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Consensus on management of metastatic colorectal cancer in Central America and the Caribbean: San José, Costa Rica, August 2016

Roberto Ivan López,[1] Jenny Lissette Castro,[2] Heidy Cedeño,[3] Dagoberto Cisneros,[4] Luis Corrales,[5] Ileana González-Herrera,[6] Mayté Lima-Pérez,[7] Rogelio Prestol,[8] Roberto Salinas,[9] Jorge Luis Soriano-García,[10] Alejandra T Zavala,[11] Luis Miguel Zetina,[12] Carlos Eduardo Zúñiga-Orlich[13]

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For numbered affiliations see end of article.

Correspondence to
Dr Roberto Ivan López; rilopez@cwpanama.net

ABSTRACT

Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide. In Latin America and the Caribbean, it has a mortality of 56%. The median overall survival for patients with metastatic colorectal cancer (mCRC) is currently estimated as ~30 months, which has substantially improved through strategic changes in treatment and in the management of patients. As opposed to other metastatic cancers where first-line regimens are often determined, mCRC requires special attention because there is controversy in the possible combinations of the available drugs and the different periods of duration for each patient. Each combination must seek to be effective and to generate the minimum adverse effects as possible. Instead of giving the first-line regimen until the tumour progresses, treatment is often individualised. Furthermore, up to 60% of colorectal tumours are considered non-mutated or wild-type CRC. Not harbouring mutations in the RAS family of genes or mutations in the signalling pathways of the epidermal growth factor receptor causes a null response to anti-epidermal growth factor receptor antibody therapy, which implies even more complex considerations regarding its management. The primary objective of this consensus is to address the main scenarios of mCRC in order to warrant the most appropriate therapeutic intervention for these patients in the Central American and the Caribbean (CAC) region. This can lead to better clinical outcomes as well as quality of life for palliative patients. This document includes the formal expert consensus recommendations for scenarios of mutated and non-mutated mCRC, including synchronous or metachronous disease, management of mCRC with liver and lung metastasis, resectable, potentially resectable or non-resectable tumours and local in the CAC context.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide, and it represented then 13% of all deaths from all causes in 2012.[1 2] Most cases occur in developed countries (55% of the total)[3]; however the mortality is is mostly in developing countries.

During the last decade, the clinical outcomes of patients with CRC, particularly those with metastatic colorectal cancer (mCRC), have improved. The median overall survival (OS) for patients with mCRC is currently estimated as ~30 months, representing more than twofold the known results 20 years ago.[4]

These outcomes are probably related to strategic changes in treatment and the management of patients such as advances in technology that provides closer follow-up of pre-malignant lesions, timely and more efficient therapies (especially second-line therapies) and increased number of patients to ablation therapies, which leads to higher relapse-free survival rates and longer and better quality of life.[5] The primary objective of the consensus is to warrant therapeutic intervention in the Central American and Caribbean region.

The levels of consensus are defined as follows:

Level 1A: Consensus based on high level of evidence established through rigorous meta-analyses or randomised controlled trials (RCTs) with unanimous agreement in the expert panel.

Level 1B: Consensus based on high level of evidence established through rigorous meta-analyses or RCTs with minor disagreement in the expert panel.

Level 2A: Consensus based on low or medium level of evidence through descriptive or observational studies with unanimous agreement in the expert panel.

Level 2B: Consensus based on low or medium level of evidence through descriptive or observational studies with minor disagreement in the expert panel.

Table 1 ESMO-revised group for stratification and treatment, according to whether the patient was 'optimal' or 'non-optimal'

Patient classification	Optimal group 1	Optimal group 2	Non-optimal
Clinical presentation	Conversion and evolution to NDE	Asymptomatic patients	Best supportive care
	Imminent clinical threat, imminent organ dysfunction and severe disease-related symptoms	Without imminent clinical threat Without resection option	
	Biomarker-driven treatment: KRAS wt, RAS mt, BRAF mt patient subgroups	Biomarker-driven treatment: KRAS wt, RAS mt, BRAF mt patient subgroups	
Therapeutic objective	Debulking followed by R0 reduction, NDE achieved through LAT	Disease control and prolonged survival	Palliative
	Symptomatic improvement and prevention of rapid evolution; prolonged survival		

LAT, local and ablative therapy; mt, mutant; NDE, no disease evidence; wt, wild-type.

