

Major prognostic parameters for stage II risk assessment [II] [48–50]:

- Lymph nodes sampling <12;
- pT4 stage including perforation;

Minor prognostic parameters for stage II risk assessment [49] [II]:

- High grade tumour;
- Vascular invasion;
- Lymphatic invasion;

- Perineural invasion;
- Tumour presentation with obstruction;
- High preoperative CEA.

In general, it has been established that adjuvant systemic therapy decreases the risk of death by an absolute 3%–5% in high-risk stage II colon cancer with single-agent 5-fluorouracil (5-FU) and by 10%–15% in stage III disease with fluoropyrimidines alone, with a further 4%–5% improvement with oxaliplatin-containing combinations [I, A].

MSI/MMR status is the most validated prognostic molecular marker used in deciding adjuvant therapy next to clinical prognostic factors.

Deficient DNA MMR status can be identified by immunohistochemistry detecting loss of MMR protein expression (MLH1, MSH2, MSH6 or PMS2), or by polymerase chain reaction (PCR) assays of MSI status (microsatellite mutations). Determining MSI/MMR status in localised colon cancer patients has two objectives: to characterise the prognosis and prediction of adjuvant benefit and determine potential genetic predisposition.

MSI/MMR status determination is important to rule out Lynch syndrome. The presence of MSH2 and or MSH6 loss by IHC indicates suspicion of Lynch syndrome, while MLH1 and PMS2 loss needs to be investigated further by determining *BRAF* mutation or hypermethylation of the promoter region of *hMLH1*. The identification of either of these alterations suggests with high probability the presence of a *MLH1* gene somatic acquired alteration rather than Lynch syndrome [11]. Besides its implications for Lynch syndrome diagnosis, MSI/MMR status defines, in localised colon cancer, a subgroup of patients with a better prognosis and less expected benefit from chemotherapy [51-55]. In particular, MSI/MMR may be useful to identify a small (10%–15%) subset of stage II patients who are at a very low risk of recurrence and in whom the benefits of fluoropyrimidines have not been demonstrated and thus adjuvant chemotherapy should not be indicated [I, A] [51-55].

Nomograms have been developed as tools to standardise decision-making in the adjuvant setting; however, their use is not widely implemented [56].

Assessment of risk of complications from adjuvant treatment:

Administration of an adjuvant treatment should only be done by experienced sites, with a good knowledge of side-effects and (necessary) dose reduction schedules. Despite the proven benefit for patients with stage III and II disease, the (relative) counter-indications have to be considered: E.g. Eastern Cooperative Oncology Group (ECOG) performance status >2, uncontrolled infection, severe liver and renal dysfunction and heart failure [New York Heart Association (NYHA) III and IV]. Furthermore, other life-prognosis determining comorbidities have to be taken into account.

Dihydropyrimidine dehydrogenase (DPD) is the main enzyme involved in fluoropyrimidine metabolism. Approximately 3%–5% of patients have deficiencies of DPD function due to genetic polymorphisms leading to increased fluoropyrimidine toxicity, that can be lethal [57]. Based on the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) dated the 13 of March 2020, testing for DPD insufficiency should be conducted before initiating fluoropyrimidine-based chemotherapy [III, A]. There are two main ways to assess DPD functionality: through genotyping the *DPYD* gene or through phenotyping DPD function.

Genotyping identifies pathologic polymorphisms in the *DPYD* gene: mainly DPYD*2A, c.1679T>G, c.2846A>T or c.1236G>A [56]. In the presence of a heterozygous polymorphism, fluoropyrimidine dose should be reduced by 50%, while with homozygous polymorphisms, fluoropyrimidines should not be used due to the high risk of complications [III, A], according to a Dutch cohort observational trial [56]. Phenotyping allows assessment of DPD functionality by measuring the dihydrouracil/uracil ratio in blood [58]. For levels >0.16 ng/ml dose should be reduced by 50% and for levels >100 ng/ml fluoropyrimidines are contraindicated [III, A] [57]. In this situation, raltitrexed may be an option for those patients with high risk of recurrence [V] [59].

Age is another criterion for risk assessment in the adjuvant setting although remains controversial. Analyses from a Canadian database (n= 2.801) in

Ontario indicate that patients in stage III disease between the age of 70–79 years received adjuvant treatment in 68% and for patients >80 years in 24% [59]. In this retrospective analysis, all age groups benefited about the same level. However, the indication for an adjuvant treatment had to be associated with the Charlson Comorbidity Index, ensuring that only 'fit' elderly patients receive an adjuvant treatment. However, all generalisations from clinical randomised trials are difficult to do, since patients >75yrs are underrepresented and/or excluded.

