CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for diagnosis and treatment of metastatic colorectal cancer (2018)

M. A. Gómez-España · J. Gallego · E. González-Flores · J. Maurel · D. Páez · J. Sastre · J. Aparicio · M. Benavides · J. Feliu · R. Vera

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Abstract
Colorectal cancer (CRC) is the second cause of cancer death in Spain, the objective of this guide published by the Spanish Society of Medical Oncology is to develop a consensus for the diagnosis and management of metastatic disease. The optimal treatment strategy for patients with metastatic CRC should be discussed in a multidisciplinary expert team to select the most appropriate treatment, and integrate systemic treatment and other options such as surgery and ablative techniques depending on the characteristics of the tumour, the patient and the location of the disease and metastases.

Keywords Colorectal cancer · Metastases · Surgery · Chemotherapy · Targeted agents · Ablative treatments · Frail patients

Introduction
In Spain, 41,441 new cases of CRC were estimated for 2015, representing the second most common tumour type in both sexes. It was more frequent in men (24,764) than in women (16,677) [1]. Twenty to twenty-five per cent of patients have metastatic disease at initial diagnosis and nearly 50% of patients will eventually develop metastases, which explains the high mortality rates reported for CRC. In fact, this tumour accounts for 13.7% and 14.3% of all cancer deaths in men and women, respectively, in our country. SEOM gathered ten CRC experts based on their major scientific contributions in the field. The purpose of this paper was to define the current “state of the art” through
the use of evidence based medicine. The available medical literature was reviewed according to main topics of disease management, and classified by scientific levels of evidence and grades of clinical recommendation (Table 1) [2]. The resulting text was reviewed, discussed, and approved by all authors.

**Staging**

The extent of the disease must be carefully assessed, as well as tumour biology and patient-related factors before starting cancer-specific therapy.

Table 2 shows suggested staging procedures. The recommended staging system is the 8th edition of the American Join Committee on Cancer (AJCC) [3].

**Biomarkers**

In the mCRC setting, biomarkers may be classified as prognostic or predictive biomarkers.

Prognostic biomarkers: Classical clinical and biochemical parameters such as ECOG performance status, WBC count, alkaline phosphatase (AP), lactate dehydrogenase (LDH) and number of metastatic sites have been considered as the main prognostic factors for survival. Recently, a multivariate analysis carried out by the GERCOR group in patients receiving oxaliplatin or irinotecan first-line combinations has shown that ECOG, LDH and number of metastatic sites are the independent most important clinical prognostic factors [4]. A prognostic model classify patients in low risk (0 points, median OS 29.8 months),

| Levels of evidence | Grades of recommendation |
|--------------------|--------------------------|
| I. Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity | a. Strong evidence for efficacy with a substantial clinical benefit, strongly recommended |
| II. Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity | b. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended |
| III. Prospective cohort studies | c. Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,), optional |
| IV. Retrospective cohort studies or case–control studies | d. Moderate evidence against efficacy or for adverse outcome, generally not recommended |
| V. Studies without control group, case reports, experts opinions | e. Strong evidence against efficacy or for adverse outcome, never recommended |

| Clinical examination | Laboratory tests including liver and renal function tests and prognostic markers (white blood cell count, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, and albumin) |
|---------------------|--------------------------------------------------------------------------------------------------|
| Carcinoembryonic Antigen (CEA) | Pathological review of a tumour biopsy (histological subtype, tumour grade, microsatellite status, and KRAS, NRAS and BRAF mutational status) |
| Computed tomography (CT) scan of the chest, abdomen and pelvis. Magnetic resonance imaging (MRI) could be considered in cases of hepatic metastases and locally advanced rectal tumours | Other tests such as a bone scan or a brain CT scan should be performed only if clinically indicated |
| Complete colonoscopy to locate the primary tumour, to obtain tissue for histological diagnosis, and to detect potential synchronous colorectal lesions. Virtual colonoscopy or barium enema could be useful in case of tumours that impede the progression of the endoscopic tube | Needle biopsy of a patient with known histologic diagnosis is only recommended when it may change the therapeutic strategy |
| Additional examinations, as clinically needed, are recommended prior to major abdominal or thoracic surgery with potentially curative intent | A fluorodeoxyglucose (FDG)-positron emission tomography (PET–CT) scan should be performed in the case of potentially surgically curable M1 disease |

A fluorodeoxyglucose (FDG)-positron emission tomography (PET–CT) scan should be performed in the case of potentially surgically curable M1 disease
Resectable colorectal metastases

Resectable colorectal liver metastases (RLM) are defined as metastatic liver disease in that a R0 resection can be performed, leaving at least a 20–25% of total liver volume as future liver remnant [10].

