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Guidelines

Metastatic colorectal cancer (mCRC): French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR)

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ABSTRACT

Introduction: This document is a summary of the French intergroup guidelines regarding the management of metastatic colorectal cancer (mCRC) published in January 2019, and available on the French Society of Gastroenterology website (SNFGE) (www.tncd.org).
Methods: This collaborative work was realized by all French medical and surgical societies involved in the management of mCRC. Recommendations are graded in three categories (A, B and C), according to the level of evidence found in the literature, up until December 2018.
Results: The management of metastatic colorectal cancer has become complex because of increasing available medical, radiological and surgical treatments alone or in combination. The therapeutic strategy should be defined before the first-line treatment, mostly depending on the presentation of the disease (resectability of the metastases, symptomatic and/or threatening disease), of the patient's condition (ECOG PS, comorbidities), and tumor biology (RAS, BRAF, MSI). The sequence of targeted therapies also seems to have an impact on the outcome (angiogenesis inhibition beyond progression). Surgical resection of metastases was the only curative intent treatment to date, joined recently by percutaneous tumor ablation tools (radiofrequency, microwave). Localized therapies such as hepatic intra-arterial infusion, radioembolization and hyperthermic intraperitoneal chemotherapy, also have seen their indications specified (liver-dominant disease and resectable peritoneal carcinomatosis). New treatments have been developed in heavily pretreated patients, increasing overall survival and preserving quality of life (regorafenib and trifluridine/tipiracil). Finally, immune checkpoint inhibitors have demonstrated high efficacy in MSI mCRC.

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Conclusion: French guidelines for mCRC management are put together to help offer the best personalized therapeutic strategy in daily clinical practice, as the mCRC therapeutic landscape is complexifying. These recommendations are permanently being reviewed and updated. Each individual case must be discussed within a multidisciplinary team (MDT).

1. Introduction

The present article is a summary of the French intergroup guidelines published in January 2019 on the SNFGE society website: www.tncd.org [1]. These guidelines are a collaborative work written by a multidisciplinary committee originating from 8 medical societies (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR) comprising several experts from different specialties involved in the management of mCRC (digestive and thoracic surgeons, pathologists, radiation oncologists, medical oncologists, gastroenterologists and radiologists). The initial document was reviewed and modified after further evaluation by a review committee, and the last version received final validation from the steering committee of the participating National Societies. These guidelines are an up-to-date comprehensive overview of pre-therapeutic exams, medico-surgical therapeutic strategies, the best chemotherapies and targeted therapy choices according to patients' and tumors' characteristics, somatic molecular alterations, the site of localized therapies and new drugs available. Recommendations based on the level of evidence were scored in 3 categories graded A, B andC), with only expert opinion (agreement or not, grade D) when no scientific evidence was validated [Table 1].

2. Pre-therapeutic assessment

2.1. Recommendations

Pre-therapy assessment typically begins by evaluating the patient's overall status, performance status, co-morbidities, tumor extension and results of molecular diagnostic tests from primary tumor tissue or metastases, focusing on:

- RAS status (KRAS, NRAS) as a predictor of EGFRi (Epidermal Growth Factor Receptor Inhibitor) resistance **(recommendation: grade A)**;
- BRAF V600E status as a poor prognosis factor (**recommendation: grade B)**;
- MSI phenotyping (by immunochemistry of MMR proteins or microsatellite testing on tumor DNA) as a poor prognosis factor and predictor of immune checkpoint inhibitors' efficacy in mCRC (**recommendation: grade C**);
- DPD phenotyping (by measuring plasma uracil concentration): fluoropyrimidine dose adjustment in case of partial DPD deficiency and fluoropyrimidine contraindication in case of complete DPD deficiency (**expert agreement**);
- Thoraco-abdominopelvic CT scan at baseline ± liver MRI to assess for resectability of liver metastases.

2.2. Options

- UGT1A1 genotyping (for irinotecan dose adjustment in case of Gilbert's syndrome);
- DPYD Genotyping in patients with abnormal plasma uracil concentration (**expert agreement**);
- TEP-scan when surgery of metastases (especially in the liver) is considered (**recommendation: grade B**).

3. Operability, resectability criteria and medico-surgical approaches

This section mainly concerns liver metastases (see Annex 1).

Surgical resection must systematically be discussed during MDT meetings, including at least one surgeon and one radiologist with experience in liver metastases.