On the other hand, the addition of oxaliplatin to any fluoropyrimidine should be used with caution in this population [60, 61]. A pooled analysis from 4 randomised trials NSABP-C08, XELOXA, X-ACT and AVANT has shown that in all age groups, treatment with oxaliplatin can be considered, if clinically indicated [62]. The Hazard Ratio (HR) for overall survival (OS) with oxaliplatin was 0.78 for patients of 70yrs or older; however, younger patients experienced a greater benefit (HR 0.62) and had a significantly lower rate of toxicity. Similar data were demonstrated in the NO16968 trial (XELOX versus bolus 5FU/FA: HR for OS in patients 70yrs or older: 0.91 (0.66-1.26) versus 0.80 at younger patients) [61]. A similar existing, but reduced benefit also occurred in the analysis of the ACCENT database [63].

Use of personalised medicine in localised colon cancer/biomarkers for risk assessment

Besides MSI status, other genetic markers, e.g. of *RAS* and *BRAF* mutations are not recommended for the routine assessment of risk of recurrence in non-metastatic patients, based on their lack of utility in the adjuvant decision-making process [64]. However other biomarkers such as gene signatures, Immunoscore™ and postoperative circulating tumour DNA (ctDNA) have demonstrated some benefit in determining the risk of recurrence and can be considered in addition to pathological features and MSI status to further tailor the adjuvant decision making in difficult cases [65-68].

Gene signatures have emerged as potential candidates for prognostic

stratification in locoregional disease. At the time of writing, only Oncotype DX® [65] and GeneFx® Colon [66] have been validated in multivariate analysis of independent prospective randomised cohorts of stage II colon cancer with formalin-fixed paraffin-embedded (FFPE) tumour samples. Although routine clinical utility is not warranted due to lack of predictive value for chemotherapy benefit and the small prognostic differentiation margins between high, intermediate and low scores, their use might be considered in complementing clinicopathological information on intermediate-risk stage II scenarios: i.e. to treat T3 N0 classified as high risk by the signature, or for avoiding chemotherapy in T4 N0 classified as low risk by the signature [II, C].

Immunoscore™ has been recently validated in a large prospective cohort of >2500 patients TNM stage I-III [67]. Immunoscore™ was a strong predictor for time to recurrence, OS and disease-free survival (DFS) (all $P<0.0001$), independently of patient age, sex, MSI and other existing prognostic factors. Immunoscore™ had the highest relative contribution to the risk of all clinical parameters, including the UICC TNM classification system [67]. Therefore, Immunoscore™ could help refine the prognosis of early colon cancer patients in conjunction with the TNM scoring [III, C]. However, its role in predicting chemotherapy benefit is uncertain and firm evidence of its prognostic role in a stage II-only dataset is currently lacking.

Finally, ctDNA monitoring, also known as liquid biopsy, is a promising tool under investigation to identify patients with high risk of recurrence after primary tumour resection. Indeed, ctDNA detection after stage II colon cancer resection has been demonstrated to provide direct evidence of residual disease and to identify patients at very high risk of recurrence [68]. The results of ongoing trials investigating the role of ctDNA as a tool to stratify patient's risk of relapse and to determine allocation to different adjuvant therapeutic strategies must be awaited before this is accepted in routine practice. The CIRCULATE-IDEA and de Circulatie-Europa collaborations seek to pool the data coming from the main national trials exploring ctDNA follow-up in the adjuvant setting. The results of this initiative will probably set the final role of ctDNA in the adjuvant decision-making process.

Recommendations

- Adjuvant therapy options should be fully discussed with the patient, taking into consideration tumour risk of recurrence, expected benefit from chemotherapy and risk of complications.
- The risk of relapse after a colon cancer resection should be assessed by integrating the TNM staging, MMR/MSI status and number of lymph nodes sampled (+/- 12) [III, A].
- Other additional clinicopathological features such as the histological subtype and grading, lymphatic or venous or perineural invasion, lymphoid inflammatory response, involvement of resection margins and serum CEA should be taken into consideration for 'fine-tuning' the risk assessment on stage II tumours [III, A].
- Patient age alone has no predictive value for or against the indication to an adjuvant treatment and must be considered in the context of (potential) benefit, underlying risk for relapse, life expectancy in relation to (biological) age and comorbidities. However, it can be generalised that benefits of treatment with both, fluoropyrimidines alone and plus/minus oxaliplatin, seem to be more limited, with a higher likelihood for toxicity.
- MSI/MMR status is the only validated molecular marker used in adjuvant decision making and should be determined in stage II CRC. In stage III, usage of MMR status is limited to detect and identify Lynch syndrome [IV, A].
- DPD genotyping or phenotyping is strongly recommended before initiating fluoropyrimidine-based adjuvant therapy according to regulatory bodies [III, A].
- Gene expression signatures are not recommended for routine practice due to lack of predictive value for chemotherapy benefit; however, clinicians and patients may consider their use to complement clinicopathological information in intermediate risk stage II scenarios although their role in predicting chemotherapy benefit is uncertain [II, C].
- Immunoscore™ could be considered to refine the prognosis of early colon cancer patients used in conjunction with the TNM scoring and thus adjust the chemotherapy decision-making process in stage II and even in low-risk stage III patients [III, C], although its role in predicting

