Management of metastatic colorectal cancer patients: guidelines of the Italian Medical Oncology Association (AIOM)

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ABSTRACT

In the past 15 years, the outcome for patients with metastatic colorectal cancer has substantially improved owing to the availability of new cytotoxic and biological agents along with many significant advances in molecular selection, the use of personalised therapy and locoregional treatment, a more widespread sharing of specific professional experiences (multidisciplinary teams with oncologists, surgeons, radiotherapists, radiologists, biologists and pathologists), and the adoption of patient-centred healthcare strategies. The Italian Medical Oncology Association (AIOM) has developed evidence-based recommendations to help oncologists and all professionals involved in the management of patients with metastatic colorectal cancer in their daily clinical practice.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the world. In Italy, 18,756 CRC-related deaths were reported in 2013 and 52,400 new cases have been estimated in 2016.1 Over the past 15 years, the treatment of metastatic colorectal cancer (mCRC) has markedly evolved and significant improvements in the overall treatment plan have been achieved, with median overall survival (mOS) reaching the unprecedented value of over 40 months in molecularly selected patients.

Many advances have led to such notable result being achieved, including the availability of novel efficacious cancer drugs, a more profound knowledge of disease characterisation with molecular biology studies, the application of personalised, patient-centred strategies, the evolution of multidisciplinary teams, and the earlier use of palliative and simultaneous care. In this changing scenario, the Italian Medical Oncology Association (AIOM) has developed evidence-based guidelines to help oncologists and all professionals involved in the management of patients with metastatic colorectal cancer in their daily clinical practice.

METHODOLOGY

The working group

The AIOM guidelines working group includes professionals from across the country with different professional skills, such as medical oncologists, surgeons, radiation oncologists and molecular biologists, which facilitated the analysis of scientific issues as well as different logistic and regulatory aspects in different regions.

A systematic review of the literature was carried out and every 2 months conference calls between authors were held. During the final consensus meeting, a preliminary report was prepared and sent to reviewers for peer review.

The guidelines were revised by several opinion leaders in CRC and by different scientific societies (table 1). The final report, including the accepted recommendations of the reviewers, was eventually published online on the AIOM website.

Recommendation’s methodology

Each recommendation has been made based on the guidelines prescribed by the Scottish Intercollegiate Guidelines Network (SIGN).

The quality of evidences according to SIGN reflects both the type of studies that have been considered, as outlined in table 2, and the clinical applicability of results.

The quality of evidences according to SIGN is reported using the letters A, B, C or D, as described in table 3.

The strength of a recommendation reflects its clinical relevance and is reported as ‘strong for’, ‘strong against’, ‘conditional for’ or ‘conditional against’, as explained in table 4.

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology has been applied...
only for specific debated interventions. The GRADE approach specifically assesses:

► methodological flaws within the component studies
► consistency of results across different studies
► generalisability of research results to the wider patient base
► how effective the treatments have been shown to be.

Treatment comparisons are given one out of four GRADE scores, reflecting the quality of the evidence: high-quality, moderate-quality, low-quality or very low-quality evidence.

### MCRC GUIDELINES

The AIOM guidelines consider the management of all CRC settings, including both adjuvant and metastatic settings. Moreover, the guidelines specifically consider rectal cancers. This first report focuses on advanced CRC.

### MULTIDISCIPLINARY TEAM

A multidisciplinary team discussion is crucial for modern diagnostic and therapeutic decision making. Oncologists, surgeons, radiotherapists, molecular biologists and pathologists must give their specific recommendations for an adequate and personalised treatment strategy for each mCRC patient. The treatment quality is directly proportional to the number of treated patients: each multidisciplinary team should discuss and treat at least 50 patients per year (including early stage and advanced disease), while teams dealing with less than 50 cases per year should collaborate with referral hospitals. Recommendations are provided in table 5.

### Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Scientific society</th>
</tr>
</thead>
<tbody>
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<td>AIGO</td>
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<td>SICO</td>
</tr>
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<td>AIOM</td>
</tr>
</tbody>
</table>

AIGO, Italian Association of Gastroenterology; AIOM, Italian Medical Oncology Association; AIRO, Italian Association of Oncologic Radiotherapy; SIAPEC, Italian Society of Pathology and Cytology; SICO, Italian Society of Oncologic Surgery; SIMG, Italian Society of General Medicine.

### Table 2

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1++</td>
<td>Very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Low risk of bias</td>
</tr>
<tr>
<td>1−</td>
<td>High risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>Very low risk of bias and high probability of a causal relationship</td>
</tr>
<tr>
<td>2+</td>
<td>Low risk of bias and moderate probability of a causal relationship</td>
</tr>
<tr>
<td>2−</td>
<td>High risk of bias and significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytical studies, such as case reports and case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review or randomised clinical trial classified as 1++ and directly applicable to the target population</td>
</tr>
<tr>
<td>B</td>
<td>Studies classified as 2++ and directly applicable to the target population</td>
</tr>
<tr>
<td>C</td>
<td>Studies classified as 2+ and directly applicable to the target population</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4</td>
</tr>
</tbody>
</table>

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MOLECULAR BIOLOGY

CRCs are characterised by a number of molecular alterations that may combine to determine malignant transformation. Notably, around 80% of CRCs are sporadic, while 15%–20% are familial and 5% are considered genetic or linked to specific genetic syndromes. In the carcinogenic process, three different pathways have been recognised: (1) microsatellite instability, (2) chromosomal instability and (3) DNA methylation. In particular, abnormal hypermethylation has been detected in a significant percentage of CRC patients, and around 20% of CRCs have a methylated phenotype that corresponds to CpG island methylator phenotype (CIMP)-high.

KRAS and NRAS mutations are predictive of resistance to anti-epidermal growth factor receptor (EGFR) drugs. Therefore, mutational analysis of RAS genes is mandatory whenever treatment with an anti-EGFR monoclonal antibody is indicated. In particular, KRAS gene mutations are reported in at least 40% of CRCs. Contraversial data are reported regarding the prognostic value of KRAS mutations, and some studies suggest a negative prognostic value for the p.G12V KRAS mutation. The mutational analysis of KRAS and NRAS genes must cover at least codons 12, 13, 59, 61, 117 and 146 of both genes and can be performed either on primary or on metastatic tumour tissue. The use of circulating tumour DNA for RAS analysis is not routinely recommended, but it could be an option when adequate tissue for molecular testing is not available. AIOM, in collaboration with the Italian Society of Pathology and Cytology (SIAPEC), has implemented a quality control programme for laboratories that perform the RAS mutation test. The list of certified laboratories is published in the websites of these two scientific societies.

Although the evidence of BRAF V600E mutation as a predictive factor for resistance to anti-EGFR drugs has not been definitely ascertained, its analysis is recommended owing to its strong negative prognostic value.

Analysis of mutations in mismatch repair genes is not currently recommended in clinical practice (at the moment it is recommended for genetic counselling), although it could help in selecting patients to be enrolled in specific clinical trials evaluating immunotherapy. While a number of studies have suggested that PIK3CA and PTEN mutations may be linked to resistance to EGFR-inhibitors, PI3KCA and PTEN analyses are not currently recommended in clinical practice.

MCRC TREATMENT

About 25% of patients with CRC present with advanced disease at the time of diagnosis and a further 35% will develop metastases during the course of the disease. The aims of therapy for mCRC are cure (if possible in very selected cases), prolongation of life, palliation of symptoms, improvement of quality of life, delay disease progression and tumour shrinkage.

