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ADVANCES IN CLINICAL MANAGEMENT AND THERAPY OF CANCER

Treatment recommendations for metastatic colorectal cancer

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Abstract Metastatic colorectal cancer (CRC) represents an important health problem in which several biological predictive and prognostic factors have been identified, including clinical features and molecular markers that might influence the response to treatment. Actually, certain prognostic factors are considered key elements, along with disease extent, for deciding the therapeutic approach. However, a distinction between resectable/potentially resectable and unresectable patients must be made in order to establish an adequate therapeutic strategy. Different drugs and chemotherapy regimens are currently available, and their administration depends on patient characteristics, disease-related factors and the treatment objective. Moreover, special situations such as peritoneal carcinomatosis and local treatment of CRC in the setting of metastatic disease should be considered when deciding the most appropriate treatment strategy. This article reviews all the previously mentioned issues involved in the management of metastatic CRC and suggests some general recommendations for its treatment.

Keywords Metastatic colorectal cancer · Chemotherapy

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Introduction

Nowadays, colorectal cancer (CRC) represents an important public health problem due to its high incidence and mortality. In the United States, it is currently the third leading cause of death from cancer in both genders after lung and prostate cancer in men, and after breast and lung cancer in women [1, 2].

In 2006, in Europe, CRC occupied the second place in terms of incidence after breast cancer and was the second leading cause of death from cancer after lung cancer [3, 4].

Colon cancer accounts for 15% of tumours diagnosed in men and its incidence is increasing. According to data from the Ministry of Health published in 2005, the current incidence in Spain is 14,204 new cases in men and 11,461 cases in women; age-adjusted rates are 63.58 and 39.01 per 100,000 inhabitants respectively. In 2004, 7,394 men and 5,545 women died in Spain from CRC [5]. The 5-year survival rate is over 50% for both genders.

Twenty percent of patients diagnosed with CRC will have metastases at the time of the first consultation and an additional 25–50% of those initially diagnosed with local or locally advanced disease will have metastases in the future. Among patients with an initial finding of metastasis, 50% will have disease limited to the liver and at the time of death 20% will continue to have liver metastasis only [6].

From 50% to 60% of CRC patients develop metastasis [7, 8]. Patients with stage IV (any T, any N, M1) colon cancer (Table 1) or with recurrent disease may have synchronous liver, lung or peritoneal metastases. Approximately 15–25% have synchronous liver metastases, of which 80–90% are considered unresectable at onset [8–11]. Liver metastatic disease is often metachronous, appearing after initial treatment, and liver is the target organ more commonly affected. The occurrence rate of metastases at the different sites is as follows: liver 60–71%, lung 25–40%,

Table 1 Correlation between TNM, Dukes and survival

TNM		Dukes	5-year survival (%)
Stage I	$T_1N_0M_0$	A	95
	$T_2N_0M_0$	B1	85–90
Stage IIA	$T_3N_0M_0$	B2	80
IIB	$T_4N_0M_0$	B3	65–75
Stage IIIA	$T_{1-2}N1M_0$	C1	60
IIIB	$T_{3-4}N1M_0$	C2	45
IIIC	Any TN_2M_0	C3	30
Stage IV	Any T, any N, M_1	D	<5

bone 5–10%, ovary 3–5%, adrenal gland 1%, central nervous system 1%.

Diagnostic evaluation

In metachronous disease, diagnostic assessment is aimed at knowing whether the lesion is or may be potentially resectable.

Laboratory tests

The following laboratory tests are carried out: complete blood count and coagulation tests, liver and kidney chemistry, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA).

Posteroanterior and lateral chest X-rays

These are performed to assess the lungs, mediastinum and bone structures. Although they may detect lung metastases, these may sometimes be overlooked and computed tomography (CT) of the chest is a more sensitive technique.

Ultrasonography

This simple and affordable technique allows for examination of the liver (the organ most commonly affected by CRC metastasis). It usually detects lesions larger than 1 cm, and may identify their number, size and location with 90% sensitivity. Ultrasonography may also identify other lesions such as lymphadenopathies, masses, ascites and infiltration of structures such as bladder, prostate, uterus, peritoneal implants, etc. However, it has limitations for retroperitoneum study and is a highly examiner-dependent technique.

Abdominopelvic spiral CT scan (with contrast)

Staging of colon and rectal cancer should include a spiral abdominal or abdominal-pelvic CT, and when lung metastases are suspected, a thoracic scan should be performed. This is useful to locate the tumour and regional lymph nodes, and to determine whether or not adjacent structures are infiltrated and if there are distant metastases (liver, lung, bone, carcinomatosis, ascites, ovary, etc.). Its limitations include examination of primary tumour and regional lymph nodes.

Magnetic resonance imaging (MRI)

This is not a first-choice technique for extension assessment, but may help to identify doubtful lesions detected by CT. Pelvic MRI has a sensitivity of 81–86% to assess the degree of wall infiltration by rectal tumours and of 63–69% for locoregional lymphadenopathies. This is always indicated when contrast CT scan is not possible.

Positron emission tomography (PET)

This may be more sensitive and specific than CT in the detection of metastases. Bipat et al.'s [12] meta-analysis of 61 studies comparing the sensitivity of CT, helical CT, MRI and PET reported significant differences in detection of liver metastases in favour of PET, but for single lesions <1 cm, MRI was the most sensitive. Another recent prospective study assessing the sensitivity of different techniques found that CT and MRI are more sensitive in the detection of liver metastases, while PET is more specific, and CT-PET is more sensitive than CT alone for detecting extrahepatic disease [13].

The indications for PET-CT are the detection of recurrence after clinical suspicion or elevation of CEA, the remaining tests being negative and being prior to metastasectomy, to rule out involvement at other levels [14].

Predictive and prognostic factors

Highly recommended factors

Clinically, Köhne et al. [15] classified patients with metastatic colon cancer in three prognostic groups based on a study on 3825 patients: low risk, with a median survival of 15 months, which included patients with ECOG 0/1 and a single metastatic site; intermediate risk, with a median survival of 10.7 months, including patients with ECOG 0/1, more than one tumour site and alkaline phosphatase levels <300 U/l, or patients with ECOG>1, white blood counts $<10\times10^9$/l and one tumour site; and high risk, with a median survival of 6.1 months, in patients with ECOG 0/1, more than one tumour site and alkaline phosphatase levels ≥300 U/l, or patients with ECOG >1 and more than one tumour site or a white blood counts $>10\times10^9$/l.

The presence of mutations at codons 12 and 13 of the K-ras oncogene determines resistance to treatment based on antibodies against the epidermal growth factor recep-

tor (EGFR) [16–18] showing a predictive role (evidence level 2A). Lievre et al. [19] found no cetuximab responders among the 24 patients with mutated K-ras in their series, as compared to 40% responders in the group of 65 patients with non-mutated K-ras. A mutated K-ras was also associated to a significantly shorter time to progression as compared to wild-type K-ras (median time to progression: 10.1 vs. 31.4 weeks) and overall survival (median overall survival: 10.1 vs. 14.3 months). In the CRYSTAL study, hazard ratio for progression-free survival in patients with wild-type K-ras metastatic CRC on first-line treatment was 0.68 (95% CI: 0.50–0.94) in favour of the FOLFIRI-cetuximab group (median, 9.9 vs. 8.7 months, p=0.02), with an objective response rate of 59% in the FOLFIRI-cetuximab arm vs. 43% with FOLFIRI alone [20]. In the OPUS study, the objective response rate in the cetuximab plus FOLFOX-4 arm was 46%, as compared to 36% in the chemotherapy alone arm, and a significant reduction in the risk of disease progression was also shown in patients treated with the cetuximab combination (HR: 0.57; p=0.0163) [21]. In the PRIME study, the group of patients with wild-type K-ras administered first-line treatment with FOLFOX-4 plus panitumumab showed a statistically significant difference of 9.6 months as compared to the 8.0 months of the chemotherapy alone group (HR: 0.80, 95% CI: 0.66 0.97), and a response rate of 55%, as compared to 48% when panitumumab was not associated [22].