chemotherapy benefit is uncertain.

TREATMENT OPTIONS

Stage III disease

The current standard of care for adjuvant therapy in stage III colon cancer is a combination of fluoropyrimidine and oxaliplatin. The benefit of these combinations over fluoropyrimidine monotherapy, the prior standard of care, has been demonstrated in three landmark trials: MOSAIC, NSABP C-07 and XELOXA. All showed significant improvement in DFS compared with fluoropyrimidine as single agent [69-71]. The MOSAIC study used an infusional fluoropyrimidine regimen in both arms [leucovorin/5-fluorouracil (LV5FU2) and leucovorin/5-fluorouracil/oxaliplatin (FOLFOX)], the NSABP C-07 study used a bolus fluoropyrimidine regimen in both arms [Roswell Park and leucovorin/5-fluorouracil /irinotecan/oxaliplatin (FLOX)], whereas the XELOXA study used a bolus fluoropyrimidine regimen (Mayo Clinic or Roswell Park) compared with capecitabine plus oxaliplatin (CAPOX). The MOSAIC and NSABP C-07 studies included both stage II and stage III colon cancer, while the XELOXA study included only stage III colon cancer.

Although the chemotherapy regimens in the three studies were different, the addition of oxaliplatin resulted in a similar reduction in risk of recurrence in all three studies (23% in MOSAIC and 20% in NSABP C-07 and XELOXA). With longer follow-up, all three trials showed improved OS from the addition of oxaliplatin with a risk reduction of death of 16% in MOSAIC, 12% in NSABP C-07 and 17% in XELOXA [62, 69,72]. However, a significant improvement in OS was only shown to be significant for stage III colon cancer.

FOLFOX and CAPOX remain the current standard of care. As the FLOX regimen results in increased incidence of diarrhoea compared with FOLFOX or CAPOX, FLOX is not currently recommended in clinical practice; in addition,

irinotecan, cetuximab and bevacizumab have not demonstrated clinical activity in the localised setting and therefore they should never be used as adjuvant treatment in this setting [I, E] [73-77].

IDEA collaboration, choice of regiment and treatment duration of adjuvant treatment

The major cumulative toxicity from a fluoropyrimidine/oxaliplatin doublet is sensory peripheral neuropathy. Worldwide, there have been six studies investigating whether 3 months of adjuvant chemotherapy is non-inferior to 6 months treatment, with the aim of thereby diminishing the incidence of neuropathy and healthcare costs. These six trials have been examined prospectively by an international collaboration and published as the IDEA study [78]. In this pooled analysis, 12,834 patients with stage III colon cancer were randomised to receive either 3 months or 6 months of a fluoropyrimidine/oxaliplatin doublet (either FOLFOX or CAPOX); the choice of regimen was mainly the clinician's choice and not randomised. The 3-year DFS rates was similar (overall: 74.6% and 75.5% for 3 months and 6 months, respectively) but the pre-defined non-inferiority margin, accepting a 12% decrease as upper limit of inferiority to be ruled out, was not confirmed in the overall study population (HR, 1.07; 95% confidence interval [CI], 1.00 to 1.15).

However, sensory peripheral neuropathy grade 2 or worse was significantly reduced from 34% with 6 months of treatment to 11% with 3 months of treatment.

In the IDEA study, the treatment duration depends on the choice of regimen. For patients receiving CAPOX, 3 months treatment was non-inferior with 3-year DFS of 75.9% and 74.8% for 3 and 6 months respectively whereas for FOLFOX, 3 months treatment was inferior with 3-year DFS of 73.6% and 76.0% for 3 and 6 months respectively. Therefore, non- inferiority of the shorter regimen was seen for CAPOX (HR, 0.95; 95% CI, 0.85 to 1.06) but not for FOLFOX (HR, 1.16; 95% CI, 1.06 to 1.26).