Table 4

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong for</td>
<td>The intervention should be considered as the first treatment option (benefits are higher than risks)</td>
</tr>
<tr>
<td>Conditional for</td>
<td>The intervention can be considered as a possible treatment option (not sure that benefits are higher than risks)</td>
</tr>
<tr>
<td>Conditional against</td>
<td>The intervention should not be considered as the first treatment option; it could be considered in selected cases after discussion with the patient (not sure that risks are higher than benefits)</td>
</tr>
<tr>
<td>Strong against</td>
<td>The intervention should not be considered as a possible treatment option (risks are higher than benefits)</td>
</tr>
</tbody>
</table>

Table 5

<table>
<thead>
<tr>
<th>Quality of evidences (SIGN)</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>The diagnostic and therapeutic strategy should be proposed by a multidisciplinary team. Each decision must be recorded and archived.</td>
<td>Strong for</td>
</tr>
<tr>
<td>D</td>
<td>The diagnostic and therapeutic decision must be in line with guidelines. Different proposals should be well explained.</td>
<td>Strong for</td>
</tr>
<tr>
<td>D</td>
<td>The multidisciplinary team must provide adequate documentary evidence to the patient and the family doctor.</td>
<td>Strong for</td>
</tr>
<tr>
<td>D</td>
<td>The treatment quality is directly proportional to the number of treated patients: each multidisciplinary team should treat at least 50 patients per year (including early stage and advanced disease). Teams with less than 50 patients should collaborate with referral hospitals.</td>
<td>Strong for</td>
</tr>
</tbody>
</table>

SIGN, Scottish Intercollegiate Guidelines Network.
It is possible to identify four different scenarios with different medical approaches:

► patients with limited resectable disease: surgery with perioperative or postoperative ‘adjuvant’ chemotherapy
► patients with limited unresectable disease: conversion therapy followed by radical surgery when possible
► patients with widespread and aggressive mCRC and disease-related symptoms: palliative therapy with the aim of rapid tumour shrinkage
► patients with widespread, unresectable and asymptomatic disease: palliative therapy with the aim of disease control to maintain a good quality of life.

Before planning the treatment strategy, it is essential to consider:

► overall conditions and emotional status of patients: fit versus unfit for a combination therapy (triplet vs doublet vs monotherapy), taking into account Eastern Cooperative Oncology Group performance status, age, comorbidities, patient’s attitude as well as his or her disease history (e.g., a previous oxaliplatin-based adjuvant treatment);
► tumour characteristics and clinical course: indolent versus aggressive tumour, considering disease presentation (synchronous vs metachronous), tumour load and mutational status (RAS and BRAF);
► treatment goal: (1) tumour shrinkage to achieve a radical surgery of metastases or palliation of disease-related symptoms and (2) disease control to delay progression and worsening of patient’s general condition.

Several drugs are actively used for the treatment of mCRC, such as fluoropyrimidines, irinotecan, oxaliplatin, mytomycin C, EGFR-inhibitors (cetuximab and panitumumab), antiangiogenic drugs (bevacizumab, aflibercept and ramucirumab), regorafenib and TAS-102.

The choice between monochemotherapy versus a polychemotherapy (doublet or triplet) should take into consideration the patient’s fitness and ‘aggressiveness’ of the tumour.

The introduction of biologics, including EGFR- and VEGF-inhibitors, improved chemotherapy efficacy and, consequently, the outcome for patients with mCRC.

As a first-line treatment, bevacizumab can be combined with:
capecitabine, in elderly and/or unfit patients, on the basis of results from the AVEX study which demonstrated a significant improvement of progression-free survival (PFS) in comparison to capecitabine alone\(^\text{10}\);
oxaliplatin- or irinotecan-based doublet leading to a significant benefit in patient outcome versus doublet alone.\textsuperscript{12–15}

Several trials suggest that prolonging bevacizumab in combination with fluoropyrimidine as maintenance treatment until disease progression can improve PFS, without a significant improvement in OS. When deciding on maintenance treatment, risks and benefits should be evaluated on an individual basis, taking into account previous toxicities, general condition, comorbidities, disease characteristics and patient’s motivation.\textsuperscript{16 17}

Cetuximab or panitumumab can be combined with a first-line chemotherapy in RAS and BRAF wild-type patients to achieve a significant increase in RR and improve patient outcome.\textsuperscript{18–24}