Level 3: Major controversies in the expert panel.

METHODOLOGY

The consensus was developed with the oncology experts from eight Central American and Caribbean countries (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama, Dominican Republic and Cuba). The participants were organised in three different evaluation groups, and each group had the duty to develop the review of the assigned topic. The assigned topics for evaluation were (1) mCRC first-line treatment, (2) mCRC subsequent lines of treatment after the first line and (3) maintenance strategies, locoregional treatment and future management directions. Every item was analysed in the context of the resectable and non-resectable disease when applicable.

Recommendation 1: classification of patients with mCRC

Consensus level: 1A

The optimal management strategy for patients with mCRC must be discussed in a multidisciplinary group.

According to the patient assessment, age, performance status, vital organ function, comorbidities and patient preference, tumour characteristics (location, tumour burden and tumour biology) and characteristics of treatment received or to be received (toxicity, socioeconomic factors, access to treatment and quality of life) should be considered for appropriate patient classification.[4]

According to criteria assessment, patients may be classified as (table 1):

- Optimal: patients with no contraindication for first-intention surgery or systematic treatment.
- Non-optimal: patients with a clinical impediment (organ dysfunction or severe disease-related symptoms).

Recommendation 2: management of mCRC according to synchronous or metachronous disease

Consensus level: 1B

Multiple primary carcinomas often occur in the rectum and colon. The time lag between the first and second malignant transformation is variable. Two or more primary carcinomas can coexist at the time of diagnosis (synchronous) or develop consequently (metachronous), sometimes years after resection of the first primary.

Synchronous adenocarcinomas can be two or more in number, detected either preoperatively/intraoperatively or in a 6-month period postoperatively. They should be distinctly separate by at least 4 cm distance and they should not consist of submucosal spread or a satellite lesion of each other. In any other case, they are considered as regional spread or metastatic lesions. In contrast, metachronous carcinomas can be defined as those diagnosed 6 months after the operation for the primary lesion, and located in a different part of the large intestine, so as to not represent a recurrence.[6]

Synchronous disease

If a patient is a candidate for surgery (liver metastatic disease or resectable pulmonary disease), the recommendations are as follows:

- Option 1: colectomy and resection of synchronous metastases, followed by adjuvant CT (chemotherapy)*, preferably the FOLFOX schedule.
- Option 2: neoadjuvant CT* for 2–3 months, followed by colectomy and resection of metastases synchronously or in stages. It is recommended in patients without primary tumour-related symptoms, particularly in borderline resectable disease.
- Option 3: colectomy, followed by adjuvant CT* (using the same neoadjuvant schedules) and then resection of metastases in stages.[7 8]

Metachronous disease

If a patient is a candidate for surgery (liver metastatic disease or resectable pulmonary disease), the recommendations are as follows:

- Option 1: neoadjuvant CT for 2–3 months (oxaliplatin-based schedules), followed by resection of metastases and then adjuvant CT.
- Option 2: initial resection of metastases, followed by adjuvant CT, preferably oxaliplatin-based schedules.[7 8]

Note

*All treatments combined with adjuvant and neoadjuvant chemotherapy must not exceed 6 months because of the potential risk of toxicity or of liver failure or both.