Preoperative factors found to be independent predictors of poor survival are a primary tumour at stage T4, ≥ 4 liver metastases, the largest liver metastasis ≥ 5 cm in diameter, and a serum CEA level ≥ 5 ng/ml. According to these factors, resectable patients could be divided in high-risk patients (3 or more factors) and low-risk patients (less of 3 factors) [11].

The optimal sequencing of systemic therapy and resection in RLM remains unclear. Patients with resectable disease may undergo resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) systemic therapy can be used.

A 2012 meta-analysis identified 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy. The analysis showed a benefit of chemotherapy in PFS (progression free survival) and DFS (disease free survival) but not in OS (overall survival). Another meta-analysis combined data on 1,896 patients and also found that perioperative chemotherapy improved DFS but not OS. Additional recent meta-analyses have also failed to observe an OS benefit with adjuvant chemotherapy [12].

In low-risk patients, perioperative treatment may not be necessary. (I,C) In high-risk patients, perioperative combination chemotherapy should be administered. (I,B) In high-risk patients, those who had received neoadjuvant chemotherapy had a better overall median survival (38.9 m vs. 28.4 m) than those had not received it, and 5 years OS rate of 39% vs 33% (p = 0.028). In low-risk patients, this difference in median survival (60.0 m vs. 60.0 m) was not found according to whatever received preoperative chemotherapy. In the case of low-risk patients, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy (II, C) whereas patients with unfavourable criteria may benefit from adjuvant treatment.

The preferred treatment in RLM should be FOLFOX (or alternatively CAPOX) as reported for the EPOC trial [13] (IV, B). EGFR-targeting monoclonal antibodies are not recommended to be used in this setting, based on the data from the New EPOC trial [14]. No data with bevacizumab are available for this specific patient group.

Colorectal metastatic disease sometimes occurs in the lung. Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required. Ablative...
techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to ablation or resection. Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.

In patients with limited peritoneal carcinomatosis, complete cytoreductive surgery and HIPEC can be considered in centres with experience.

**Recommendations:** Resection is recommended for resectable liver metastases. Criteria of resectability and prognostic factors are necessary for guiding the need to administer systemic perioperative/adjuvant therapy. Surgery for resectable lung metastases may be considered. Complete cytoreductive surgery and HIPEC can be an option if limited peritoneal carcinomatosis is present.

**Potentially resectable metastatic disease**

Patients with initially unresectable, organ-confined liver and/or lung metastases should be considered candidates for secondary surgery. Conversion therapy offers the best means of achieving the goal of resectability. Survival times for patients resected after chemotherapy are slightly shorter than for those patients with upfront resectable disease, but far better than when surgery is not possible at all. Response to systemic therapy is a strong prognostic indicator and correlates well with resection rates [15]. With the increasing efficacy of current regimens, resectability has to be reevaluated every 2 months (to attain the maximal tumour shrinkage) and surgery scheduled as soon as possible (to minimize chemotherapy-induced liver toxicities and perioperative morbidity). CT morphologic criteria are more predictive of pathological tumour response than RECIST in patients treated with bevacizumab [16].

For fit patients, the most active induction regimens should be administered upfront, generally chemotherapy doublets combined with a biologic agent or chemotherapy triplets plus/minus a biologic. Combinations of either oxaliplatin or irinotecan with fluoropyrimidines are considered adequate options with similar efficacy albeit different toxicity profiles. Patient’s molecular profile should be considered for adding targeted therapies. Comparative trials and meta-analyses suggest that anti-EGFR agents may be more effective in terms of tumour shrinkage than bevacizumab for RAS WT patients [17], especially in left-sided primary tumours [18]. Triplet combination of FOLFOXIRI with or without bevacizumab may be considered in selected (RAS- or BRAF-mutant) patients at the expense of an increased toxicity [19].

**Recommendations:** Fit patients with borderline resectable metastases should receive intensive induction therapy with chemotherapy doublets and a biologic agent, or chemotherapy triplets with or without biologics (II, A). In RAS WT tumours, anti-EGFRs may be more effective than bevacizumab in terms of tumour shrinkage, especially for left-sided primary tumours (II, B). Figure 1.