A head-to-head comparison between bevacizumab and cetuximab has been investigated in two large phase III randomised studies. The FIRE-3 trial, a negative study according to its primary end-point (RR), demonstrated a significant increase in OS in favour of the cetuximab arm\textsuperscript{25}; on the other hand, the CALGB study (OS as primary end-point) did not confirm this difference.\textsuperscript{26}

On the basis of these results, in RAS and BRAF wild-type patients, both bevacizumab and EGFR-inhibitors can be considered valid options, even if recent preliminary data seem to show that the primary tumour site (left vs right) might be a helpful predictive factor in the decision of which biological agent should be combined with a first-line doublet.\textsuperscript{27}

There are several options for second-line antiangiogenic treatment:

- bevacizumab beyond progression\textsuperscript{28 29};
- bevacizumab in patients who have not been treated with bevacizumab as first-line treatment\textsuperscript{30};
- afiblercept in combination with FOLFIRI in patients who progressed to a previous oxaliplatin-based therapy\textsuperscript{31};
- ramucirumab in combination with FOLFIRI in patients treated with oxaliplatin and bevacizumab as first-line treatment.\textsuperscript{32}

To date, no specific predictive factors can help us in the choice of the most adequate antiangiogenic drug; therefore, our decision must be based on clinical factors such as the kind of first-line chemotherapy, the magnitude of benefit from first-line bevacizumab and previous toxicities.

Studies evaluating the role of cetuximab and panitumumab in combination with a second-line irinotecan-based chemotherapy demonstrated a significant benefit in terms of RR and PFS, but not in OS.\textsuperscript{33–35}

Considering third and subsequent treatment lines, an increasing number of options is available. Cetuximab (alone or combined with irinotecan) and panitumumab showed prolongation of OS compared with best supportive care (BSC) alone in RAS and BRAF wild-type pretreated patients with mCRC.\textsuperscript{36 37}

Regorafenib, an oral multikinase inhibitor, and TAS-102, an oral combination of the nucleoside analogue trifluridine and a thymidine phosphorylase inhibitor, showed a similar benefit of prolongation of OS in heavily pretreated patients with mCRC compared with BSC alone.\textsuperscript{38 39}

Furthermore, the recent phase II HERACLES study suggested the potential use of HER-inhibitors in HER-2 overexpressed patients with mCRC.\textsuperscript{40}

Algorithms for the management of mCRC are shown in figure 1a–c.

SIGN and GRADE recommendations are provided in tables 6 and 7, respectively.

### Table 7  mCRC treatment: GRADE recommendations

<table>
<thead>
<tr>
<th>Quality of evidences (GRADE)</th>
<th>Recommendation</th>
<th>Strength of clinical recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>Starting a treatment for metastatic disease at the time of diagnosis, also without disease-related symptoms, is recommended. A wait-and-see period might be considered in well-selected cases (elderly, comorbidities, minimal tumour load) after an adequate evaluation of risks/benefits.\textsuperscript{62 63}</td>
<td>Strong for</td>
</tr>
<tr>
<td>Moderate</td>
<td>A maintenance treatment with bevacizumab±fluoropyrimidine can be considered in patients with mCRC after a first-line treatment with bevacizumab, after an adequate evaluation of risks/benefits and patient’s motivation.\textsuperscript{16 17}</td>
<td>Conditional for</td>
</tr>
</tbody>
</table>

GRADE, Grading of Recommendations, Assessment, Development and Evaluations; mCRC, metastatic colorectal cancer.

### Table 8  Evaluation of elderly patients: SIGN recommendations

<table>
<thead>
<tr>
<th>Quality of evidences (SIGN)</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Functional evaluation, before treatment, is recommended. Prescreening with a fast test (G8 test) helps the individuation of patients for evaluation according to CGA.\textsuperscript{64}</td>
<td>Strong for</td>
</tr>
</tbody>
</table>

CGA, comprehensive geriatric assessment; SIGN, Scottish Intercollegiate Guidelines Network.
Evaluation of elderly patients

Comprehensive geriatric assessment (CGA) is recommended to define the presence or absence of frailty. Frailty could be detrimental if patients are to receive chemotherapy, both in adjuvant and metastatic settings. To improve this evaluation, several simpler tests have been recently introduced; the G8 test is one such recommended test.