Thus, both CAPOX for 3 months and FOLFOX for 6 months can be recommended as adjuvant chemotherapy regimens for stage III colon cancer [I,

A]. It is important to mention that CAPOX and FOLFOX assignment in the IDEA trials was not randomised, precluding any formal comparison between the two regimens.

CAPOX mitigates the need for central venous access and decreased neurotoxicity rates if 3 months is adequate but is associated with more diarrhoea and hand-foot syndrome than FOLFOX; thus, it may be relatively contraindicated if a patient has an ileostomy and in cases of renal insufficiency. FOLFOX has higher reported neutropenia rates. Immediate oxaliplatin cessation following occurrence of grade >1 neuropathy is recommended in all cases (whatever the regimen and treatment duration) to avoid long-lasting symptomatic neurotoxicity that will impair the patient's quality of life.

Definition of risk groups in stage III

The IDEA study also conducted an exploratory analysis based on risk subgroups. In the lower-risk subgroup (defined as patients with T1, T2 or T3 with N1 disease), 3 months of adjuvant therapy appeared to be sufficient, when CAPOX was chosen [II, B]. In the higher-risk group (patients with T4 or N2 or both), 6 months of treatment may be necessary, especially when FOLFOX is the chosen regimen, but also with CAPOX, which missed the non-inferiority margin on this subgroup [II, B].

However, the panel believes that the establishment of stage III risk subgroups should be used with caution, since this was a *post hoc* analysis on the IDEA collaboration: T4 versus T1–3 and N2 versus N1 subgroups analyses were pre-specified in the protocol but their combination in high versus low-risk subgroups was not, and moreover, its interaction test was not significant (P=0.11). Thus, the panel agrees that the established high- versus low-risk subgroups in stage III based on IDEA should have level of evidence [V] (see Figure 3 for adjuvant treatment recommendations in stage III).

Recommendations

- Combinations of fluoropyrimidines, either 5-FU or capecitabine, and oxaliplatin constitute the bases for stage III colon cancer adjuvant

treatment [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: B].

- The length of oxaliplatin-based adjuvant treatment for stage III colon cancer based on the IDEA data may be tailored to 3 or 6 months for CAPOX [I, A] or 6 months for FOLFOX [I, A] also taking into consideration pathological risk characteristics, patient comorbidity and risk assessment.
- Further adaptation of the treatment according to risk subgroups: 3 months for CAPOX (T1–3 N1 disease), 6 months for CAPOX (T4 or N2 disease) or 6 months for FOLFOX (T1–3 N1 or T4 or N2 disease) based on IDEA collaboration should be made with caution, since this was based on a *post hoc* analysis, non-significant for interaction [V].
- For patients not fit for or not tolerating oxaliplatin, either capecitabine or LV5FU2 (de Gramont) infusion are acceptable adjuvant regimens for a 6-month duration [I, A].

Stage II disease

As already discussed, there are major and minor clinicopathological factors that impact on the risk of relapse on stage II colon cancer. The presence of major factors including pT4 stage or <12 lymph nodes assessed confers increased risk of recurrence, while the presence of other additional risk factors is less significantly associated with risk of relapse [48-50]. While follow-up is an option for low-risk stage II patients, chemotherapy is recommended for intermediate and high-risk patients [I, B].

Although the de Gramont is the only regimen that has demonstrated efficacy in the setting [I, B], capecitabine is an option especially with contraindications for insertion of a central line [V]. It is also felt by the panel members that patients with high risk, patients with pT4 and/or less <12 lymph nodes or accumulation of several intermediate risk factors, might be considered for the addition of oxaliplatin therapy based on a trend to an increased benefit, although this did not achieve statistical significance in the stage II high-risk subgroup analysis of MOSAIC trial [I, B] [69]. For this high-risk population, the IDEA trial explored the optimal duration of the oxaliplatin-based adjuvant treatment, finding identical

results to those reported for stage III patients, a non-proven non-inferiority for 3 months of treatment and, there was a proven non-inferiority of CAPOX and inferiority of FOLFOX 3 months when compared with 6 months of FOLFOX [79] with all the limitations of these *post-hoc* analyses as stated before. The presence of MSI/MMR in localised disease confers better prognosis and less benefit to adjuvant therapy so chemotherapy should be indicated with caution and always in combination with oxaliplatin [51–55] (see Figure 4 for integration of clinicopathological and molecular factors with therapeutic recommendations).

Lifestyle factors are likely to have an important impact on survival following adjuvant chemotherapy in either stages II or III patients, as reported for physical activity and nut consumption [80, 81]. In addition, aspirin reduces the risk of polyp formation and may also improve survival after adjuvant chemotherapy in *PI3K*-mutant colon cancer patients (approximately 20% of all patients) [82]. The ADD-ASPIRIN and ASPIK randomised studies are aiming to answer this question definitively.