On the other hand, it appears that other molecular markers might also modulate the response to anti-EGFR antibodies such as B-RAF [23, 24], PTEN [24–26], PI3K, EGFR status [23, 26], other K-ras mutations [27] or the expression of EGFR ligands; however, these genetic alterations cannot be considered for clinical use.

Furthermore, Amado et al. [28] reported that a wild-type K-ras status was required for CRC treatment based on panitumumab to be effective. In this study, the hazard ratio for time to progression in the wild-type K-ras group was HR: 0.45 (95% CI: 0.34 0.59), as compared to 0.99 (95% CI: 0.73–1.36) in the group with mutated K-ras. Determination of K-ras is therefore mandatory before an anti-EGFR therapy would be indicated.

Desirable factors to be considered in clinical practice

Irinotecan is hydrolysed to its active metabolite SN-38 through the action of carboxylesterase present in serum, bowel and tumour tissue, and at high levels in the liver. The enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) mediates glucuronidation of SN38 to form a conjugate with beta-glucuronic acid (SN-38G), which is the main detoxification route of SN38. The UGT superfamily has been divided into two large subfamilies: UGT1 and UGT2 [29–32]. There is a polymorphism in the $(TA)_6TAA$-box promoter region of the UGT1A1 gene that is involved in gene expression control, resulting in a 30–80% enzymatic variation. Some studies have shown that an increase in seven or more repeated units in this UGT1A1*28 polymorphism is associated to an increased risk of developing leukopenia and severe delayed diarrhoea after irinotecan treatment [33]. Other studies have shown a good agreement between UGT1A1*28 genotyping and a decreased efficiency of SN-38 glucuronidation, and thus a significant relationship between the AUC of SN-38 and the number of TA alleles [34].

5-Fluorouracil (5-FU) is inactivated in the liver by dihydropyrimidine dehydrogenase (DPD). Total or partial absence of this enzyme is in fact closely correlated with severe toxicity occurring as mucositis, granulocytopenia, neuropathy and sometimes death. Analysis of the prevalence of some DPD gene variants among patients with deficiency of this enzyme has shown that the most common mutation is G→A transition, leading to a splice donor site mutation at exon 14 (IVS14+1G>A) in the Caucasian population [35]. This mutation is responsible for the absence of exon 14 in the messenger RNA transcript, which causes the production of a truncated messenger RNA with virtually no enzymatic activity. This allele is known as DPYD*2A and is one of the variants associated to severe toxicity caused by 5-FU treatment [36, 37].

These two genetic alterations (UGT1A1*28 polymorphisms and DPD mutations) show a role predicting toxicity to irinotecan and 5-FU, respectively.

Investigational factors

The factors discussed below are investigational in nature and cannot currently be recommended on a routine basis, but it would be desirable to consider them in clinical trials.

One of these recently reported markers is the number of circulating tumour cells (CTC) in peripheral blood, assessed by immunomagnetic methods, which allowed for identification of groups of patients with longer or shorter survival based on the cutoff point, established at 3 CTC per 7.5 ml of blood [38, 39]. Patients with CTC numbers during treatment higher or lower than 3 CTC/7.5 ml had median survival times of 12.6 and 21.1 months respectively [40]. This method was the most significant independent prognostic factor when it was included in the multivariate analysis along with performance status (PS), age, and line and type of treatment.

Overexpression of thymidylate synthase (TS) has been found to be significantly associated to a lower response to 5-FU-based treatment in both patients on adjuvant treatment and those with metastatic colon cancer [41, 42]. Several studies have proposed that polymorphisms of the gene encoding for TS may affect response to 5-FU [43, 44]. Expression of this enzyme appears to depend on the number of tandem repeat polymorphic copies of 28 base pairs present in the 5'-promoter region. Polymorphisms in this region (TSER) were found to be involved in modulation of TS protein levels and could affect response to fluoropyrimidines [45]. Most Caucasian individuals may be carriers of

2–3 repeats in this polymorphic region, but sequences with more copies have been reported. An increased number of repeats would cause higher levels of both messenger RNA and protein [46, 47]. Three copies of these repeats would lead to a 2.6-fold increase in TS expression, as compared to only two copies. CRC patients homozygous for three repeats show high levels of messenger RNA for intratumoral TS, increased protein levels and a lower response rate to fluoropyrimidine-based chemotherapy as compared to patients homozygous for two repeats. Similar results were obtained in patients with metastatic colon cancer and on adjuvant therapy [48]. A meta-analysis of 20 studies [49] examined the association between TS levels and survival in patients with CRC. Results showed that high TS levels in patients at any stage are prognostic predictors.

X-ray repair cross-complementing group 1 (XRCC1) contains one domain that functions at protein protein interaction level and acts on poly-ADP polymerase. A polymorphism has been described in exon 10 of the XRCC1 gene that causes a substitution of arginine by glutamine at position 399, corresponding to the PARP binding domain. The enzyme carrying this polymorphism is therefore less able to start DNA repair due to its impaired binding capacity [50]. Individuals with this polymorphism have an increased tolerance to damage, so that patients with at least two of these polymorphic alleles have an up to 5-fold greater risk of failing treatment with oxaliplatin and 5-FU as compared to patients with the two wild-type alleles [51].

Multiple surrogate biomarkers that may indicate response to these drugs have been assessed, including dynamic MRI, PET systems evaluating tumour blood flow with fluorodeoxyglucose (FDG) and labelled water, mutations in K-ras, B-raf or p53 [52], as well as circulating endothelial stem cells, circulating mature endothelial cells, or plasma levels of some angiogenic markers such as vascular endothelial growth factor (VEGF) or fibroblast growth factor (bFGF) [53–56]. However, no studies showing the value of these biomarkers in peripheral blood or at the tumour immunohistochemical level are available yet. Considering current data, it is important to note that bevacizumab activity is independent from the K-ras mutation status [52].

A combination of three CT radiographic factors that allows for predicting in a statistically significant manner which patients with liver metastases will respond to bevacizumab combined with chemotherapy, as well as the time to progression for both resectable and unresectable tumours, has recently been reported [57]. Along the same lines, Kopetz et al. [58] reported a combination of cytokines and angiogenesis factors whose expression profiles in plasma might identify patients with a better response to bevacizumab combined with FOLFIRI.

However, very different prognostic and drug-response markers are being assessed by means of genetic signatures and proteomic profiles using high-throughput platforms, and results from these studies are very likely to allow for devising new tools to assess patients and identify the best therapeutic approach.

Patient groups

Certain prognostic factors are a key element, along with disease extent, in choosing a therapeutic approach. As regards liver metastases, three different situations are found. Not all patients have resectable metastases and not all resectable metastases share the same characteristics. Based on analyses of prognostic factors by Gayowski (1994) [59], Nordlinger (1996) [60], Fong (1999) [61], Iwatsuki (1999) [62], Figueras (2001) [63] and, more recently, Tomlinson (2007) [64], and looking at those with overall significance, we can establish a series of prognostic factors that significantly affect survival. Their presence in these studies decreased the 5-year survival rate to 0–15%, as compared to the 42% that may be achieved according to data from the LiverMetSurvey (www.livermetsurvey.org) and the MD Anderson Center [64]. The study by Cummings [65] based on a population registry including 13,599 patients and showing a 5-year survival rate of 32.8% in resected patients as compared to only 10% in unresected patients deserves special mention. Patient groups must be distinguished in order to establish an adequate treatment strategy. Based on the Fong criteria [61] and on data from other studies, a distinction is made between patients with *unresectable* and *resectable* metastases.