The main criteria for the surgical decision are:

- Patient's condition: feasibility of anesthesia and resection?
- Tumor: possibility of R0 resection?
- Anatomy: expected healthy residual liver volume >25%–40%, depending on the presence or absence of another liver pathology.

Once the assessment is completed, complexity levels are defined in 3 classes (see Annex 2).

3.1. Resectable liver metastases

3.1.1. Recommendations

- In case of class 1 resectability: Simplified FOLFOX 4: 6 pre-operative + 6 post-operative cycles [2,3] (**recommendation: grade C**). Up front liver surgery: if pathological examination is required or if small (<2 cm) and limited number of metastases and are likely to disapear after chemotherapy (**recommendation: grade C**).
- In case of liver metastasis disappearance on imaging after chemotherapy: Hepatic resection should remove the site of missing lesions because pathologic complete response (pCR) is obtained in less than 20% of cases [4] (**recommendation: grade C**).
- Synchronous primary tumor and metastases: If metastases are identified pre-operatively and accessible to minor resection (class 1), one-stage liver metastases and primary tumor resections may be considered. In other cases, liver-first approach (reverse strategy) should be considered.
- Class 2 resectability: Surgery needs to be performed in a center specialized in hepatic surgery (**expert agreement**) and up-front chemotherapy is recommended (**expert agreement**).
- In case of hepatic pedicle and celiac lymph nodes: Surgery is therefore not indicated in case of class 2 resectability (**recommendation: grade C**).

3.1.2. Options

- Pre-operative right portal vein embolization (±right portal branch ligature) [5] in case of right hepatectomy with remaining left-side liver volume <25% (if between 25 to 40%, embolization should be discussed according to the hepatic function).
- Two-stage hepatectomy [6,7].
- Radiofrequency ablation or stereotaxic radiotherapy [8].
- Post-operative chemotherapy (**recommendation: grade B**): LV5FU2 [9,10] or simplified FOLFOX4 regimen for 6 months if no pre-operative chemotherapy; or using the induction chemotherapy which enabled resectability for a total duration of 6 months (pre- and post-operative) [11] (**expert agreement**). For the post-

Table 1
Grade of recommendations.

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on robust scientific evidence (e.g., several randomized controlled trials/meta-analyses) Further research is very unlikely to change our confidence in the estimate of effect
B	Moderate	Usually recommended based on scientific presumption (e.g., one randomized controlled trial) Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Low	Option based on weak scientific evidence (*e.g.*, one or several non-randomized trials) Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Very low	Expert opinion (agreement or not) Any estimate of effect is very uncertain

operative regimen, maintenance of the pre-operative targeted therapy should be discontinued as its benefit is not demonstrated in this setting (**expert agreement**).
- In case of liver metastasis disappearance after chemotherapy: if the site of the missing metastases is not resected, adjuvant hepatic intra-arterial chemotherapy may be considered as it could decreased recurrence rates based on retrospective series [12] (**expert agreement**).

3.2. Resectable extra-hepatic metastases

3.2.1. Recommendations

- Lung metastases: as hepatic metastases, surgery is indicated only if complete resection is possible (**recommendation: grade B**)
- Peritoneal carcinomatosis: complete resection ± hyperthermic intraperitoneal chemotherapy (HIPEC) [13–15] should be discussed in a specialized center in case of isolated carcinosis with moderate extension (**recommendation: grade B**). As for hepatic metastases, perioperative chemotherapy is indicated for a total duration not exceeding 6 months (**expert agreement**). In case of HIPEC expected morbidity must be low and mitomycine should be the preferred agent (not oxaliplatin) (**expert agreement**).
- Resection ± HIPEC is proposed if the following criteria are met [16]:
  - ○ age < 65–70
  - ○ WHO performance status <2
  - ○ no extra-peritoneal metastasis (or <3 hepatic metastases)
  - ○ complete resection of all lesion >2 mm is possible
  - ○ no progression under chemotherapy
  - ○ peritoneal carcinomatosis index (PCI) <17

Peritoneal carcinomatosis discovered at laparotomy: the procedure is stopped after PCI calculation and the case must be discussed during a MDT meeting (**expert agreement**).

3.2.2. Options

- ○ Lung metastases: percutaneous radiofrequency ablation or microwave ablation or stereotactic radiotherapy (**expert agreement**).