Recommendations

- For patients with low-risk stage II colon cancer, follow-up is recommended [I, A].
- For patients with intermediate risk (non-MMR/MSI + any risk factor except pT4 or <12 lymph assessed) 6 months fluoropyrimidines should be recommended [I, B].
- Patients with high-risk stage II (pT4 or <12 lymph nodes or multiple intermediate risk factors, regardless of MSI) may be considered for the addition of oxaliplatin [I, C].
- Patients with high-risk stage II colon cancer may be considered for 3 months of CAPOX, as the IDEA-pooled analysis showed non-inferiority of 3 months of CAPOX and inferiority of 3 months of FOLFOX when compared with 6 months of FOLFOX, with all the limitations of *post-hoc* analyses [II, B].

Timing of adjuvant chemotherapy

Delay between surgery and the beginning of adjuvant chemotherapy is a matter of debate. In view of the evidence, it is important to commence adjuvant chemotherapy as soon as possible after surgery and ideally not later than 8 weeks [II, B]. A meta-analysis of 14 studies showed that a delay of >8 weeks in starting adjuvant chemotherapy is associated with a higher relative risk of death (HR 1.20; 95% CI 1.15–1.26, *P*=0.001) [83]. This observation has been confirmed by other groups [84, 85]. However, population-based studies have shown that adjuvant chemotherapy might still provide some benefit, even with delays up to 5–6 months [86, 87], but it seems that the benefit of adjuvant chemotherapy is minimal or completely lost if treatment is started >6 months after surgery.

Recommendation

- It is important to start adjuvant chemotherapy as soon as possible after surgery and ideally not later than 8 weeks [I, A].

FOLLOW-UP AND LONG-TERM IMPLICATIONS

Follow-up

Overall, between 30% and 50% of all patients treated for localised colon cancer will eventually relapse and die from the disease [88, 89]. The main goal of follow-up protocols is detecting relapse on an early basis, thereby maximising patient survival on the metastatic setting. Systematic reviews have shown disparate results regarding the use of intensive follow-up as a tool to increase OS [90, 91]. However, it has been shown that there is an advance in the detection of recurrences [II, B] with intensive follow-up [91]. Detection of isolated local recurrences was increased in the intensive group (15% compared with 9%, with risk ratio 1.61 and *P*=0.011), along with a small, non-significant increase in the detection of hepatic metastases [91]. However, heterogeneity of the studies included in these meta-analyses does not allow precise assessment of algorithms for optimal surveillance in clinical practice. Only trials including clinical assessment, CEA testing and/or liver imaging achieve significant improvements in survival, though all studies considering liver imaging also

included blood CEA monitoring [92].

CT scan including optimal liver assessment has been shown to be more sensitive than ultrasonography (0.67 compared with 0.43) for liver relapse follow-up and, in addition, can detect chest recurrences. On the other hand, liver MRI may be an alternative when a CT scan has shown confusing liver lesions [93].

Regarding the timing and duration of follow-up, protocols need to be sensitive to the patterns of relapse of colon cancer. Among recurring patients, 80% of relapses occur during the first 3 years and an additional 15% between the 3rd and 5th year, which supports a more intensive follow-up during the first 3 years and a stop after 5 years [88, 93].

In addition to CEA and CT scans, colonoscopies should also be included on the follow-up since metachronous primary cancer can be detected with an incidence of 0.7% within the first 2 years after curative surgery [94]. However, there is no indication for intensive endoscopic follow-up. If a colon without tumour or adenoma is observed 1 year after resection, colonoscopy should be carried out after 3–5 years [94] (see Figure 5 for colon cancer follow-up after curative resection).

Recommendations

- Intensive follow-up allows earlier detection of relapses in patients at risk [II, B].
- History and physical examination and CEA determination are advised every 3–6 months for 3 years and every 6–12 months at years 4 and 5 after surgery [II, B].
- Colonoscopy must be carried out at year 1 and every 3–5 years thereafter, looking for metachronous adenomas and cancers [III, B].
- CT scan of chest and abdomen every 6-12 months for the first 3 years can be considered in patients who are at higher risk of recurrence according to the TNM classification [II, B].
- Other laboratory and radiological examinations are of unproven benefit and must be restricted to patients with suspicious symptoms [V, C].

