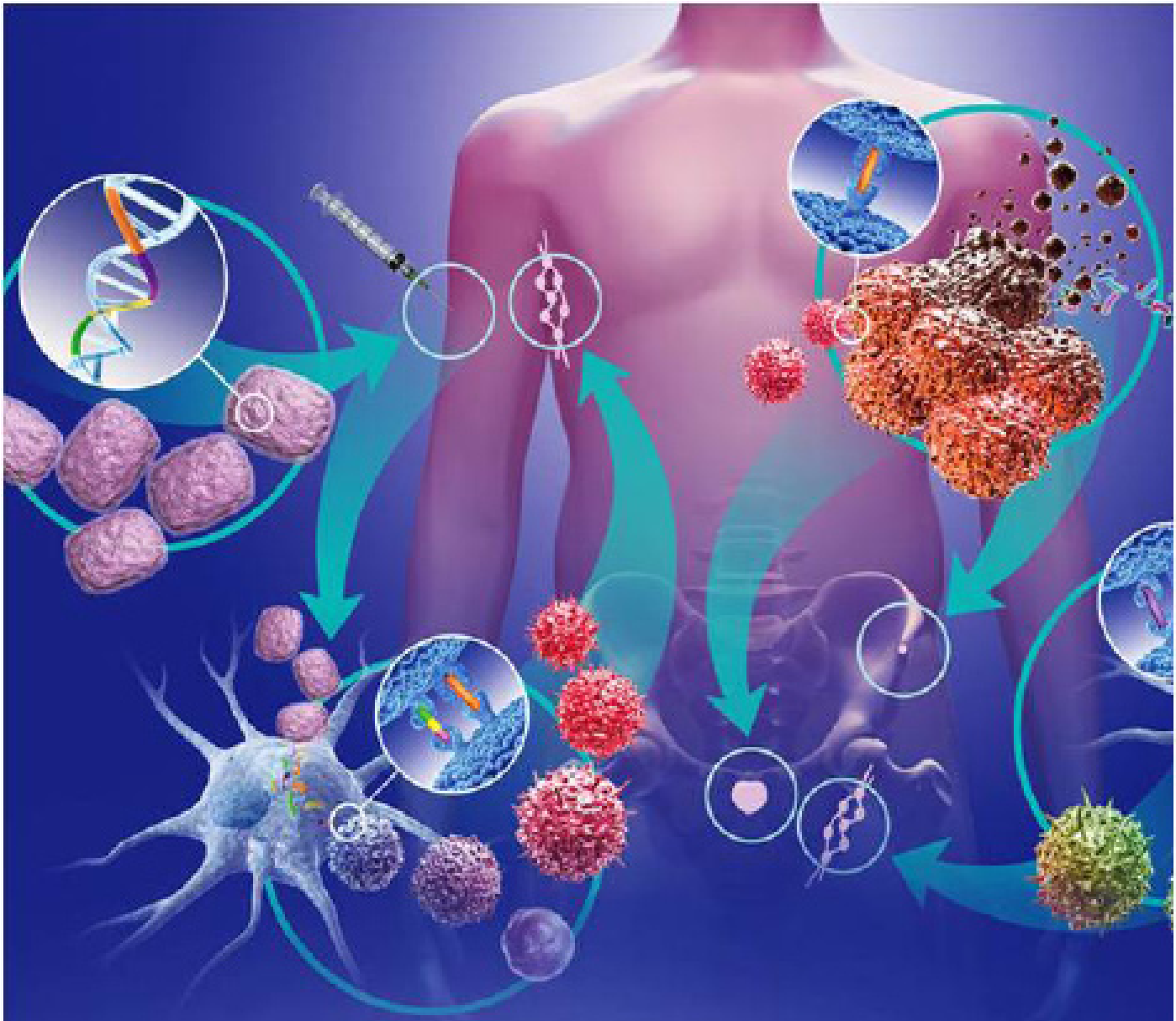

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Therapy in Colorectal Cancer with Liver Metastasis – A Multidisciplinary Management