3.3. Borderline resectable metastases (or potentially resectable metastases)

3.3.1. Recommendations

- A chemotherapy regimen with a high response rate (objective responses as per RECIST1.1 criteria) should be performed in order to allow secondary resection [11]: triplet chemotherapy ± targeted therapy or doublet chemotherapy ± targeted therapy (anti-EGFR are preferred in RAS wild-type tumors) [17,18]. Resectability should be reassessed after 4–6 cycles (**expert agreement**).
- BRAF V600E mutation is not predictive of resistance to anti-EGFR but provides a poor prognosis. Treatment intensification is indicated (triplet chemotherapy plus bevacizumab is recommanded if possible) (**recommendation: grade B**).
- Recommendations regarding initially unresectable metastases showing response to chemotherapy for potential secondary resection:
  - ○ Surgery should be performed as soon as the metastases become resectable, with a maximum of 4 months of chemotherapy;
  - ○ Wait 4–6 weeks after chemotherapy before surgery [19,20].
- Hepatic intra-arterial chemotherapy (HIA) has shown high response rates in phase II trials (HIA oxaliplatin + IV chemotherapy LV5FU2 ± targeted therapy) and may be considered as an alternative to IV chemotherapy alone (**recommendation: grade C**) or as a salvage treatment (**expert agreement**).
- For patients with resection of metastases:
  - A total of 6 months of peri-operative chemotherapy is recommended (**expert agreement**).
  - No evidence in the literature supports the post-operative continuation of targeted therapy when previously used with the pre-operative regimen (**expert agreement**).

3.3.2. Options

- Pre-operative bevacizumab treatment must be stopped at least 5–6 weeks before surgery (expert consensus). There is no evidence supportting targeted therapy continuation following resection surgery (**expert agreement**).
- FOLFIRI (or FOLFOX) + cetuximab/panitumumab (RAS WT) [21–27] (**recommendation: grade B**)
- FOLFOXIRI or FOLFIRINOX [28–32] + bevacizumab (**recommendation: grade B**) in patients with few comorbidities. This regimen is prefered for patients with BRAF-mutated tumors.
- FOLFIRI or FOLFOX (XELOX) + bevacizumab [33–38] (**recommendation: grade C**)
- FOLFOXIRI (or FOLFIRINOX) + cetuximab/panitumumab (RAS WT) [39,40] (**recommendation: grade C**)
- FOLFOX 4 simplified or FOLFIRI [41–43] (**recommendation: grade C**)
- HIA with oxaliplatin + LV5FU2 IV ± targeted therapy [44] (**recommendation: grade C**) for liver metastases only and in specialized centrers.

3.4. Unresectable metastases

Unresectability is defined by the MDT, with a focus on:

- comorbidities impairing the surgical procedure;
- profile of the metastatic disease (site, number and lymph nodes involvement).

Palliative chemotherapy aims at maintaining patients' quality of life and prolonging survival (**recommendation: grade B**).

Concerning chemotherapy there are two main options:

- up-front polychemotherapy (doublet or triplet ± targeted therapy)
- monotherapy (LV5FU2 or capecitabin ± targeted therapy)

These strategies have been compared (without targeted therapy) in four phase III trials, which have shown similar results. That is to say, median overall survivals of about 16 months for both groups, explained by the inclusion of elderly patients with polymetastatic CRC and poor performance status [45–48]. Moreover, the 2001-02 FFCD trial showed no superiority of a doublet chemotherapy (FOLFIRI) over monotherapy (LV5FU2) in elderly patients aged 75 years or older [49].

If a poor performance status is observed as a result of tumor aggressivity, a doublet ± targeted therapy is indicated, if possible. When the deterioration results from patient frailty or comorbidities, first-line monotherapy is prefered [50].

- Response assessment is based on the same radiological technique, after 2–3 months of therapy (CT-scan is the gold-standard)
  - ◯ if major response: surgery should be discussed
  - ◯ if response or stability: chemotherapy is continued or paused until new progression; with a reassessment every 2 months. In case of initial doublet or triplet chemotherapy, maintenance therapy may be proposed. A major response may justify a break in chemotherapy (**recommendation: grade C**) [51,52]. 5FU/capecitabin is the best maintenance treatment option ± combined with bevacizumab (**recommendation: grade B**). During maintenance therapy or chemotherapy break, a stable response does not justify resuming induction chemotherapy. In case of progression after maintenance/chemotherapy break, chemotherapy ± targeted therapy that initially induced disease control may be re-introduced.
- If targeted therapy is used:
  - The choice of targeted therapy for first-line treatment is based on RAS, BRAF and MSI status.
  - Right versus left colon cancer: studies have shown that cancer sideness is a prognosis factor regardless of mutational status in mCRC, with poor prognosis for right-sided colon cancers [53,54]. Current data on the impact of tumor side (right/left colon) on therapeutic options suggest that left-sided colon cancer could be a predictor of EGFRi efficacy, and conversely, right-sided colon cancer is rather a predictor of bevacizumab efficacy [55–57]. The level of evidence remains too weak however to use tumor site as a main criterion to select the targeted therapy (EGFRi vs VEGFi) (**expert agreement**).