Long-term implications/survivorship care plans

CRC survivors represent the third largest group of long-term cancer survivors in Western countries, ~11% of this population. For this group, additional post-therapeutic follow-up interventions have demonstrated to improve patient outcomes [95]. In this setting, the primary practitioner should have a significant role in collaborating with the oncological teams [96,97].

Major elements in survivorship care are as follows:

1. Prevention of recurrent and new cancer (classic end point of follow-up).
2. Intervention for cancer sequelae and their treatment (rehabilitation).
3. Assessment of medical and psychological late effects (modern end point of follow-up).
4. Health promotion (lifestyle promotion, comorbidity prevention, etc.).

Most long-term survivors of CRC report good quality of life following treatment, but several problems are still observed [98]. A significant proportion of patients have persistent bowel dysfunction. It is important to refer for dietary counselling and suggest use of over-the-counter medications (e.g. fibre laxatives, stool softeners, antidiarrheals). Colostomies and ileostomies represent also a source of physiologic distress and disturbances at the level of social functioning. Patients should be encouraged to take part in ostomy management programmes and psychological distress management programmes must be recommended in case of discomfort with their body changes.

Colon cancer survivors experience higher rates of sexual distress and psychological depression [98]. Assessment of distress should be considered, but evidence on the effectiveness of psychosocial interventions among survivors of CRC is limited. Patients should be encouraged to maintain a healthy lifestyle including exercise, quitting smoking, avoidance of excessive alcohol intake and adoption of a healthy diet rich in vegetables, fruit and berries adapted to the remaining gastrointestinal function [99].

Recommendation:

- Long-term follow-up, rehabilitation and survivorship care programs

should be implemented, aiming at detection of recurrent or new cancers, assessment and management of late and psychosocial effects and implementation of health promotion measures [III, A].

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with ESMO-MCBS scores is included in **supplementary Table S2**, available at *Annals of Oncology* online [100]. ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in **supplementary Table S3**, available at *Annals of Oncology* online [101]. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

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Table 1. Diagnostic work-up for localised CRC

Figure 1. Diagnostic algorithm for localised colon cancer

Figure 2. Factors to guide adjuvant decision making

Figure 3. Recommendations for adjuvant treatment of stage III colon cancer

CAPOX, capecitabine plus oxaliplatin; FOLFOX, leucovorin/fluorouracil/oxaliplatin; MCBS, magnitude of clinical benefit scale; MSI, microsatellite instability; MSS, microsatellite stability.

Figure 4. Recommendations for adjuvant treatment of stage II colon cancer

CAPOX, capecitabine plus oxaliplatin; CEA, carcinoembryonic antigen; FOLFOX, leucovorin/fluorouracil/oxaliplatin; MSI, microsatellite instability; MSS, microsatellite stability.

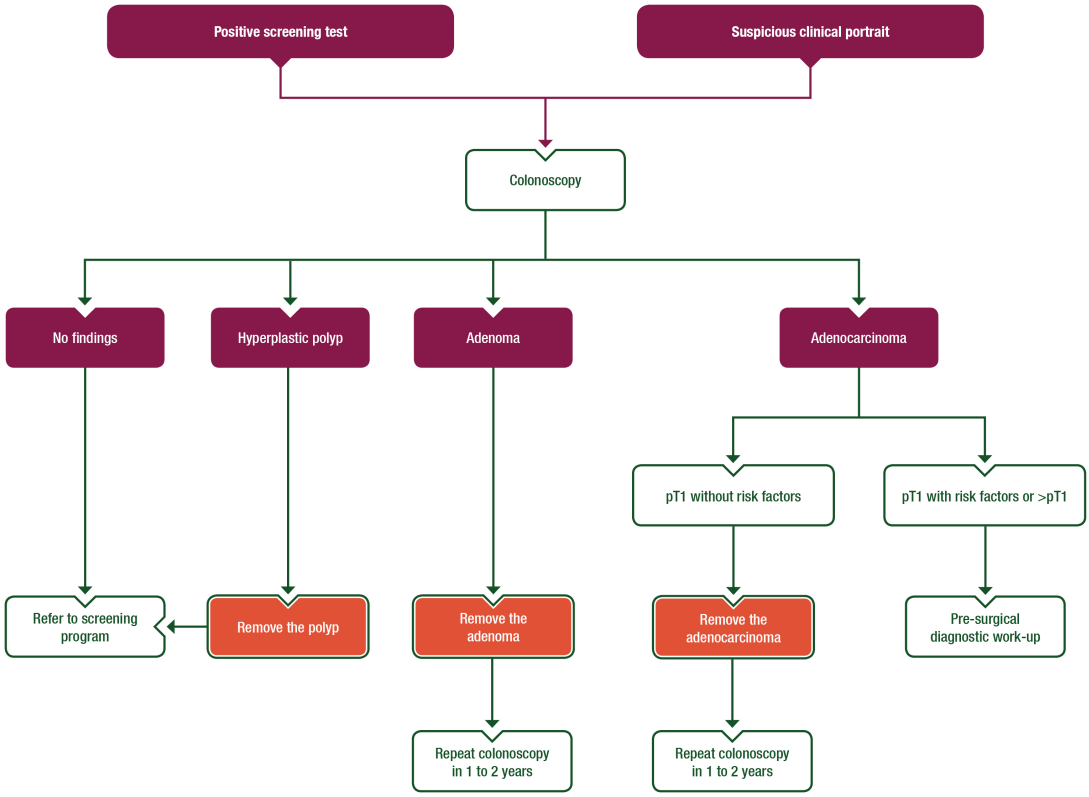
[a] For pT4 MSI: pT4 is a major risk factor but adjuvant chemotherapy benefit in the presence of MSI is uncertain.