Recommendation 3: management of mCRC with liver, lung metastatic disease

Consensus level: 1A

Disseminated disease to one or more organs, as measured by the available clinical and radiological methods, is known as metastatic disease. The use of PET/CT scan in

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Table 2 Contraindications for liver resection in patients with colorectal carcinoma with liver metastases[11]

Category	Contraindication
Technical (A)	
Absolute	Impossibility of R0 resection with ≥30% of residual liver or resectable extrahepatic disease
Relative	R0 resection: resection only possible with a complex procedure (embolisation of the portal vein, two-stage hepatectomy, hepatectomy combined with ablation (including ablation through radiofrequency)) R1 resection
Oncological (B)	
1	Concomitant extrahepatic disease (non-resectable)
2	No of lesions: ≥5
3	Tumour progression

Patients must be classified as A1 or A2/B1, B2 or B3.

metastatic disease is not currently considered a standard for disease staging. Nevertheless, in patients considered potentially resectable, the use of PET/CT scan could be considered for the measurement of extrahepatic or pulmonary disease.[1 2 4 5 9 10]

Liver metastatic disease only

The treatment strategy in patients with mCRC must be addressed to full resection whenever possible, considering prognostic and technical criteria (surgical) (table 2).[11]

In patients who have not received presurgical treatment and who have undergone full surgery for their metastatic disease, the evidence level is low to recommend adjuvant treatment. Nevertheless, it should be considered according to the Fong Score criteria and/or agreement from the multidisciplinary team.[12]

Lung metastatic disease

The benefit and feasibility of treatment should be discussed with the patient, considering there is no high level of evidence.

Full resection may be feasible based on anatomical principles, extension of the disease and maintenance of an adequate pulmonary function. The primary tumour must have been completely resected (R0). Resection of extrapulmonary metastases does not exclude pulmonary resection.

Other metastatic sites

The benefit of treatment must be discussed within the multidisciplinary team and with the patient, considering there is no high level of evidence.

Potentially resectable tumours[13–17]

Patients who technically may undergo full resection of the disease without relative contraindications are considered to have a resectable disease.[8 17]

- Treatment must be started based on chemotherapy plus monoclonal antibodies and according to the response, and after assessment by the disciplinary team, surgery shall be considered as long as a full resection is feasible. In potentially resectable patients (when conversion is the objective), a regimen leading to high response rates and/or reduction in tumour size (debulking) is recommended. There are several options, and a reason why there could be discussion related to the best combination to be used, considering there are a limited number of trials to address this scene. In patients with non-mutated RAS disease, a cytotoxic doublet plus an endothelial growth factor receptor (EGFR) inhibitor seem to hold the best risk/benefit relationship although the combination of FOLFOXIRI plus bevacizumab may also be considered. To a lesser degree, a cytotoxic doublet plus bevacizumab may be used.[18 19] In patients with mutated RAS disease, a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab is recommended. Resectable patients must be periodically assessed given that the expectation of a maximum response is set after 12–16 weeks of treatment in most patients.[4]

Non-resectable tumours

The optimal treatment strategy for patients with evident non-resectability of mCRC disease is rapidly evolving and must be viewed as a continuum of care and in which the main objective is to maintain the quality of life and improvement of tumour-related and/or metastasis-related symptoms[20]

- Palliative resection of the colon may be considered for patients with a non-resectable primary tumour and significant local symptoms (intestinal obstruction and bleeding).
- Implantation of an endoscopic prosthesis (if available) represents an alternative approach widely used to alleviate tumour obstruction.
- Whenever metastatic lesions become a resectable disease after chemotherapy, colon and metastasis resection must be done, either simultaneously or in stages.
- The best supportive care or support treatment is an option for patients with a poor general condition or for those who have received all active chemotherapy regimens, both in resectable and non-resectable disease.

Management of primary tumour and non-resectable metastatic disease at diagnosis

- Resection of the colon primary tumour before onset of CT.

In rectal primary tumour lesions and in non-resectable metastatic disease at diagnosis, obstructive or bleeding tumour or both, or in severe risk of obstruction or bleeding or both:

- Option 1: surgical intervention by resection or bypass surgery (ostomy), and then systemic CT. Eventually, palliative radiotherapy (RT) may be considered.