**Unresectable disease. First-line treatment**

For the purpose of this guideline, treatment with chemotherapy for fit patients with unresectable mCRC at diagnosis or deemed not eligible for radical treatment in the evolution of the disease is considered. In this scenario, main treatment endpoints include prolonging patient survival, relieving symptoms caused by the disease while improving and sustaining quality of life.

Factors considered to influence on first-line treatment decision for unresectable mCRC, once established that all components included in the recommendation should have formal approved indication by national and local regulatory agencies, are patient characteristics and wishes, as well as characteristics of the disease. Unfit patients treatment will be covered anywhere in this guideline, hence we will only concern for patients without conditions which would made them unable to fulfil inclusion criteria for clinical trials that scientifically endorse treatment combinations for first-line treatment of mCRC. Patient personal wishes and circumstances should always be taken into account before establishing any treatment plan.

![Conversion therapy](image_url)

**Fig. 1** Conversion therapy. * The benefit of adding anti-EGFRs in right-sided RAS wild type metastatic colorectal cancer is controversial. Data from meta-analysis suggest a beneficial effect on response rates but not on survival times. ** Combination of FOLFOXIRI plus panitumumab or cetuximab has not been extensively evaluated.
final treatment recommendation. On the other hand, regarding disease characteristics, tumour KRAS, NRAS and BRAF mutational status, as well as tumour sidedness are factors to be considered when selecting first-line treatment for mCRC.

First-line treatment relies on a chemotherapy combination in association with a biologic agent, either bevacizumab or one of the two agents against the epidermal growth factor receptor (EGFR), panitumumab or cetuximab [20, 21]. Chemotherapy combinations include doublets of fluoropyrimidine (5-fluorouracil or capecitabine) and oxaliplatin or irinotecan. Considering all possible treatment combinations, association of capecitabine and irinotecan, as well as association of anti-EGFR antibodies with capecitabine are not recommended. The use of triplet combinations of chemotherapy including 5-fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) has demonstrated safety and efficacy in phase III trials, alone or combined with bevacizumab [22] (I, A).

Evidence of tumour RAS (KRAS, NRAS) mutation has demonstrated to be a negative predictive factor for treatment with antibodies against EGFR, cetuximab and panitumumab (I, A). The consideration of tumour BRAF mutation as a negative predictive factor is still nowadays a controversial issue, although analysis done so far suggest lack of benefit of the treatment with panitumumab and cetuximab in these patients [23].

For patients with RAS and BRAF wild type tumours, primary tumour location may influence in treatment selection. Results from the joint analysis of trials of chemotherapy associated to anti-EGFR antibodies demonstrated greater benefit of first-line treatment with these combinations in left-sided tumours; while for right-sided tumours greater benefit in terms of survival is suggested for chemotherapy combined with bevacizumab [5] (I, A) (Fig. 2).

In case of RAS or BRAF mutated tumours, independently of primary tumour location, first-line treatment recommendation is chemotherapy combinations associated with bevacizumab (I, A) (Fig. 2).

Regarding first-line treatment combinations including bevacizumab, intensified chemotherapy with FOLFOXIRI provides greater benefit to patients with right-sided tumours, and this regime has been also suggested as preferred option for BRAF mutated tumours [22] (II, B) (Fig. 2).

Although molecular knowledge of mCRC has introduced new molecular factors to be considered (microsatellite instability, HER2 amplification or mutation, BRAF subgroups, RET fusions, and ALK, ROS, NTR1K rearrangements, among others), whilst generating consensus molecular subgroups of CRC (immune, canonical, metabolic and mesenchymal), none of these have been established in clinical practice for first-line treatment of mCRC thus far.

The recommendation concerning duration of first-line treatment in mCRC, historically considered to be until disease progression, unacceptable toxicity, or patient desire, has been modified in recent years so that nowadays it is subjected to patient personal circumstances, cumulative treatment toxicity, and aggressiveness of the disease. Hence different strategies have emerged, including stop-and-go and intermittent treatment, as well as maintenance treatment consisting of fluoropyrimidines with or without bevacizumab, for patients for whom disease control has been achieved (I, A). The approach to include these treatment options goes through essential individualization and discussion with the patient.

Recommendations: first line treatment for fit patients with unresectable metastatic colorectal cancer should be based upon patient characteristics and wishes, tumour sidedness and RAS y BRAF status.