3.4.1. Recommendations for patients with non life threatening metastases, BRAF wild-type tumor, low tumor load and good performance status

- Treatment escalation starting with mono-chemotherapy (5FU/capecitabin) ± bevacizumab. Response is evaluated every 2 months. In case of progression, subsequent lines of treatment are proposed (**recommendation: grade A**).
- Polychemotherapy ± targeted therapy to facilitate chemotherapy break (**recommendation: grade A**), or maintenance chemotherapy with 5FU/capecitabin ± bevacizumab (**recommendation: grade B**) (Optimox 1 or CAIRO 3 strategies) [51,52].

3.4.2. Options for patients with non life threatening metastases, BRAF wild-type tumor, low tumor load and good performance status

- In case of an objective response or stability after 4–6 months of chemotherapy: chemotherapy break should be discussed with tumor reassessment every 2 months until progression [58–61]. Predictive factors of slow progression during chemotherapy break or maintenance therapy are:

partial or complete response, normal LDH and alkaline phosphatases, WHO performance status 0–1, initial normal platelet count, one or two metastatic sites, normalization or high decrease of CEA [60,62] (**recommendation: grade C**).

MSI tumors: anti-PD-1 or anti-PDL-1 treatment should be considered in a clinical trial pending marketing authorization (**expert agreement**).

BRAF mutation: chemotherapy intensification with triplet ± targeted therapy, preferably bevacizumab (**expert agreement**) [63,39].

3.4.3. Recommendations for patients with life threatening metastases, BRAF mutated tumor, rapid tumor growth, high tumor load and/or poor performance status (WHO 2) due to tumor aggressiveness

- High-response doublet or triplet therapy ± targeted therapy is recommended, according to performance status and comorbidities (**expert agreement**).

3.4.4. Options for patients with life threatening metastases, BRAF mutated tumor, fast tumor progression, high tumor load and/or poor performance status (WHO 2) due to tumor aggressiveness

- Doublet ± cetuximab or panitumumab (RAS WT) (**recommendation: grade B**)
- Triplet (FOLFOXIRI or FOLFOXIRINOX) ± bevacizumab (**recommendation: grade B**)
- BRAF mutation: triplet ± bevacizumab (grade B) or triplet ± anti-EGFR (cetuximab or panitumumab) (**recommendation: grade C**) [63,39]
- Doublet ± bevacizumab (**recommendation: grade C**)
- Triplet + cetuximab or panitumumab (RAS WT) (**expert agreement**)

3.4.5. Recommendations for patients with non life threatening unresectable metastases, aged, frailed, with severe comorbodity-related and/or with poor performance status (WHO 2)

- Mono-chemotherapy (5FU/capecitabin) ± bevacizumab is recommended (**recommendation: grade A**) or mono-chemotherapy ± EGFRi if RAS WT (**expert agreement**) [64]. Doublet ± EGFRi if RAS WT or bevacizumab with adjusted cytotoxic chemotherapy dosage (and/or 5FU bolus suppression) can be considered.

3.4.6. Options for patients with non life threatening unresectable metastases, aged, frailed, with severe comorbodity-related and/or with poor performance status (WHO 2)

- 5FU/capecitabin ± bevacizumab (**recommendation: grade A**)
- Doublet chemotherapy ± cetuximab or panitumumab (RAS WT) (**recommendation: grade B**)
- Doublet chemotherapy ± bevacizumab (**recommendation: grade C**)

4. What to do after a first-line chemotherapy?

4.1. Recommendations

- Recent data indicate that the L1–L2 therapy sequence may impact treatment efficacy. Given the relevance of continuous angiogenesis blockade in 3 phase III trials [11,65,66] and biological rationale [71], the work group recommends:

Maintaining angiogenesis blockade in L2 when bevacizumab was used in L1, including cases of RAS WT tumors (**Expert agreement**); as phase II and retrospective data indicate a non-optimal efficacy of EGFRi in L2 following bevacizumab treatment [68,69]

Conversely, in case of L1 with EGFRi therapy, an antiangiogenic should be prescribed in L2.