- Option 2: placement of an endoscopic prosthesis (if available) and eventually systemic CT (in patients with a high surgical risk).
- Option 3: palliative RT–CT, and then systemic CT; palliative endoscopic treatment (if available).

Non-stenosis and non-bleeding tumour

- Option 1: systemic CT and, eventually, palliative RT.
- Option 2: surgical intervention of the primary tumour, and then systemic CT.
- Option 3: systemic CT, followed by surgery of the primary tumour.

Abdominal and/or peritoneal metastatic lesions

- With obstruction: surgical options such as colon resection, derivative colostomy or placement of an endoscopic prosthesis (if available), and then systemic CT.
- Without obstruction: CT for advanced disease.
- Peritoneal carcinomatosis: options such as debulking surgery plus systemic CT, systemic CT and then debulking surgery, and systemic CT alone. Intraperitoneal CT with hyperthermia is used in the context of clinical trials (not yet available in our region).

Obstructive tumour

- Option 1: surgical intervention (resection, bypass or ostomy) and then CT.
- Option 2: placement of endoscopic prosthesis (if available) and then CT (in patients with a high surgical risk).

Primary colon tumour lesions and potentially resectable disease at diagnosis

- Tumour under risk of obstruction: placement of endoscopic prosthesis (if available) or surgical intervention (resection, bypass or ostomy) and then CT.
- Bleeding tumour or tumour under risk of bleeding: surgical intervention (resection, bypass or ostomy) and then CT.
- Non-stenosing, non-bleeding tumour*:
  - Option 1: systemic CT and then surgical intervention.
  - Option 2: surgical resection and then CT.

*Depending on status of metastases.

Primary rectal tumour lesions and potentially resectable metastatic disease at diagnosis

- Obstructive and/or bleeding tumour or under serious risk of obstruction and/or bleeding:
  - Option 1: surgical intervention with total mesorectal excision, then CT; local or systemic treatment of metastases; pelvic RT.
  - Option 2: derivative surgical intervention (ostomy), then CT–RT and later surgery of the primary tumour, local and systemic treatment of metastasis.
  - Option 3: placement of endoscopic prosthesis (if available) and eventually palliative RT–CT (in patients with a high surgical risk).
  - Option 4: neoadjuvant RT–CT, then surgery of the primary tumour, and local and systemic treatment of metastasis.
- Non-stenosing, non-bleeding tumour:
  - Option 1: systemic CT and then surgery of the primary tumour; local and systemic treatment of metastasis; pre-surgical and post-surgical pelvic RT.
  - Option 2: surgical intervention of the primary tumour and of metastasis (in one single operating time or sequential), and then systemic RT+CT.

Recommendation 4: local and regional management

Consensus level: 1B

Local ablative therapies are a treatment option in CRC. Techniques such as radiofrequency[20–22] and embolisation, with or without chemotherapy, have demonstrated a survival benefit in well-selected patients.

Radiofrequency is a strategic treatment approach that must be assessed and continue to be developed in adequate patients considering it might help with the eradication of visible metastatic lesions.

In the case of ablation techniques in patients with single or a few non-resectable liver metastases (oligometastatic disease, OMD), local ablation techniques may be considered, such as thermal ablation or high-conformation radiation techniques (eg, stereotactic body radiation technique (SBRT)[23] and high-dose-rate intraoperative radiation).[24] The decision has to be taken by the multidisciplinary team, based on local experience, tumour characteristics and patient preference.