Resectable and potentially resectable patients

Among resectable patients, two situations are found: patients with a good prognosis and patients with poor prognostic factors. *Resectable patients with a good prognosis*, also called initially resectable, are those with an interval free from surgery for the primary tumour and occurrence of metastasis longer than 12 months, four or less metastases, involvement of only one lobe, no vascular involvement and a diameter smaller than 5 cm. *Resectable patients with poor prognostic factors*, also known as initially unresectable or with a high risk of relapse, are those with less than 50% of liver parenchyma involved, five or more nodules, bilobar involvement, vascular (resectable) involvement, diameter equal to or larger than 5 cm and resectable extrahepatic disease.

Treatment strategy

The therapeutic approach should be multidisciplinary, with a careful radiographic diagnosis and an extension study that allows for definition of the patient's risk group. From the onset, treatment steps should be established jointly by the surgeon and the oncologist, since timing is key for treatment outcome, as described later. For patients with a good prognosis, surgery at the onset may be indicated, and although comparative studies are lacking, adjuvant chemotherapy is recommended in these cases [66, 67]. However, EORTC's study 40983 comparing surgery plus perioperative treatment to surgery alone showed a significant improvement with combined treatment and concluded

that surgery plus chemotherapy is better than surgery alone. Since this study recruited patients with one to four liver metastases, it can be stated that neoadjuvant chemotherapy would be indicated also for initially resectable patients [68]. The first published studies with preoperative chemotherapy in patients with risk factors used oxaliplatin-based chemotherapies with an acceptable and manageable toxicity, and achieved survival rates ranging from 35% to 50% [69–71]. The largest series, by Adam et al. [72], reported a 35% survival rate. Differences were reported in this study between the good prognosis group (49% 5-year survival and 31% 10-year survival) and the poor prognosis group, which achieved a 5-year survival rate of 30% and a 10-year survival rate of 18% with preoperative chemotherapy, which in this case could be called induction chemotherapy (aimed at inducing objective response to reduce tumour volume).

The combination of conventional oxaliplatin schemes such as FOLFOX or irinotecan schemes such as FOLFIRI with monoclonal antibodies, or use of triplet therapy, achieved high response rates with very satisfactory R0 resection percentages in some studies. A phase II study with FOLFOX-4 plus cetuximab achieved a rate of confirmed responses of 72%, and 23% of previously unresectable patients were recovered for surgery, with R0 surgery achieved in 21% [73]. The combination of cetuximab plus FOLFIRI also yielded good results in unresectable metastases, with 30% rescues for surgery [74]. Bevacizumab has also shown activity in this situation. In the review by Ellis et al. [75], despite its effects on wound healing, bevacizumab was shown to be safe when minimum precautions were taken, including the 8-week delay in surgery recommended in this study. A very recent study of bevacizumab combined with capecitabine and oxaliplatin, where 52 of 56 patients were resected after 6 cycles of neoadjuvant chemotherapy, set 5 weeks as a protection period [76]. Another recent study using oxaliplatin-based chemotherapy showed that bevacizumab increased the percentage of pathologic remissions and decreased the incidence of severe hepatic sinusoidal dilation [77]. Bevacizumab was also safe when combined with irinotecan [78]. The triple combination of chemotherapeutic agents has shown high activity, with high resectability rates with R0 surgery, reaching 36% in an Italian study by the GONO group with FOLFIRINOX and 40% in the Spanish study by the Digestive Tumour Treatment Group (*Grupo de Tratamiento de los Tumores Digestivos*, TTD) with FUOXIRI, although toxicity was high, especially in the GONO study [79, 80].

Preoperative chemotherapy would therefore be indicated in the poor prognosis group as induction treatment, but chemotherapy should also be started in unresectable patients without foregoing the possibility of reconsidering surgical resection if a good response is achieved (conversion chemotherapy).

The first prospective, comparative study on patients with liver metastasis has only recently been published. This study (CELIM) compared preoperative treatment with FOLFOX+cetuximab vs. FOLFIRI+cetuximab [81]. Two groups of patients considered initially unresectable, those with more than five metastatic nodules, and unresectable patients were included. Overall response rate was 75%, with 34% R0 surgery. R0 surgery for the group with more than five metastases reached 40% and 28% of patients considered unresectable before chemotherapy converted to resectable. These data support the idea that both induction and conversion chemotherapy are indicated to significantly improve the results.

There are other elements that will influence outcome and should be considered. Induction of response to preoperative chemotherapy has been shown to be significantly related to the percentage of resections in both selected and non-selected patients with a significance of p=0.002 and p=0.001, but this correlation does not reach significance for R0 resections [82]. Although R0 rates are not significantly increased, use of chemotherapies with a high response rate in this indication is recommended. Based on literature results, the recommended first-choice therapy is the combination of fluoropyrimidines plus oxaliplatin and a monoclonal antibody. Other options should not be ruled out as alternatives for some patients (such as those with oxaliplatin hypersensitivity), but their toxicity should be monitored.

A very important aspect of preoperative multidrug chemotherapy is the hepatotoxicity induced. In this regard, oxaliplatin combinations again provide a more favourable profile as compared to other regimens (less steatohepatitis and lower 90-day mortality) [83]. The number of cycles is also related to toxicity, which worsens significantly after the fourth or fifth cycle. For this reason, surgery should be performed as soon as possible.

Patients with progression should not be operated on, as outcomes are very poor. The best results are achieved when surgery is performed during response to treatment [71]. The goal of complete remission should be avoided, because complete radiographic remission is not real or curative in 83% of cases [84]. Close monitoring of response is therefore required, with patient assessment every three or four treatment cycles depending on the regimen used, and surgery should be indicated once response is achieved. In this situation, patients whose treatment includes an antiangiogenic agent should be treated without this agent until the 6th week of safety for resection. Lastly, it should be noted that lung metastases have prognostic factors similar to liver metastases and should be approached in the same manner. Resectable lung disease is not a contraindication for surgery of liver metastases and liver disease does not contraindicate lung surgery.

Radiofrequency ablation should be considered in the treatment strategy for liver and lung metastases. Radiofrequency is not, and should not be, considered as a substitute for surgery, which continues to be the most curative method, but as a complementary technique. Its main indication is intraoperative use as a complement to surgery in patients with multiple bilobar metastases in whom liver paren-

chyma must be spared. It is also indicated for percutaneous treatment of unresectable metastases such as deep relapses after hepatectomy or in patients whose general condition does not allow for resection surgery [85].

Follow-up after resection of metastases and after completion of adjuvant treatment is another important aspect. No study is currently available to support follow-up recommendations, but it should not be forgotten that in patients with metastatic cancer follow-up should be intensive. Such follow-up should include CT scans of the abdomen and chest. We recommend a first post-resection visit at 3 months at which marker measurements and an abdominal CT should be performed, followed by visits every 6 months including marker tests and CT scans of the chest and abdomen scans for 5 years. All these recommendations have an evidence level 2A.

Unresectable patients

Most patients with advanced colon cancer experience metastases in several locations and are therefore unlikely to be amenable to curative surgical resection of metastases. In some circumstances, the presence of metastasis in a single site but with multiple lesions also precludes resection with curative intent.

Unresectability criteria include occupation of more than 70% of liver parenchyma, portal infiltration, bilateral venous infiltration, infiltration of three hepatic veins, lymphadenopathies in the hepatic hilum and unresectable extrahepatic disease. Patients with one or more of these factors constitute the unresectable group.

Pretreatment evaluation

These patients should be carefully assessed before any therapeutic action is started. PS, symptoms caused by the metastatic disease, comorbidities and the risk or history of cardiovascular problems should be defined.

Leukocytosis or anaemia are considered unfavourable factors. Liver and kidney function tests will allow for assessment of general aspects related to the patient and the disease. Elevated alkaline phosphatase or LDH levels are also unfavourable prognostic factors. A decrease in creatinine clearance to 30–50 ml/min allows for adjustment of capecitabine dose, while the drug should be avoided if creatinine clearance drops to less than 30 ml/min. Administration of irinotecan to patients with hyperbilirubinaemia is contraindicated. In patients with elevated indirect bilirubin levels secondary to Gilbert syndrome, an increased gastrointestinal and haematologic toxicity is expected.