Charlène Viana[1*]; Sónia Vilaça[1]; Joaquim Falcão[1]; André Goulart[1]; Fernanda Nogueira[1]; Pedro Leão[1,2,3]; Mesquita Rodrigues[1]; Adhemar Longatto-Filho[2,3,4,5,6]; Sandra F Martins[1,2,3*]

[1]Department of Surgery, Braga Hospital, Portugal

[2]Life and Health Science Research Institute (ICVS), University of Minho, Portugal

[3]ICVS/3B's-PT Government Associate Laboratory, Portugal

[4]Molecular Oncology Research Center, Brazil

[5]Department Hepatobiliar Unit, Braga Hospital, Portugal

[6]Laboratory of Medical Investigation (LIM), University of Sao Paulo, Brazil

***Corresponding Author (s): [1]Charlène Viana**, Department of Surgery, Braga Hospital, Portugal

Email: vianacharlene@gmail.com

[2]Sandra Fátima Fernandes Martins, Life and Health Science Research Institute (ICVS), University of Minho, Portugal

Email: sandramartins@med.uminho.pt

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Introduction

Colorectal Cancer (**CRC**) is the second cancer most commonly diagnosed in Europe and a leading cause of death both in Europe and worldwide [1].

At initial diagnosis, 25% of CRC patients have detectable Liver Metastasis (**LM**) and approximately 50% will develop LM during their disease course. In 20-30% of cases, metastases are confined to the liver [2,3,4].

Surgery (sometimes in combination with other local treatment modalities), radiotherapy and chemotherapy have been till now the main therapeutic strategies for disease control and improvement of Overall Survival (**OS**) [2,3].

Surgical resection is known to be the most effective treatment for synchronous CRC Liver Metastases (**CRCLM**) however, only a minority of patients is suitable for surgery [4].

Therefore, a lot of regimens of QT have been studied to convert unresectable to resectable LM, in order to acquire the cure. Many studies verify that, better results could be obtained combining chemotherapy with target drugs like anti-VEGF and anti-EGFR monoclonal antibodies [2].

The last few years, the concept of Multidisciplinary Team (**MDT**) grew up in decision making for cancer patients. For CRCLM, MDT should be constituted at least by a colorectal surgeon, hepatobiliary surgeon, oncologist, diagnostic and interventional radiologist with expertise in hepatobiliary disease, nuclear medicine physician, hystopathologist and clinical nurse specialist [2,4,5].

Relevance of This Subject

CRC is the third cancer most commonly diagnosed in males and the second in women [2]. In 2012, there were 447000 new cases of CRC in Europe with 215000 deaths and worldwide there were 1.4 million new cases with 694000 deaths [1].

The liver is the most common metastatic site, probably due to tumor spread via portal system, hepatic artery or retrograde lymphatic permeation [2,6].

Despite the fact that Metastatic CRC (**mCRC**) is responsible by a large number of deaths, the clinical outcome for the patients with this diagnosis has been improved in last decade. Today, the median OS for patients with mCRC being treated is ~30months, more than double that of 20 years ago. Many factors seem to be responsible for the improved treatments outcomes for these patients like earlier detection, efficacy of imaging to detect and characterize metastatic disease, improvements in the efficacy of systematic therapies, trained surgical teams doing surgery in this patients and the management of all of that by MDT organized and designed to carry out the best treatment in each case [1,4].

So, this shows that if further strategies are studied, further improvements can be obtained.

The importance of imaging in the detection of CRCLM and in evaluating response to preoperative treatment

Imaging is used routinely to detect and characterize liver nodules and evaluate resectability. Many modalities can be used like: ultrasonography (with or without contrast), Computed Tomography (**CT**), Magnetic Resonance Imaging (**MRI**) and Positron Emission Tomography (**PET-CT**). For staging, the best methods are CT and MRI [4,7].

The characterization of LM before any treatment cannot be devalued. Thoraco-abdominal-pelvic computed tomography, when performed with triphasic or quadriphasic technique (with optimal contrast administration) seems to be the best for initial staging [8,9].

If synchronous CRCLM seems to be resectable initially, liver MRI may be performed.4 Studies have shown that MRI is more sensitive than CT in detecting subcentimetre LM and so after neoadjuvant chemotherapy [10]. MRI should also be performed when characterization with other modalities is difficult (ex.: many small nodules including benign lesions or steatotic liver) [4].