In patients with only one lung or with OMD of the lung, ablative high conformational radiation or thermal ablation may be considered if resection is limited considering the patient's comorbidities, extension of the pulmonary parenchyma resection or other factors. Treatment with extracranial SBRT is a safe and feasible alternative treatment for liver and lung OMD, in patients not fit for surgery or other ablative treatments. SBRT may be used in addition to surgery to eradicate all visible metastatic sites. Combined with chemotherapy, ablative therapy may improve the progression-free period but not OS.[22–24]

The case of embolisation for patients with liver disease limits the available chemotherapeutic options, but may be considered a therapeutic option. For patients in whom available systemic CT has failed,[24 25] radioembolisation with microspheres of yttrium-90 may be considered or chemoembolisation may be considered. Radioembolisation and chemoembolisation of liver colorectal metastasis in previous treatment lines may be interesting as 'consolidation treatment', but must be limited to clinical trials.[5] The decision must be made by the multidisciplinary team based on local experience, tumour characteristics and patient's preference.

Debulking surgery and peritonectomy with full peritoneal chemohyperthermia (HIPEC) may be considered for patients with limited peritoneal metastasis at a centre with extensive experience in the use of HIPEC.[4]

Other local treatments

Evidence is insufficient in terms of the efficacy of electrocoagulation, percutaneous ethanol injections and other techniques.[26 27]

Recommendation 5: treatment for the different scenes for RAS and BRAF wild-type colorectal carcinoma

Consensus level: 1B

Wild-type, non-mutated CRC or a CRC that does not harbour mutations in the RAS (HRAS, NRAS and KRAS) family of genes or mutations in the signalling pathways of the EGFR.

The concept of traditional mutation was established with a mutation in codons 12 and 13 of exon 2 from the KRAS gene.[13] This concept has been extended to other codons from other exons, and traditionally it has been observed in codon 61 of exon 3 and in codons 117 and 146 from exon 4; this applies for KRAS and for NRAS. With the current evidence, BRAF mutation should not be considered as a reference for therapeutic decision-making. BRAF mutation is currently used as a prognostic factor.[14 15]

All mCRC biopsies must undergo testing for:

- KRAS
- NRAS
- BRAF

In the treatment of CRC, there are three scenes we wish to address:

- Resectable disease
- Potentially resectable disease
- Non-resectable disease

The condition of patients with symptomatic non-resectable disease and with asymptomatic non-resectable disease is not addressed here.

The approach to the different scenes is based on the 'general condition of the patient' and on the patient's fitness to receive treatment. Likewise, a non-fit patient, with an Easten Cooperative Oncology Group (ECOG) performance status 3–4, with important comorbid disease, depending on support therapy, shall be referred to palliative care units (table 3).

Resectable disease

Within the context of resectable disease and tumours less than 2 cm (Scene 1 A. Synchronous), after resection, the patient should receive 6 months of CT. Pre-surgical CT can also be offered for 2 to 3 months. Schedules investigated for such purpose are FOLFOX or FOLFIRI+an anti-angiogenic drug.[28]

In the ESMO clinical guidelines, they propose to use cetuximab+FOLFOX3. In the IB scene, with metachronous disease, the patient may or may not have received pre-surgical chemotherapy 2–3 months before surgery.

Potentially resectable disease

The chemotherapy schedule must be aggressive before surgery; 2–3 months of treatment are offered. Liver function must be periodically assessed given the probability of toxicity.

An alternative to the cytotoxic doublet+anti-angiogenic, anti-vascular endothelial growth factor (anti-VEGF), is the use of FOLFOXIRI plus an anti-VEGF.[29 30]

Non-resectable disease

The symptoms described for this scene refer to those directly related to tumour disease.

In the case of emergency due to obstruction, bleeding or bone metastasis, consider surgery or local treatment (RT).

Non-fit patients to receive a chemotherapy schedule should be referred to palliative care.

In the case of patients fit for treatment, they may be offered a doublet or triplet plus a biological drug. In the case of non-fit patients, they may receive the anti-angiogenic or biological agent, as monotherapy or in combination with a doublet, or in chemo-monotherapy.[31]

Response to CT must be assessed after 2–3 months, depending on the selected regime.

In second-line treatment, a doublet different from the one used in first line shall be assessed, deciding on the continuity or the switch of the biological agent to an EGFR inhibitor or an anti-VEGF antibody.