An imaging test allows for assessment of the location of metastases. A thoracoabdominal and pelvic CT scan should be done as a baseline test before any treatment. This examination and its comparison with a post-treatment assessment will allow for analysis of the effect of treatment and for classification of the patient as responder, stabilised or in progression.

Treatment objectives

In patients in whom resection of metastases is not possible, the main treatment objective is to prolong survival, as well as to control or prevent symptoms, improve quality of life or prevent its impairment, and delay tumour progression. Treatment should be adapted to the characteristics of patients, taking into account their needs and peculiarities.

Treatment strategy

A multidisciplinary approach to the patient should be taken when initial treatment is decided. Patient's evaluation and confirmation of the presence of unresectable metastases should be done together with a surgeon. In patients with metastases synchronous with the primary tumour, palliative resection of primary tumour to prevent bleeding or obstructive symptoms or the possibility of implanting prosthesis to prevent obstruction should also be considered.

In patients with aggressive disease, defined as disease showing unfavourable prognostic factors, multiple metastases in various locations, or an impaired general condition due to symptoms cause by tumour growth, initial polychemotherapy is recommended. This group of patients is not often well represented in phase III trials of first-line treatments. An analysis of 6286 patients in nine randomised clinical trials of first-line treatment showed that only 8% of the selected patients had PS 2. PS 2 was confirmed to be an unfavourable factor, but the benefit achieved by these patients when given polychemotherapy regimens is similar to that seen in patients with PS 0 or 1. However, they have a higher risk of dying in the first 60 days and experiencing greater toxicity [86].

An essential aspect of the treatment strategy for advanced CRC is consideration of treatment as a continuum. Sequential administration of different drugs or drug combinations along the different treatment lines, dictated by disease progression or the failure of a given therapeutic scheme, results in a significantly longer survival. When the proportion of patients sequentially receiving three drugs during the entire natural history of the disease is increased, median survival is also increased [87].

In patients in good general condition with clinically indolent disease, an initial treatment with drug combinations may be similar to sequential administration of active drugs over the natural course of the disease. The FOCUS and CAIRO-1 studies usually include such patients, of whom only 8% and 4% respectively had PS 2 [88, 89], and their results confirm that, in well selected patients, a sequential strategy is not inferior to intensive treatment. However, although there were no significant differences in overall survival between the different treatment strategies used in these two studies, their overall survival was somewhat lower than that reported by other studies where patients were given polychemotherapy from the onset [90]. The MRC COIN trial looked at whether advanced colon cancer patients could survive longer if cetuximab was added to their standard chemotherapy. Secondly, it tested whether taking breaks from standard chemotherapy could minimise

side effects, reduce time on treatment and improve patients' quality of life without affecting how long they would live. Adding cetuximab did not improve survival in these patients, but the results also showed that an alternative drug combination to standard chemotherapy, fluorouracil/oxaliplatin in combination with cetuximab, did show a trend to benefit. Results from the second part of the trial revealed that patients given intermittent chemotherapy suffered fewer side effects, but on average they survived for 1.4 months less than those who received continuous chemotherapy [91]. Although these results do not give a clear indication that one treatment option is better than another, they do provide more information about the potential effect different treatment options can have. The results will help inform patient–clinician discussions and ultimately decisions on individual treatment. Comparisons between the results of different studies must however be put into perspective due to the potential biases and differences between the populations treated.

Very few randomised studies have been conducted on fragile and elderly patients. This is a common group of patients that is not well represented in clinical trials and always includes patients with more favourable prognostic characteristics. A British study (FOCUS 2) conducted on fragile subjects (median age: 75 years; PS 2: 30%) showed that the benefits from adding oxaliplatin to a capecitabine or 5-FU regimen may be marginal (HR: 0.86; p=0.06) [92].

Chemotherapy for advanced disease

There are currently various drugs available that have been shown to be effective for the treatment of advanced disease, both as monotherapy and in different combinations. These drugs include 5-FU, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab and panitumumab. The choice of one of these drugs and its administration as monotherapy or in combination depends on aspects related to the disease, treatment objective and patient. In any case, it should be noted that the therapeutic strategy for advanced disease should be based on a continuum of care, rather than on the mere succession of independent lines of therapy [93]. The goals of this strategy are, on the one hand, to achieve responses that allow for surgery of metastases and primary tumour with a curative intent and, on the other hand, to delay disease progression as much as possible and ensure that the patient maintains an adequate general condition that allows for sequential administration of the different drugs available with the least possible toxicity.

For patients with an adequate general condition, polychemotherapy with oxaliplatin or irinotecan and fluoropyrimidines plus a biologic drug (anti-VEGF or anti-EGFR) is currently considered as the best option as first-line treatment (Figs. 1.1 and 1.3). Various chemotherapy regimens have proved to be beneficial in this situation and may be considered standard as the first treatment for advanced disease: oxaliplatin+5-FU in continuous infusion with or without folinic acid (FOLFOX4, mFOLFOX6, FUOX) [90, 94–99], irinotecan+5-FU in continuous infusion with folinic acid (FOLFIRI) [90, 100, 101] or capecitabine+oxaliplatin (XELOX, CapeOx) [102–104]. The choice of polychemotherapy regimen should mainly be based on the toxicity profile and patient characteristics, since comparative studies have shown no differences in survival favouring a given sequence of regimens [90]. On the other hand, pooled analysis of the results from seven phase III studies comparing various chemotherapy regimens demonstrated a longer survival for patients receiving the three drugs available at that time over the course of their disease (5-FU/folinic acid, oxaliplatin and irinotecan), regardless of their administration sequence [87]. These data, together with the results of other phase III studies comparing irinotecan vs. supportive care [105] or irinotecan vs. 5-FU as a continuous infusion [106] after failure of first-line treatment, support administration of second and third lines of chemotherapy to patients who maintain an adequate general condition. When the patient cannot tolerate polychemotherapy with oxaliplatin or irinotecan, administration of 5-FU/folinic acid [107, 108] or capecitabine monotherapy [109, 110] are valid therapeutic options (Figs. 1.2 and 1.3).

There are some issues of interest regarding chemotherapy toxicity when choosing one regimen or another. Some polymorphisms determine a greater predisposition to severe haematologic and gastrointestinal toxicities with irinotecan [31]. Peripheral neuropathy is the main dose-limiting toxicity of treatment regimens containing oxaliplatin, often conditioning treatment continuation in the absence of progression. Several approaches have been developed to try and reduce this problem, including early discontinuation of oxaliplatin before neurotoxicity occurs. Thus, the patient has drug-free periods that delay occurrence of neurological symptoms. This "stop-and-go" strategy was successfully assessed in the OPTIMOX1 study, which reported less neurotoxicity without impairing the overall efficacy of the FOLFOX treatment given to patients as first treatment for advanced disease [111]. In light of these results, it is recommended that oxaliplatin treatment is interrupted after three months of therapy (or before, in the event of early significant neurotoxicity). Resumption of treatment is considered when progression occurs in the absence of limiting neurotoxicity. However, all other drugs administered with oxaliplatin should be maintained until the disease progresses or limiting toxicity related to each drug occurs, because their early discontinuation has been associated to impaired patient survival [112].

More recently, studies support the use of different conventional chemotherapy regimens combined with monoclonal antibodies targeting VEGF or the extracellular domain of EGFR because of their greater efficacy.

As regards anti-VEGF antibodies, and irrespective of the selected chemotherapy regimen, there is currently adequate evidence to recommend addition of bevacizumab to first-line treatment [102, 113–118].