Second and successive treatment lines

More than 50% receive second line and more 25% receive third line of treatment. Therapy after first progression will depend on prior treatments, ECOG and adequate organ function, RAS/BRAF status and MSS.

For patients who received oxaliplatin based therapy, FOLFIRI, or irinotecan alone are the preferred options. When the previous treatment was an irinotecan-based combination, the recommended options are FOLFOX or XELOX. With respect to the use of targeted therapies, recommendations are as follows:

Adding bevacizumab or aflibercept to chemotherapy is an option in second-line therapy (I, A) [24, 25]. For patients treated with first-line bevacizumab-containing chemotherapy, the continuation of bevacizumab in conjunction with a second-line chemotherapy improves
OS as compared to just switching the chemotherapy regimen alone although the amount of benefit is inferior compared with bevacizumab-naïve patients [26]. Aflibercept added to FOLFIRI in patients previously progressing on a prior oxaliplatin containing regimen is superior to FOLFIRI plus placebo in RR, PFS and OS [25].

Cetuximab and panitumumab appear to have efficacy when used for salvage therapy in all RAS WT patients EGFR-naïve chemotherapy-refractory mCRC (II,A) [27, 28]. The reintroduction of EGFR inhibitors in subsequent treatment lines is not recommended for previously exposed patients (I, C).

Regorafenib and TAS 102 give a modest benefit in third line therapy [29, 30] compared with best supportive care, and therefore, its use should be restricted to selected patients (I, B).

Immunotherapy with pembrolizumab [31], nivolumab ± ipilimumab [32, 33] for MSI-H/dMMR (4% of mCRC) could be an option for resistant colorectal cancer patients, but at the moment checkpoint inhibitors are approved by the FDA, but not by EMA.

**Recommendations:** the second-third line therapies will depend on the prior line, ECOG and organ functions.

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**Treatment of frail unresectable mCRC patients**

No consensus guidance exists regarding the definition of frailty in patients with cancer, otherwise this term almost always associated with aging. Frailty is associated with dependence, comorbidity, polypharmacy, nutritional and functional status or geriatric syndromes. Treatment results may be biased because acting as a competing cause of death and tolerability in this particularly vulnerable group of patients.

ASCO recently published guidelines for geriatric oncology, recommends a geriatric assessment (GA) for the management of vulnerabilities in older patients (> 65 years) receiving chemotherapy. This GA should include at a minimum, the assessment of function, comorbidity, falls, depression, cognition, and nutrition to obtain estimates of chemotherapy toxicity risk and mortality [34]. However, GA is not a routine in daily practice, but may serve for future research including frail younger patients too.

Evidence-based treatment decisions for unresectable mCRC in this population derives from trials in relatively healthy elderly or different types of frail patients with very few ECOG-2 represented in the trials. To date, integration in a palliative care unit associated or not to specific systemic therapy, is the most important support in these patients.

Both NCCN [35] and ESMO [36] or the adapted for sidedness ESMO-ASIA guidelines [37], recommend some form of therapy in unresectable mCRC patients defined as not appropriate for intensive therapy (NCCN) or unfit (but may be suitable) for ESMO. Fluoropyrimidine monotherapy is the most recommended in patients unable to tolerate aggressive treatment [I,B]. Bevacizumab has been largely study in randomized or not studies and may be added because was safe and increased PFS [38–40].

In wt-RAS and left-sided, anti-EGFR (2B NCCN) therapy can be recommended. A Spanish phase II study with first-line single-agent panitumumab in frail elderly patients with wt-KRAS mCRC and poor prognostic factors showed activity and good tolerance and may be an option for patients not candidates for chemotherapy [41].

If treatment is given, dose-attenuated chemotherapy is always recommended and maintenance therapy or chemotherapy holidays may be appropriate. A randomized study of reduced chemotherapy in elderly and/or frail patients with mCRC (38% with both advanced age and frailty) suggested some benefit in PFS, significant increase in the ORR adding oxaliplatin to 5-FU and that the substitution of intravenous FU with capecitabine had no effect on quality of life [42].

Local ablation techniques are generally used for more selected mCRC but may be considered in patients not amenable to surgery (IV, B).
Early palliative care is recommended for patients with metastatic colorectal cancer.

**Recommendations:** for vulnerable or frail patients with unresectable mCRC, best supportive care should make integral part of their management. In unfit (but may be suitable) patients, dose attenuated chemotherapy with or without monoclonal antibodies may be an option according to RAS/BRAF and location.