When the patient is not fit, a biological agent in combination with a single agent or a doublet may be used, depending on the assessment.

In general, concerning the evaluation of patients for second-line or third-line therapy, the following may be considered: disease progression after previous lines or limited toxicity limiting the continuity of treatment.

Finally, several studies support maintenance therapy after the initially chosen treatment.[28–30 32] Second-line treatment may be used in any patient who experiences disease progression, clinical, radiological or serological, with a good performance status.[33–35]

Table 3 Sequencing of treatment

	(A) Scene 1: resectable disease	(B) Scene 2: potentially resectable disease	(C) Scene 3: non-resectable disease and symptomatic patient
First line	Cytotoxic doublet+anti-angiogenic	Cytotoxic doublet+anti-angiogenic	Cytotoxic doublet+anti-EGFR inhibitor
Second line	Cytotoxic doublet+anti-angiogenic or aflibercept	Cytotoxic doublet+anti-EGFR inhibitor	Cytotoxic doublet+anti-angiogenic or aflibercept
Third line	Irinotecan or FOLFIRI+anti-EGFR inhibitor	Regorafenib	Regorafenib
Fourth line	Regorafenib, TAS		

TAS, t rifluridine/ t ipiracil h ydrocloride.

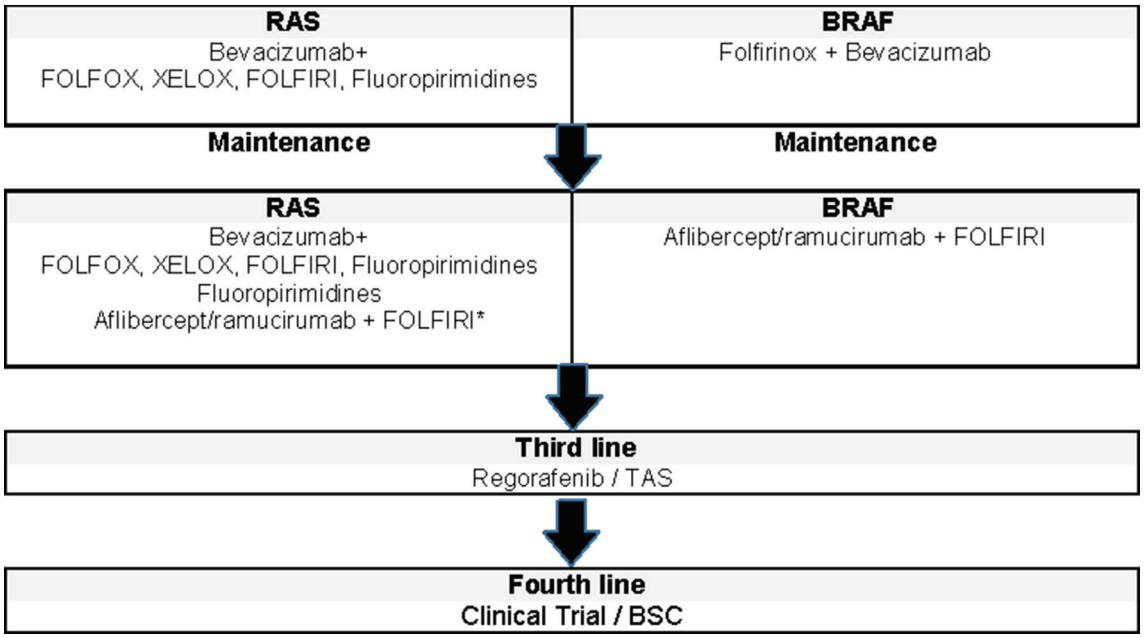

Figure 1 Management diagram for non-resectable, mutated, metastatic colorectal carcinoma. BSC, best supportive care.