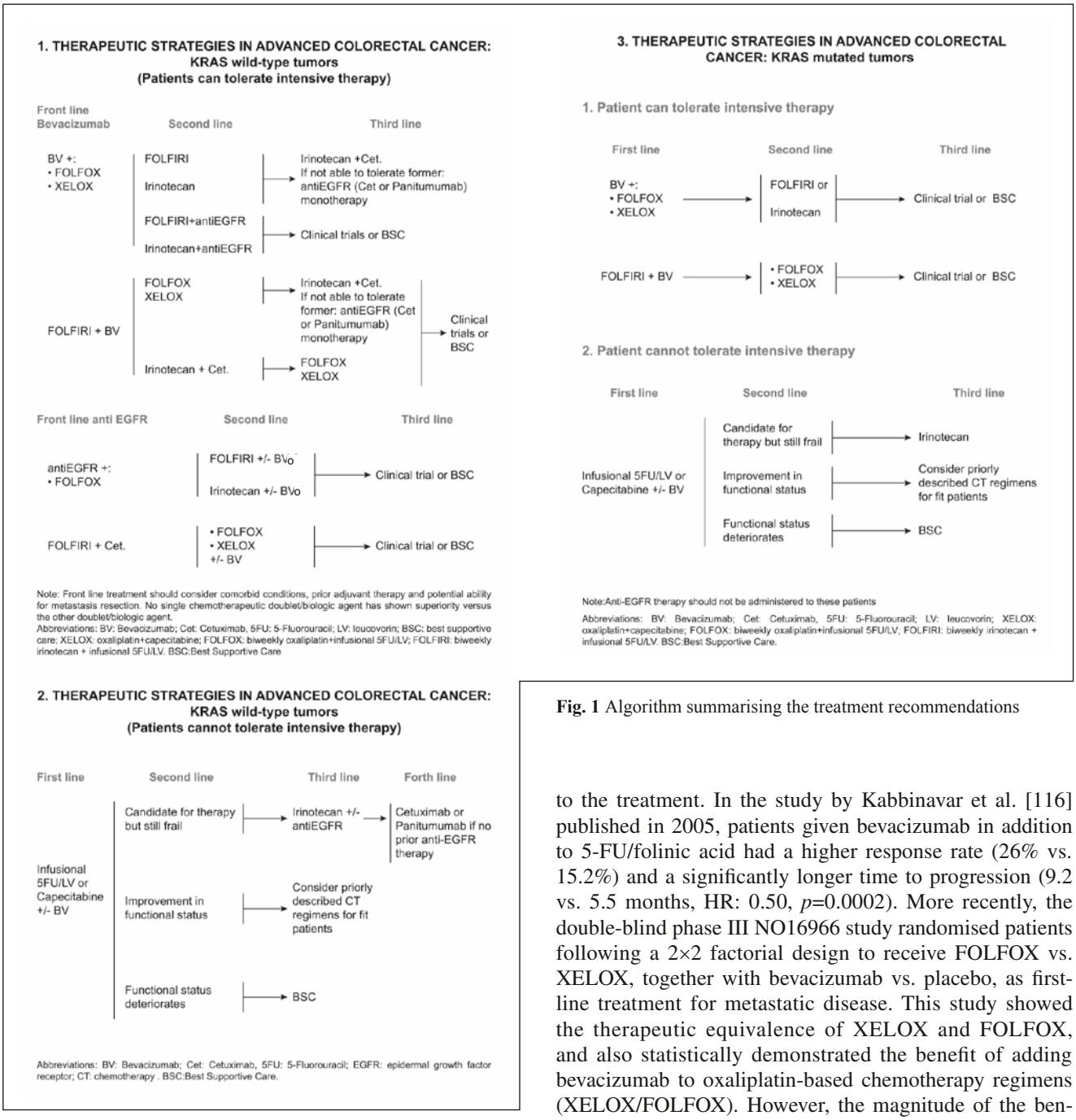

Fig. 1 Algorithm summarising the treatment recommendations

The pivotal study by Hurwitz et al. [115] published in 2004 provided the first evidence in favour of using bevacizumab in this context. This randomised study showed that, as compared to placebo, bevacizumab added to a scheme of irinotecan and 5-FU as a bolus (IFL) increased median survival (20.3 vs. 15.6 months, HR: 0.66, $p<0.001$). Subsequent studies have supported these results with different polychemotherapy regimens based on irinotecan [113, 118]. More fragile patients who cannot be treated with polychemotherapy and receive monotherapy with 5-FU/folinic acid also benefit from the addition of bevacizumab to the treatment. In the study by Kabbinavar et al. [116] published in 2005, patients given bevacizumab in addition to 5-FU/folinic acid had a higher response rate (26% vs. 15.2%) and a significantly longer time to progression (9.2 vs. 5.5 months, HR: 0.50, $p=0.0002$). More recently, the double-blind phase III NO16966 study randomised patients following a 2×2 factorial design to receive FOLFOX vs. XELOX, together with bevacizumab vs. placebo, as first-line treatment for metastatic disease. This study showed the therapeutic equivalence of XELOX and FOLFOX, and also statistically demonstrated the benefit of adding bevacizumab to oxaliplatin-based chemotherapy regimens (XELOX/FOLFOX). However, the magnitude of the benefit was smaller than in prior studies. Patients receiving bevacizumab had a longer progression-free survival (9.4 vs. 8.0 months, HR: 0.83, $p=0.0023$), but the response rate was similar, and the overall survival benefit did not reach statistical significance (21.3 vs. 19.9 months with/without bevacizumab, HR: 0.89, $p=0.077$) [102]. Subgroup analysis suggests a greater benefit in patients whose treatment with bevacizumab was maintained until disease progression (HR: 0.63, $p<0.0001$). Additionally, the ECOG E3200 study showed that use of bevacizumab combined with oxaliplatin and 5-FU (FOLFOX) in patients receiving a previous line of chemotherapy increased the response rate (21.8% vs. 9.2%) and overall survival (12.9 vs. 10.8

months, HR: 0.76, p=0.0018) as compared to patients receiving chemotherapy+placebo [119].

An observational registry (BRiTE) was conducted in the USA to assess the efficacy and safety of bevacizumab plus chemotherapy (regimen at the investigator's choice) as first-line treatment for patients with metastatic CRC. The most recent data, with 1953 patients assessed, corresponded to a median follow-up of 20.1 months. The most commonly used chemotherapy regimen was FOLFOX, toxicities were similar to those reported in randomised clinical trials, median time to progression was 9.9 months and median overall survival was 22.9 months [120].

As regards safety, addition of bevacizumab did not significantly increase the adverse effects of chemotherapy, but was associated to an increased risk of developing hypertension, which was easily managed. Gastrointestinal perforation was much less common, being reported in less than 2% of patients treated [111, 114, 121]. Another adverse effect to be considered, especially in patients with vascular risk factors, is the increase in arterial thrombotic events associated to bevacizumab. Its incidence reached 2% in patients treated with bevacizumab and chemotherapy [120, 122].

Lastly, despite the potential interference with wound healing derived from its mechanism of action, there is wide evidence suggesting that administration of bevacizumab as a neoadjuvant treatment does not seem to increase postoperative complications in patients undergoing resection of liver metastases [76, 114, 123, 124]. In the Ribero et al. study [77] a significant decrease of liver sinusoid dilation was detected in patients undergoing resection of liver metastases after treatment with bevacizumab, oxaliplatin and 5-FU as compared to patients receiving oxaliplatin and 5-FU only (p<0.01). In this study, a significant reduction in viable tumour was also seen in the pathologic examination, but no differences were found in the complete response rate. Recently reported data from the First BEAT and NO16966 studies, where 1965 and 699 patients respectively were treated with chemotherapy+bevacizumab, showed similar safety results [123]. A total of 215 patients in the BEAT study and 59 patients in the NO16966 study underwent metastasis resection with radical intention (resection rates of 7.6% and 8.4% respectively) [123]. Since the half-life of bevacizumab is 3 weeks, drug discontinuation 6 weeks before surgery is considered as an adequate safety margin.