In patients over 75 years, due to weak evidence, CGA and evaluation of expected remaining life are recommended. Recommendations are provided in table 8.

**SURGERY FOR ADVANCED DISEASE**

Many factors may affect the timing and type of surgery in patients with unresected primary tumour and synchronous metastatic disease: performance status, extension of metastatic disease and symptoms from primary tumour. A multidisciplinary evaluation must define the best strategy.
Radical surgery of liver metastases can be curative, but it is dependent on the surgeon’s expertise. Radical resection of lung metastases may also be considered in selected cases. Recommendations are provided in table 9.

Chemotherapy after radical liver resection
The vast majority of evidence on this point are retrospective. Nevertheless, patients can receive postoperative treatment with fluoropyrimidine with or without oxaliplatin after surgical resection of secondary lesions or a perioperative treatment with FOLFOX or XELOX (capecitabine+oxaliplatin).41 42

LOCOREGIONAL TREATMENTS
Liver-directed therapies
Liver-directed therapies could represent an effective treatment option for unresectable liver metastases. Oligometastatic liver metastases could be treated by ablative techniques (radiofrequency ablation, microwaves, cryoablation) or by external irradiation with stereotactic procedures (stereotactic body irradiation, 3D conformal radiotherapy, intensity modulated radiotherapy).

Although all these procedures are active and well tolerated, the lack of randomised trials on these procedures limits the understanding of their role in the treatment algorithm.

For ‘extended’ liver metastases, ablative techniques and external irradiation are contraindicated. In these situations, the use of radioembolisation with 90Y resin microspheres, intrahepatic chemotherapy and transcatheter arterial chemoembolisation with DEBIRI (irinotecan-loaded drug-eluting beads) might be considered.

A single phase III randomised trial evaluated the role of 90Y resin microspheres associated with FOLFOX-based chemotherapy in patients with dominant liver metastatic disease. Although the trial failed its primary endpoint (overall PFS), an advantage was observed in terms of liver PFS for patients receiving 90Y resin microspheres.35 Recommendations are provided in table 10.

Non-liver-directed therapies
Isolated peritoneal carcinomatosis is a clinical condition characterised by an extremely poor prognosis. In this population, cytoreductive surgery and intraperitoneal chemohyperthermia performed in centres of expertise could improve PFS and survival, especially in cases with limited peritoneal spread and without macroscopic residual disease after surgery.

Radiation therapy is effective in bone metastases to improve pain control and to reduce the risk of bone fracture or spinal cord compression in cases of spine involvement.

Patients with local recurrence or unresectable T4b lesions with no distant metastases could undergo concomitant radiochemotherapy with the aim of achieving a radical resection of the tumour.

In selected patients with pulmonary oligometastatic disease unsuitable for surgery, stereotactic radiotherapy treatment may be indicated. Recommendations are provided in Table 11.

CONCLUSIONS
To date, several treatment options are available for patients with mCRC, and the complex choice of the optimal strategy must take into consideration patient and tumour characteristics. Owing to the progress in medical therapy, surgery and locoregional approaches, the outcome for patients with mCRC has notably improved.

In this changing scenario, the AIOM guidelines aim to simplify the complexity in the choice of the optimal treatment strategy by providing evidence-based recommendations to help Italian oncologists in their daily clinical practice.

The methodology followed while writing and updating the AIOM guidelines, the multidisciplinary nature of the working group and the final systematic review by independent CRC experts and different medical societies have contributed to the strong scientific value of the current Italian guidelines.

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5Department of Oncology, Humanitas Cancer Center, Rozzano (MI), Italy
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