Recommendation 6: approach to RAS and BRAF mutated non-resectable mCRC

Consensus level: 1A

Mutated CRC shows mutations in the EGFR signalling pathways. The traditional mutation concept was a mutation of codons 12 and 13 from exon 2 of the KRAS gene. The concept has been extended to other codons from other exons; it has been regularly observed in codon 61 of exon 3 and in codons 117 and 146 of exon 4; this applies for KRAS and for NRAS. BRAF mutation is observed in codon 600 and PIK3 in exons 9 and 20. Whenever it happens or occurs in both, the prognosis is worse.[32 33]

The management of mutated colorectal metastatic carcinoma is summarised in figure 1.

General objectives of treatment

- To prolong OS and/or progression-free survival.
- To improve tumour-related symptoms.
- To obtain a clinical benefit using all available therapies.
- To maintain the quality of life.

Time for treatment onset

Although evidence is limited for patients with non-resectable mCRC, it is recommended to initiate chemotherapy upon diagnosis or as soon as possible.[4]

First-line treatment

ECOG 0–2

Considerations

- Monotherapy, in the case of patients who are not candidates for combined therapies due to their clinical conditions.
- The typical first line of chemotherapy holds a basic backbone involving fluoropyrimidines (intravenous 5-fluoracil or oral capecitabine), and it is used in several combinations and sequences, along with irinotecan or oxaliplatin.[33–35] The combination of pyrimidine-based chemotherapy with oxaliplatin or irinotecan (FOLFOX or FOLFIRI) allows for higher response rates and a longer progression-free survival.

Standard of treatment

The treatment defined as current 'standard of treatment' is chemotherapy plus a biological agent (anti-VEGF).[4 16 36–41]

Biological agents as molecular targets ('target therapies') are indicated in first line in most patients, unless there are contraindications.

Antibodies targeting vascular growth factors must be used in combination with cytotoxic doublets, such as FOLFOX/CAPOX/FOLFIRI or with cytotoxic triplets, such as FOLFOXIRI, in optimal patients fit to receive such therapy, in patients in whom debulking is the goal and in patients fit to receive treatment with BRAF mutations. In the case of patients who do not tolerate aggressive treatment, it must be administered as monotherapy with fluoropyrimidines[16 36 38–42]

Treatment with biological agents may trigger antibody formation. If such is the case in a patient with mutant anti-EGFR, it is convenient to use chemotherapy with drugs not previously used; and such a schedule must be managed in a customised manner.[36]

Patients with mutated BRAF

For patients with mutated BRAF, triplets are recommended.

Patients with contraindication for the use of anti-angiogenic drugs

Patients with a contraindication for the use of an anti-angiogenic drug must be treated with chemotherapy alone, and the alternatives are:

- Monotherapy with fluoropyrimidines
- Doublet
- Triplet
- Among high-risk patients with complications using these drugs, the adverse events are as follows:
- Arterial or venous thromboembolic events
- Surgery in less than 4 weeks
- Healing problems with the surgical wound
- Gastrointestinal (GI) bleeding
- GI ulcer or fistula
- Hypertensive crisis, or non-controlled high blood pressure[16 39]

ECOG 3

ECOG 3 patients must be managed in a comprehensive manner with palliative care.

Maintenance16 36 38–40 42

- In patients who have received FOLFOX or CAPOX combined with an anti-angiogenic as induction therapy, maintenance therapy may be considered after 6 cycles of CAPOX and 8 cycles of FOLFOX. The ideal maintenance treatment is a combination of fluoropyrimidines plus anti-VEGF. Monotherapy treatment with an anti-angiogenic is not recommended.[43]
- Patients receiving FOLFIRI may continue induction treatment while the tumour size reduction is documented and treatment remains tolerable.
- In patients who have received initial treatment with FOLFOXIRI, with or without an anti-angiogenic drug, fluoropyrimidines plus an anti-angiogenic agent may be considered for maintenance therapy (as performed in clinical trials evaluating FOLFOXIRI).
- For patients receiving initial therapy as monotherapy with fluoropyrimidines (plus anti-angiogenic), induction therapy should be maintained.
- It is necessary to always customise the therapy and hold discussions with the patient.
- Induction therapy or second-line therapy must be re-introduced if there are radiological signs or signs and symptoms of progression. If a second line is selected, re-introduction of the initial induction treatment must be part of a therapeutic strategy, and treatment must be continued until residual toxicity is present.