There is ample evidence about the use of EGFR receptor inhibitors both as monotherapy and combined with different chemotherapy regimens in different therapeutic contexts. Cetuximab is a chimeric monoclonal antibody that recognises the extracellular domain of EGFR. Its most common toxicities include skin toxicity, which occurs in 75–100% of cases and is frequently manifested as acneiform reactions, dry skin, paronychia or pruritus. Other less common toxicities include conjunctivitis, asthenia, nausea, vomiting, abdominal pain, diarrhoea and hypomagnesaemia. Hypersensitivity reactions are uncommon, occurring in 3–5% of patients, and are severe in 50% of cases. Bronchospasm, interstitial pneumonitis, acute pulmonary oedema, etc. may occur and require permanent treatment discontinuation. Administration of cetuximab was initially tried as monotherapy in non-selected patients with advanced CRC refractory to conventional chemotherapy. In this setting, cetuximab induced a modest rate of response (8 11%) in patients previously treated with irinotecan [125, 126]. This rate increased when the drug was combined with irinotecan in the same patient population. BOND was a randomised study that showed that the cetuximab+irinotecan combination induced a rate of response twice that of cetuximab monotherapy (22.9 vs. 10.8%, p=0.007) and a longer progression-free survival (4.1 vs. 1.5 months, p<0.001) [125], which demonstrated that addition of the drug was able to reverse irinotecan resistance in a significant number of patients. In the same subgroup of patients refractory to irinotecan, the BOND-2 study [127] reported interesting results with the combination of irinotecan, bevacizumab and cetuximab, with response rates (38%) and times to progression (8.5 months) that are truly remarkable for this population of pretreated patients. In 2008, the presence of mutations in the K-ras gene was shown to be a relevant negative predictive factor, selecting ~40% of patients who would not benefit from treatments targeting EGFR. Thus, in patients with wild-type K-ras, cetuximab monotherapy, compared to the best support treatment, significantly prolonged progression-free survival (3.7 vs. 1.9 months, HR: 0.40, p<0.001) and overall survival (9.5 vs. 4.8 months, HR: 0.55, p<0.001), with response rates of 12.8% vs. 1.2% [128].

In second-line treatment, the results from the EPIC study, comparing irinotecan monotherapy vs. irinotecan+cetuximab after progression on first-line treatment based on oxaliplatin, showed benefits in response rate (16.4% vs. 4.2%, p<0.0001) and progression-free survival (4.0 vs. 2.6 months, HR: 0.69, p<0.0001), but the study did not achieve the primary objective of an increased overall survival (10.7 vs. 10 months, HR: 0.975, p=0.71) [129]. However, this study was conducted on a non-selected population in terms of K-ras.

Cetuximab has also been tested as first-line treatment combined with both oxaliplatin-based schemes and FOLFIRI. These studies were again conducted before use of K-ras was common practice, although the gene was retrospectively analysed in most of the population included. The OPUS study was a phase II randomised study comparing FOLFOX4+cetuximab vs. FOLFOX [21]. Statistical significance was not reached for the primary objective of rate of responses confirmed by an independent committee (46% vs. 36%, p=0.064) or for the secondary objective of progression-free survival (7.2 months in both study arms). However, the subpopulation with wild-type K-ras did clearly benefit from cetuximab treatment, showing significantly better response rates (57% vs. 34%, p=0.003) and progression-free survival (8.3 vs. 7.2 months, HR: 0.567, p=0.006) than patients receiving FOLFOX alone. Rates of R0 me-

tastasis resections were also higher (9.8% vs. 4.1%). By contrast, the subpopulation with K-ras mutations not only did not benefit from cetuximab treatment, but showed some deleterious effect from the drug (lower response rate and shorter time to progression) [130, 131]. Similarly, the overall results from the CRYSTAL study [20] comparing FOLFIRI vs. FOLFIRI+cetuximab in patients with advanced CRC on first-line treatment showed a modest benefit in favour of the cetuximab arm in terms of response rate (46.9% vs. 38.7%, p=0.0038) and progression-free survival (8.9 vs. 8 months, HR: 0.85, p=0.04), as well as a higher proportion of patients undergoing metastasis resection with radical intention (6% vs. 2.5%, 9.8% vs. 4.5% in the population with hepatic metastases only). However, a retrospective reanalysis of efficacy considering K-ras mutation status again confirmed that the benefits associated to addition of cetuximab (in this case to FOLFIRI) were only seen in the population with wild-type K-ras. The magnitude of such benefits was much larger than previously reported, with significant increases in response rate (57.3% vs. 39.7%, p<0.0001), progression-free survival (9.9 vs. 8.4 months, p=0.0012) and overall survival (23.5 vs. 20 months, p=0.009) being noted in patients receiving FOLFIRI plus cetuximab as compared to those given FOLFIRI alone [131].

Based on these studies, EMEA has granted approval for use of cetuximab in first-line treatment of metastatic CRC, restricted to patients with no K-ras mutations.

A meta-analysis of the CRYSTAL and OPUS studies reported a 34% reduction in risk of progression (HR: 0.66, p<0.0001) and increased overall survival (HR: 0.81, p=0.0062) and response (OR: 2.16, p<0.0001) in wild-type K-ras patients with metastatic CRC treated with first-line chemotherapy plus cetuximab [132].

The CELIM study analysed the response rate and resectability of liver metastases in patients treated with cetuximab plus FOLFOX6 or FOLFIRI and confirmed the results of prior studies. In wild-type K-ras patients, response rate was 70%, as compared to 41% in patients with mutated K-ras (OR: 3.42, p=0.080). No statistically significant differences were found depending on the chemotherapy regimen used, with an R0 resectability rate of 34% [81].

Preliminary data from the COIN study, a British study comparing FOLFOX/XELOX with or without cetuximab, did not support these results. This study found no significant differences in any of the efficacy parameters analysed, though some positive trend was seen in the subgroup treated with FOLFOX [91].

There is increasing evidence of the activity of panitumumab, a humanised monoclonal antibody targeting EGFR, in advanced CRC. It has a similar toxicity to cetuximab, skin toxicity being the most common toxicity occurring in 90% of cases. Hypersensitivity reactions are minor, and occur in 0 1% of treatments. The pivotal study showed that panitumumab monotherapy induced tumour response in 8% of patients and significantly prolonged progression-free survival (HR: 0.54; 95% CI: 0.44–0.66) in patients with wild-type K-ras advanced CRC who had progressed on conventional chemotherapy [133]. Panitumumab was also tested in combination with conventional chemotherapy. The PRIME study compared the combination of FOLFOX4 plus panitumumab vs. FOLFOX4 alone in treatment-naïve patients with advanced CRC. Patients with wild-type K-ras who received the combination with panitumumab showed higher response rates (55% vs. 48%) and longer progression-free time (9.6 vs. 8 months, HR: 0.8; p=0.023) than those given FOLFOX4 alone. As seen in the OPUS study with cetuximab, patients with mutated K-ras who received FOLFOX+panitumumab had a shorter progression-free survival than those receiving FOLFOX alone (7.3 vs. 8.8 months). That is, anti-EGFR therapy not only did not improve the results of conventional chemotherapy, but appeared to be harmful [22].

Results of second-line treatment with panitumumab combined with FOLFIRI vs. FOLFIRI alone also favoured panitumumab in patients with wild-type K-ras, improving the response rate (35% vs. 10%) and time to progression (5.9 vs. 3.9 months) (HR: 0.73; 95% CI: 0.59 0.903; p=0.004). A trend to a longer overall survival was also seen, but did not reach statistical significance (14.5 vs. 12.5 months, p=0.115) [134].