### Locoregional ablative treatments

Non-surgical approaches for metastases confined to a single organ (most frequently the liver) may offer survival advantages beyond that of systemic therapy alone. If resection is not feasible, image-guide ablation, embolization or stereotactic body radiation therapy (SBRT) are reasonable options. In patients with a limited number of lesions and involved sites, the selection of the best locoregional ablative therapy strategy should be discussed within a multidisciplinary team (Fig. 3).

#### Thermal ablation

Although there are many different thermal ablation techniques (microwave ablation, ethanol ablation, cryoablation), the use of radiofrequency ablation (RFA) to treat cancer that has spread to the liver is the best understood. In the phase II CLOCC trial, 119 patients with non-resectable colorectal liver metastases were randomized to systemic treatment or systemic treatment plus RFA. The study met the primary end point on 30-month OS rate > 38%; however, this rate was also achieved in the control arm. RFA plus systemic treatment improved PFS rate at 3 years for combined treatment (27.6% vs 10.6% for systemic treatment alone; HR, 0.63; 95% CI 0.42–0.95; \( p = 0.025 \)) [43]. For lung metastases from CRC most evidence supports surgery as the most effective treatment option.

#### Chemoembolization

Hepatic transarterial chemoembolization (TACE) therapy with drug-eluting beads loaded with irinotecan (DEBIRI) has been used in several prospective studies demonstrating an acceptable toxicity profile. In a randomized phase II trial, median OS was significantly longer for patients treated with DEBIRI than for those treated with FOLFIRI (22 mos vs. 15 mos \( p = 0.031 \)) [44]. A recent trial showed that the simultaneous administration of modified FOLFOX (with or without bevacizumab) and DEBIRI significantly increased the objective responses in comparison with the FOLFOX/bevacizumab arm (78% vs 54% at 2 months; \( p = 0.02 \)) [45].

#### Radioembolization

Hepatic arterial radioembolization with yttrium-90 bound to resin microspheres plus fluorouracil (FU) was well tolerated and significantly improved time to liver progression compared with FU alone in a small phase III trial in patients with refractory unresectable colorectal liver metastasis [46]. More recently, in a phase III trial (SIRFLOX study), 530 chemotherapy-naïve patients with liver metastases were randomly assigned to receive either modified FOLFOX ± bevacizumab or modified FOLFOX ± bevacizumab plus selective internal radiation therapy using yttrium-90 resin microspheres (SIRT). Although the primary endpoint was not met, SIRT delayed disease progression in the liver (20.5 vs. 12.6 months in the chemotherapy only arm; HR, 0.69; 95% CI 0.55–0.90; \( p = 0.002 \)) [47].

### High conformal hypo fractionated irradiation

In several retrospective and prospective studies, SBRT and high dose rate brachytherapy have been reported to achieve high local control rates. SBRT offers a safe alternative and non-invasive therapeutic option, for the treatment of selected patients not amenable to surgery with limited number of liver or lung metastases.

**Recommendations:**

1. Local ablative techniques such as thermal ablation or high conformal radiation techniques (e.g., SBRT) can be considered for colorectal liver and lung metastases in patients not suitable to surgery. (IV, B).
2. Chemoembolization and radioembolization are options in highly selected patients with predominant hepatic metastases (IV, B and II, B respectively).

### Compliance with ethical standards

**Conflict of interest** MAGE reports financial support from Angen, Kyowakirin, Merck, Roche and Servier, outside the submitted work. JG reports advisory board from Amgen, Bayer, Ipsen, Lilly, Merck, Roche and Sanofi. Speaker honoraria from Amgen, Ipsen and Lilly and Subsidies from Amgen and Novartis, outside the submitted work. EGF reports Advisory board from Roche, Amgen, Merck, Bayer, Servier and Sanofi, outside the submitted work. JM reports Grants non-renumerated (clinical trial principal investigator) from Merck and Amgen, and grants non-renumerated (Project lead principal investigator) from Nanostring and Biocartis. Also reports personal fees from Sirtex, Pierre-Fabre, Shire, Astrazeneca, Bayer, Servier, Sanofi and Roche, outside the submitted work. DP reports personal fees and non-financial support from Amgen, personal fees from Sanofi, personal fees and non
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Ethical approval The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent For this type of study formal consent is not required.

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