Duration

Optimal treatment for initial therapy is controversial. Whenever FOLFOX is used, with or without anti-angiogenic therapy, the available information suggests that it is reasonable to temporarily suspend oxaliplatin in patients who have shown a response while maintaining fluoropyrimidines, with or without the anti-angiogenic. Continuing with oxaliplatin is an option in patients who are responding to therapy and who do not show evidence of neuropathy.

An intermittent treatment schedule is recommended in the case of oxaliplatin due to cumulative neurotoxic damage. The advantage of intermittent treatment with irinotecan-based regimens is not clear.

Pause or 'holidays' in treatment

The discussion about temporary suspension of treatment may be assessed with the patient within the context of indolent or asymptomatic disease.[44–48]

Second-line treatment

The second line of treatment depends on the initial treatment schedule, length of time the schedule was received and previous toxicity. Patients with metastatic or advanced CRC are usually treated with chemotherapy. If the disease does not improve or progresses with a specific chemotherapy schedule (first line), a different chemotherapy regimen may be tried, usually called 'second line' to increase survival and/or improve the quality of life. It is necessary to decide at that point on whether the patient is to be treated with or without anti-VEGF.[43 49–51]

In the combination with other agents in the second line, the following considerations must be considered[4]:

In those patients who have never received a biological agent, treatment with an anti-angiogenic (bevacizumab or aflibercept) must be considered in second-line therapy. The use of aflibercept must be restricted to the combination with FOLFIRI for those patients who progress on an oxaliplatin-based regimen.[52]

- In patients who have received an anti-angiogenic agent, the continuation of the anti-angiogenic drug should be considered during second-line treatment.[52]
- Aflibercept or ramucirumab (in combination with FOLFIRI) is used when it is used in first line with oxaliplatin.

Third-line treatment

The use of regorafenib or trifluridine/tipiracil hydrocloride (TAS) 102 may be considered.[53] Regorafenib is recommended in patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan and bevacizumab, as well as in patients with the non-mutated RAS type with EGFR inhibitor antibodies.[54] Regorafenib is superior to placebo in terms of overall survival; in fragile patients, there are limitations due to toxicity.

Trifluridine/tipiracil (TAS 102) is recommended for patients previously treated with fluoropyrimidines, oxaliplatin, irinotecan and bevacizumab, as well as in patients with the non-mutated RAS type with anti-EGFR antibodies.[55 56]

Progression and continuation of therapy must be discussed and assessed together with the patient.

Author affiliations
[1]Oncology Department, National Oncological Institute, Panama City, Panama
[2]Department of Medical Oncology, Oncology Hospital, Salvadorian Institute of Social Security, Rosales National Hospital, San Salvador, El Salvador

[3]Department of Medical Oncology, National Oncological Institute, Panama City, Panama
[4]Medical Department, Clinical Oncology Hospital, Nicaragua
[5]Center for Research and Management of Cancer (CIMCA), San José, Costa Rica
[6]VITA Oncology Group, San José, Costa Rica
[7]Functional Unit of Digestive Tumors, Hermanos Ameijeiras University Hospital, La Habana, Cuba
[8]Department of Digestive Tumors, National School of Oncology, Dominican Republic
[9]Medical Oncology, Oncology Hospital, Salvadorian Institute of Social Security, San Salvador, El Salvador
[10]Clinical Oncology Department, Hermanos Ameijeiras University Hospital, La Habana, Cuba
[11]Clinical Oncology, San Felipe Hospital of Specialties, Honduras
[12]Cancer Consultants, Guatemala
[13]Clinical Oncology, Metropolitan Hospital, San José, Costa Rica

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