Finally, two randomised studies have been conducted combining cetuximab or panitumumab with bevacizumab and chemotherapy, as compared to bevacizumab plus chemotherapy (CAIRO2 and PACCE). Both studies showed no benefits of adding an anti-EGFR to the anti-VEGF in the wild-type K-ras population, and there was clear harm to patients carrying mutations, which has led to advising against this combination in patients with advanced CRC. In the CAIRO2 study, no differences were seen in response, time to progression or overall survival. Decreases were seen in time to progression (8.1 vs. 12.5 months, p=0.003) and overall survival (17.2 vs. 21.8 months, p=0.03) in patients with mutated K-ras given chemotherapy plus cetuximab and bevacizumab vs. chemotherapy plus bevacizumab. Results of the PACCE study confirmed a greater toxicity with a shorter time to progression when panitumumab was associated to chemotherapy plus bevacizumab (10 vs. 11.4 months) [135, 136].

In conclusion, use of polychemotherapy based on fluoropyrimidines plus oxaliplatin or irinotecan is recommended in treatment-naïve patients with no medical contraindications. XELOX, FOLFOX and FOLFIRI are the schemes most commonly used. It is recommended to add to these schemes a monoclonal antibody, which should be selected based on the K-ras mutational status and considering the toxicity profiles of drugs in the context of each patient (comorbidities, preferences, treatment objectives). In patients with mutated K-ras, bevacizumab is the indicated antibody. In patients with wild-type K-ras, both bevacizumab and anti-EGFR antibodies (with a higher level of evidence for cetuximab than for panitumumab) are valid alternatives. Currently ongoing studies such as CALGB 80405, in which patients with wild-type K-ras are randomised to receive FOLFOX or FOLFIRI with bevacizumab or cetuximab,

will help establish the relative efficacy of these treatments. In any case, chemotherapy should not be used concurrently with both types of antibodies (anti-VEGF and anti-EGFR). The second-line treatment will depend on the drugs used in the first line. Thus, if oxaliplatin-based regimens were used in the first line, irinotecan-based regimens will subsequently be used, and vice versa. In wild-type K-ras patients, both antibodies can be used sequentially combined with the different chemotherapy regimens being used. Anti-EGFR may be used as monotherapy or combined with irinotecan after progression on irinotecan-based schemes.

Special situations

Peritoneal carcinomatosis

In addition to lymphatic and blood dissemination, peritoneal dissemination occurs in colorectal carcinoma, leading to peritoneal carcinomatosis (PC).

PC results from invasion of the intestinal wall, or is iatrogenically caused during surgery by in-transit tumour cells, lymph vessel embolism or peritoneal seeding [137]. Peritoneal invasion occurs in 3–28% of patients, a variability accounted for by the different tumour cell detection methods [138]. A positive tumour cytology has been significantly related to the risk of developing PC. Two trials have correlated the presence of positive tumour cytology with an impaired overall and disease-free survival [139, 140].

Twenty-five percent of patients have isolated metastatic peritoneal involvement. The same surgical hypothesis as for liver metastases may be applied here, considering PC as the first dissemination site rather than as disseminated disease. Locoregional control based on cytoreductive surgery (CRS) followed by intraperitoneal chemotherapy (IPC), sometimes with hyperthermia (HIPEC) to sterilise minimal residual disease, has been used recently and has achieved prolonged survival.

Preoperative staging is done using the standard methods. CT and ultrasound have a sensitivity of approximately 25% for implants 1 cm or less in size [141]. PET has not been effective for detecting lesions smaller than 1 cm [142].

Median survival with systemic 5-FU-based chemotherapy ranges from 5.2 to 12.6 months [143–145]. A phase III randomised, controlled study compared ultra-radical CRS and hyperthermic IPC plus systemic 5-FU-based chemotherapy vs. systemic chemotherapy and palliative surgery in patients with PC originating in the appendix or CRC with no evidence of extraperitoneal metastatic disease. Median survival of the 50 patients treated with 5-FU-based systemic chemotherapy and palliative surgery was 12.6 months with a 2-year survival rate of approximately 18%. The better results in this series as compared to previous ones are probably explained by the selection of patients with no extraperitoneal metastasis [146].

A review of 20 studies assessing CRS and IPC with or without hyperthermia in PC from CRC found median survivals ranging from 12 to 32 months.

Survival ranged from 65% to 90% at 1 year, from 25% to 60% at 2 years, from 18% to 47% at 3 years, and from 17% to 30% at 5 years [147–165].

Administration of IPC allows for exposure to high chemotherapy doses with minimal systemic exposure. The role of hyperthermia is not well established but, theoretically, it would act by increasing penetration of chemotherapy into the cell, which would produce a synergistic effect.

This technique has a high morbidity, with grade 3–4 postoperative complication rates ranging from 14% to 55%, while treatment-related mortality ranges from 0% to 19%. The most common complications include gastrointestinal fistulisation, abdominal sepsis and haematological toxicity.

Several classification systems have been used to assess peritoneal extension; the most widely used is the semiquantitative peritoneal cancer index described by Jacquet and Sugarbaker [166], based on distribution and size of peritoneal lesions. After CRS, the size of residual disease correlates with survival.

Survival after resection of the entire macroscopic lesion ranged from 17.8 to 39 months, with a 5-year survival rate between 20% and 54% [159, 160, 164]. In a multivariate analysis of four series, only disease extension and/or complete resection had prognostic significance [148, 159, 161].

A randomised study conducted by Verwaal et al. [146] compared the efficacy of CRS plus hyperthermic intraperitoneal chemotherapy (HIPEC) to systemic chemotherapy plus palliative surgery. A total of 105 patients with PC of CRC or appendicular origin and no distant metastases were randomised to CRS and HIPEC with mitomycin C chemotherapy followed by systemic chemotherapy with 5-FU/folinic acid vs. systemic chemotherapy with 5-FU/folinic acid alone and palliative surgery when needed. Despite the higher surgical mortality of CRS (8%), median survival significantly increased in this arm vs. the control arm (22.3 vs. 12.6 months, p=0.032). In a recent study, patients with resectable PC treated with complete radical surgery plus HIPEC were compared to patients given combined systemic chemotherapy, since the surgical technique with peritoneal surgery and HIPEC was not available at that centre. Survival times were 62.7 months for combined treatment with HIPEC vs. 23.9 months for systemic chemotherapy (p<0.05, log-rank test). Results confirmed a 2-year survival for systemic chemotherapy, but long survival patients were only found in the HIPEC arm [167].

A Swedish study reported 103 patients treated with CRS and HIPEC, of whom only 38 had CRC. After a median follow-up of 13 months, a 2-year survival rate of 64% was found in patients with CRC [168].

Elias et al. [150] randomised PC patients to treatment with CRS with or without early postoperative hyperthermia. The study was terminated early with 35 patients due to

recruiting difficulties. The 2-year survival rate with CRS was 60%. Hyperthermia had no beneficial effect in this study.

Early postoperative intraperitoneal chemotherapy (EPIC) has been widely assessed after CRS with HIPEC [169], but has not been compared to other forms of IPC in any randomised study. A meta-analysis of 506 patients with PC from CRC found that EPIC does not improve results when combined with HIPEC [152].

Elias et al. [170] recently published a French multicentre, retrospective study on 523 PC patients from 23 centres treated with radical surgery and perioperative IPC, with or without hyperthermia. The mortality and morbidity rates were lower than previously reported (3% and 31%, respectively). Median survival was 30.1 months. Five-year overall survival was 27% and disease-free survival was 10%. Complete CRS was done in 84% of patients and achieved a median survival of 33 months.

The reported series suggest favourable results with this technique despite the high recurrence rate (70%), with a time to progression of 9 months and a median survival of 30 months. Patients undergoing a second CRS also had a longer survival as compared to those who did not undergo that surgery (39 vs. 20 months, $p<0.0003$) [171].