Progression and/or intolerance during cytotoxic chemotherapy (5FU, irinotecan and oxaliplatin), EGFRi antibodies (if RAS WT) therapy and VEGFi antibodies therapies:

2 systemic treatments are available for patients with good performance status (0–1): regorafenib and trifluridine/tipiracil (**recommendation: grade A**).

SIR-Spheres® (Y-90 resin microspheres) in case of exclusive or predominant liver metastases with maintained liver function (**recommendation: grade B**) [72,73]

Palliative care (ECOG PS > 2) or clinical trial (expert **agreement**)

4.2. Options

- Oxaliplatin re-introduction [74] if no previous progression on oxalipatin-based chemotherapy and/or if the neurotoxicity that justified interruption has regressed (**recommendation: grade C**)
- Re-introduction of EGFRi if no previous progression on EGFRi-based chemotherapy, the toxicities that justified interruption has regressed and for patients who underwent an interval chemotherapy without anti-EGFR and no evidence of RAS mutation when re-introduced (**expert agreement**)
- Hepatic intra-arterial chemotherapy (oxaliplatin + LV5FU2) (**recommendation: grade C**) in experienced care centers

5. Intra-arterial therapies for patients with liver exclusive or predominant disease

5.1. Recommendations

- SIR-Spheres® (Y-90 resin microspheres) when hepatic function is maintained (bilirubine <1.5 N) and metastases are liver-limited/live-predominant and chemorefractory to systemic treatment (recommendation: grade B) [72,73]

5.2. Options for exclusive or liver-predominant metastases

- HIAC (Hepatic Intra Arterial Chemotherapy):

Post-operative HIAC in combination with systemic chemotherapy in patients with suspected missing metastases or with a high risk of recurrence (**recommendation: grade C**)

Pre-operative HIAC in combination with systemic chemotherapy if first-line systemic chemotherapy did not bring sufficient downstaging, or is not likely to induce sufficient downstaging for allowing secondary surgery (**recommendation: grade C**)

Palliative HIAC, in case of resistance to all systemic chemotherapies (**recommendation: grade C**)

- ◯ DEBIRI: in palliative care setting for patients resistant to all systemic chemotherapies (**recommendation: grade B**) [75]

6. Local ablative treatments for liver-exclusive or predominant metastases

Results are optimal when metastases are small (<3 cm), few (<5), and distant from vascular and biliary structures [76].

- ◯ Resectable liver metastases:
  - ◯ When surgery is contraindicated
  - ◯ When metastases are small, with limited number of lesions and their localization would need extensive liver resection
  - ◯ When liver metastases are likely to disappear under chemotherapy, focal ablation or localization by hepatic coil before chemotherapy may be considered.
- Unresectable liver metastases:

When resection is not possible due to insufficient expected liver residual volume and/or high risk of post-operative liver failure, a combination of resection and local ablative techniques may be considered if it allows R0/R1 surgery [77]. (**recommendation: grade B**)

6.1. Recommendations

None.

6.2. Options

- Radiofrequency (expert agreement)
- Microwave (expert agreement)
- Stereotactic radiotherapy (**expert agreement**)
- Contraindications regarding radiofrequency and microwave therapy (and therefore potential indications of stereotactic radiotherapy): ascites, severe non-curable hemostasis disorder, sub-capsular localization, intra-hepatic biliary duct dilatation, metastases in contact with digestive, biliary or vascular structures, lesion with diameter >30 mm.
- Main limits to stereotaxic radiotherapy are target volume, number of lesions and remaining healthy liver percentage.

7. Overview of recommendations based on RAS status

See Annex 4 and 5.

8. Treatment selection strategies (chemo/bio) based on initial therapy

See Annex 6 [67,70].

Conflict of interest

- JM Phelip: Roche, Merck, Amgen, Bayer, Sanofi, Servier, Pierre Fabre.
- D Tougeron: Roche, Merck, Amgen, Bayer, Sanofi, Servier, MSD, BMS, Astra Zeneca, BTG.
- B Rousseau: Roche, Servier, Bayer, Novartis.
- O. Bouché: Roche, Merck, Amgen, Servier, Pierre Fabre, Bayer.

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Appendix A. Supplementary data

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