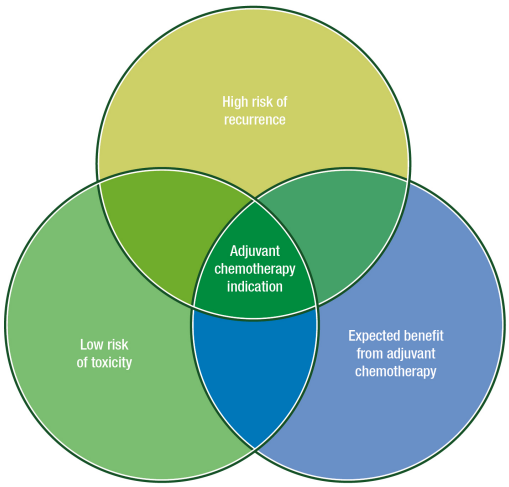
Figure 5. Recommendations for follow up after curative resection

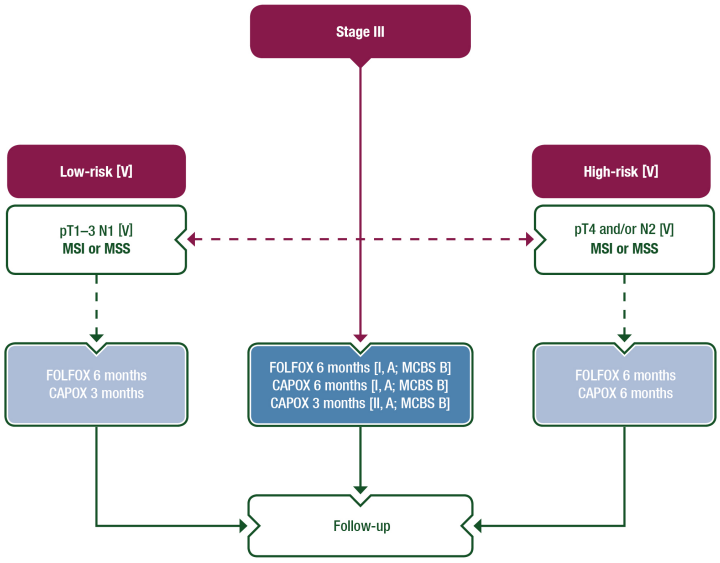
CEA, carcinoembryonic antigen; CT, computed tomography; mCRC, metastatic colorectal cancer.