Despite the scant evidence available, a consensus statement from the Society of Surgical Oncology recommended CRS with HIPEC in selected patients with PC from CRC [172, 173]. Appropriate patient selection is important. Patients must have good organ function, a good nutritional status and an adequate PS. Bone marrow function should be adequate if chemoperfusion is to be done. Liver metastases are a relative contraindication for HIPEC, but some authors have reported similar results when liver metastases were resected. Peritoneal metastases to the liver surface do not imply the same prognosis as haematogenous metastases [174]. Extensive peritoneal involvement, nodal metastases and progression on systemic chemotherapy are negative factors for selecting this technique.

Because of the difficulty in obtaining level 1 evidence, data regarding the benefits of this therapeutic strategy (CRS plus HIPEC) are considered sufficient for its relative recommendation. However, because of the complexity of the technique and its high morbidity and mortality, it should be performed on selected patients and at national reference centres with a specific programme for this treatment and with sufficient experience and training.

Local treatment of colorectal cancer in the setting of metastatic disease

In patients with locally advanced or metastatic disease, the goal of primary tumour surgery is to control obstruction and haemorrhage, rather than to cure. Modern chemotherapies and stents for subocclusive tumours add complexity to the treatment. From 15% to 20% of CRC patients have liver metastases at the time the primary tumour is diagnosed, but it has not been shown that synchronous metastases have a worse prognosis than metachronous metastases [60]. The situation for lung metastases is similar to that of liver metastases.

The therapeutic strategy will depend on primary tumour symptoms and on potential resectability of metastases.

A study by the Surveillance, Epidemiology and End Results (SEER) and the National Cancer Institute analysed, in its database, surgery for primary tumours in 9011 patients over the age of 65 years diagnosed with stage IV CRC between 1991 and 1999 [175]. Seventy-two percent of these patients underwent surgery (palliative resection), while resection of metastases was performed in only 4% (with curative intent). Chemotherapy was administered to less than 50% of patients despite its proven efficacy in metastatic disease. Operated patients had longer survivals than those not operated, especially those given chemotherapy. Other retrospective series also reported a longer survival for operated patients, but this benefit may be the result of patient selection.

The decision to perform surgery on the primary tumour will depend on disease symptoms, extension (liver or lung metastases only or further extension), possibility of resecting metastases, age and morbidity risk.

In asymptomatic patients, chemotherapy may be used without preventive surgery of the primary tumour. In a large series of 233 patients with synchronous metastases treated with the current chemotherapy regimens, 93% of patients did not require palliative surgery of the primary tumour. Emergency surgery was required in 7% of patients for obstruction or perforation, and 4% did not require surgery (stent or radiotherapy). The study confirmed that most patients with synchronous metastases never require surgery of the primary tumour [170, 176].

The clinical signs that warrant surgical treatment for the primary tumour include severe occlusion, perforation, haemorrhage and locally advanced disease.

In patients with unresectable metastatic disease, primary tumour surgery is an option for obstructive tumours. In unresectable proximal colon tumours, a decompressing bypass is usually done. In distal obstructive tumours, palliation may be achieved with a colostomy or by implanting expandable metal stents [177–179]. Advantages over palliative surgery are a faster recovery, which allows for early chemotherapy and a shorter hospital stay. Early complications, of which the most common is migration into the anal canal, occur in 19–30% of patients. For resectable or potentially resectable metastatic disease, surgery of the primary tumour and metastases is the curative option.

If the patient is a candidate for surgery, and liver and lung lesions are resectable, options include:

– Colectomy and synchronous or subsequent lung or liver resection.

– Neoadjuvant chemotherapy followed by synchronous colectomy with liver or lung resection.

– Colectomy followed by neoadjuvant chemotherapy and resection of liver or lung disease.

The sequence will depend on the prognostic factors of the patient and the disease.

In fragile and elderly patients with an increased surgical risk, resection of primary tumour and the liver or lung lesions in a single procedure is not advised.

Patients with a single lung lesion should undergo resection of the primary tumour followed by thoracotomy for resection of the lung nodule. A biological period of approximately two months can distinguish patients who would benefit most from resection of metastases because they have a more indolent disease.

In patients with primary asymptomatic disease, primary tumour management depends on the resectability of liver metastases. In the asymptomatic group, resection of synchronous liver metastases after primary tumour resection is warranted because it is the only potentially curative strategy (5-year survival rate, 25–38%) [65, 180–182]. However, it is not yet clear whether treatment should be started with surgery or with neoadjuvant chemotherapy. No randomised studies answering this question directly are available, but retrospective studies on patients with more than four liver metastases suggest that neoadjuvant chemotherapy plus surgery offers better survival than immediate surgery [183].

The LiverMetSurvey analysis of an international registry of patients undergoing surgery for CRC metastases found a similar trend. This analysis showed that neoadjuvant chemotherapy did not improve the outcome of a single metastasis, but was associated to improved survival when more than four metastases were removed.

In practice, primary surgery is the standard treatment for patients with a single metastasis, but neoadjuvant chemotherapy followed by surgery may be appropriate for multinodular disease.

The combination of surgical resection of the primary tumour and liver metastases has advantages in terms of quality of life and cost. Several series have failed to demonstrate a shorter survival or greater morbidity for one-stage surgery as compared to deferred liver surgery [153, 184]. The contraindication is based on the risk of morbidity and mortality, such as urgent surgery for the primary tumour, locally advanced tumour and the need for major hepatectomy.

One alternative is colorectal resection followed by liver resection 2–3 months later, with chemotherapy between the two procedures. In theory, combined resection decreases the risk of metastatic spread by preventing the immunosuppression associated to major surgery and chemotherapy [185]. Moreover, delayed liver resection allows for a better selection of patients who may benefit from surgery, although the choice depends on the experience of the surgical team [186].

One-stage hepatectomy is usually limited to patients with right colon cancer with a limited number of liver metastases. However, similar rates of complications are currently being reported for both the one-stage and two-stage strategies, including major hepatectomy [187]. One-stage resection has been associated to shorter hospital stays [188].

If metastatic disease in the liver or lung is unresectable or potentially resectable, chemotherapy is recommended. Patients with lesions that have become resectable should undergo synchronous resection of primary tumour and metastases, followed by adjuvant chemotherapy. Chemotherapy is able to revert inoperable liver lesions in 15% of patients, which allows rescue liver surgery to achieve 5-year survival rates of 33% [189]. This downstaging criterion also applies to the primary tumour and facilitates resection in rectal cancer and preservation of the sphincter. In patients responding to conventional treatment, primary tumour surgery is followed by surgery of the metastases. However, other authors recommend that liver metastases are resected before the primary tumour because it is metastases that determine patient prognosis [190].

In conclusion, the recommendation of this section is to perform colectomy as initial treatment if the primary tumour is symptomatic or causes obstructive or bleeding complications that cannot be corrected by other procedures. In all other cases, chemotherapy may be started with no increase in local complications (level 2C). There is currently no contraindication for bevacizumab or cetuximab combined with chemotherapy in patients who have not undergone resection of the primary tumour.

In patients with synchronous metastases, the optimal time for resection has not yet been defined. Neoadjuvant chemotherapy should be the first procedure in patients with operable metastatic disease with poor prognostic factors and in those with potentially resectable liver metastases. Immediate resection of metastases should be performed in patients with four or fewer isolated metastases (Level 1A).

One-stage surgery on the primary tumour and metastases should be performed if feasible (level 2C), but is not recommended for patients with a high morbidity and mortality risk such as the elderly, in locally advanced tumours or when major hepatectomy is required. In all other patients, the strategy should be based on the characteristics of the patient and the disease. If one-stage resection is not advisable, surgery for metastases should be performed 6–8 weeks after surgery for the primary tumour.

The recommendations provided are subject to revision, since the best strategy for synchronous disease is yet to be defined in randomised trials.

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