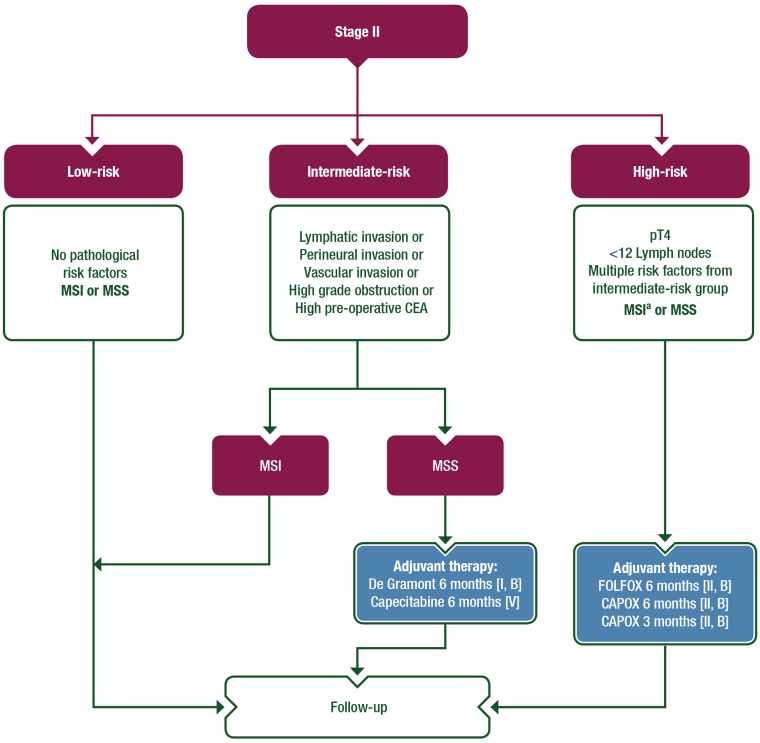
Local assessment	**LoE, GoR**
Complete colonoscopy	I, A
Imaging work-up	
CT scan: • Lung • Abdominal • Pelvic	 V I, B I, B
CT colonography (when complete colonoscopy is not feasible)	I, A
MRI abdominal (to clarify ambiguous lesions or define pT4b)	II, A
Laboratory work-up	
Complete blood count	II, A
Coagulation	II, A
Liver function panel	II, A
Kidney function panel	II, A
Albumin	III, A
CEA	III, A

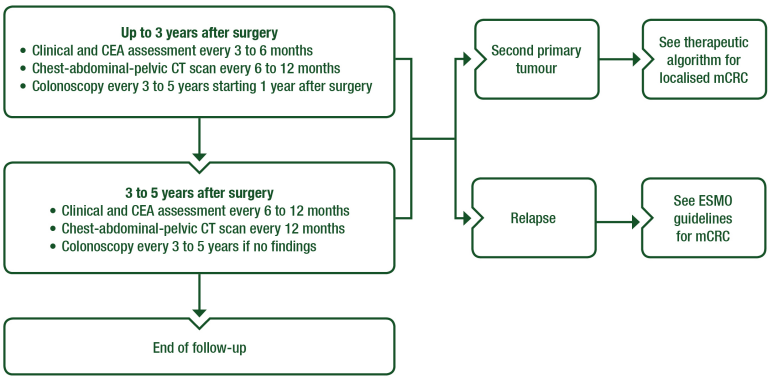
CEA, carcinoembryonic antigen; CRC, colorectal cancer; CT, computed tomography; GoR, grade of recommendation; LoE, level of evidence; MRI, magnetic resonance imaging.


Positive screening test
Suspicious clinical portrait
Colonoscopy
No findings
Hyperplastic polyp
Adenoma
Adenocarcinoma
pT1 without risk factors
pT1 with risk factors or >pT1
Refer to screening program
Remove the polyp
Remove the adenoma
Remove the adenocarcinoma
Pre-surgical diagnostic work-up
Repeat colonoscopy in 1 to 2 years
Repeat colonoscopy in 1 to 2 years


High risk of recurrence
Adjuvant chemotherapy indication
Low risk of toxicity
Expected benefit from adjuvant chemotherapy


Stage III
Low-risk [V]
High-risk [V]
pT1–3 N1 [V]
MSI or MSS
pT4 and/or N2 [V]
MSI or MSS
FOLFOX 6 months
CAPOX 3 months
FOLFOX 6 months [I, A; MCBS B]
CAPOX 6 months [I, A; MCBS B]
CAPOX 3 months [II, A; MCBS B]
FOLFOX 6 months
CAPOX 6 months
Follow-up


Stage II
Low-risk
Intermediate-risk
High-risk
No pathological risk factors
MSI or MSS
Lymphatic invasion or Perineural invasion or Vascular invasion or High grade obstruction or High pre-operative CEA
pT4
<12 Lymph nodes
Multiple risk factors from intermediate-risk group
MSI[a] or MSS
MSI
MSS
Adjuvant therapy:
De Gramont 6 months [I, B]
Capecitabine 6 months [V]
Adjuvant therapy:
FOLFOX 6 months [II, B]
CAPOX 6 months [II, B]
CAPOX 3 months [II, B]
Follow-up


Up to 3 years after surgery
• Clinical and CEA assessment every 3 to 6 months
• Chest-abdominal-pelvic CT scan every 6 to 12 months
• Colonoscopy every 3 to 5 years starting 1 year after surgery
3 to 5 years after surgery
• Clinical and CEA assessment every 6 to 12 months
• Chest-abdominal-pelvic CT scan every 12 months
• Colonoscopy every 3 to 5 years if no findings
End of follow-up
Second primary tumour
See therapeutic algorithm for localised mCRC
Relapse
See ESMO guidelines for mCRC