For detecting distant metastases, PET-CT may be useful, particularly in patients with recurrent disease or with high tumour load however, in patients with resectable CRCLM, PET-CT does not seem to change surgical management [4].

A fundamental aspect to evaluate preoperatively is the predicted Future Liver Remnant (**FLR**) after hepatic surgery, in order to avoid small for size liver remnant and catastrophic consequences of that [4,11]. For that, tests determining volume like CT volumetry or functional tests like Indocyanine Green retention at 15 minutes, can be done. As we are going to explain better later, because CT is routinely performed for both tumor staging and preoperative surgical planning, 3D CT volumetry has become the standard technique for measuring FLR [12].

After preoperative treatment, the response can be analyzed with several parameters like: tumour size, morphologic changes (unrelated to size) and metabolic activity. 4 Assessment of change in tumor burden is an important feature of clinical evaluation. Both the tumor shrinkage (objective response) and disease progression, are useful endpoints in clinical trials. Since RECIST (Response Evaluation Criteria in Solid Tumours) was published in 2000, many groups adopted these criteria in the assessment of treatment outcomes however, a recent revised RECIST was necessary to ameliorate the previous one [11].

An individualized approach should be applied, case-by-case, in order to offer the best therapeutic attitude to each patient [1].

Treatment

Patients presented with CRCLM can be part of one of three groups: initially resectable disease, unresectable that can become resectable by “conversion” therapy and those that will never be resectable [2]. A systematic review and meta-analysis with 142 studies showed 5-year survival after surgical resection of LM of 16-71% and furthermore, showed that long-term survival rates for patients with initially unresectable disease treated by chemotherapy, are similar to those considered resectable at beginning [7].

Therefore, thanks to these strategies that downsizing LM, the percentage of patients potentially eligible for curative liver resection is increasing [2].

Treatment can begin with surgery or with systemic treatment depending on tumor staging (size, resectability, etc), symptomatology associated and with the type of patient (comorbidities, performance status) that we have to treat [4].

Surgical Treatment

Resection of CRCLM offers the only potential for cure. In clinical practice, the main difficulty remains in deciding who is candidate for resection [8,2].

Hepatectomy remains the standard of care for treatment of LM. However, liver failure after hepatectomy continues to be the major cause of death after surgery and the major concern for hepatobiliary surgeon [4,2]. Hepatic insufficiency after hepatic surgery is described on 8% of procedures and hepatic insufficiency-related mortality rate from 2.8% [13].

Colorectal cancer surgery should be performed by colorectal surgeon as well as liver surgery by hepatobiliary surgeon. Quality of surgery will determine the outcome because of total mesocolon/mesorectum excision, lymph node removal and good margins of resection. Minimal optimal safe resection margins remain to be determined nevertheless, most studies indicate a minimum of 1mm [4].

Surgery in one-step when LM is resectable (resection of primary tumor plus LM in same time) can be performed in selected patients. This procedure have to be discouraged when it is expected that colorectal surgery will be associated to higher morbidity or when major hepatectomy will be performed [14].

The classical approach to surgery of synchronous CRCLM is the surgery of primary tumor (**CRC**) followed by resection of LM, 2 to 3 months later, with or without chemotherapy in the interval between two surgeries. Despite this, when CRC is asymptomatic, the recurrence to preoperative chemotherapy, even in resectable LM, is increasing. One of the objectives is downsizing metastases which will allow less aggressive and more conservative surgery. Surgery of primary tumour should be the first part of treatment if tumor is symptomatic causing occlusion or perforation. In cause of bleeding, if hemorrhage can be controlled with blood transfusions, chemotherapy should be the first step [4].

As considered before, liver failure is the major concern after hepatectomy. In fact, small remnant liver function after hepatic surgery can be catastrophic, even after partial resections. This is because the volume is not the best surrogate for liver function, particularly in patients with concomitant liver disease [2]. Systematic assessment of the anticipated functional remnant liver is essential before major hepatic resection avoiding postoperative hepatic insufficiency and all of his catastrophic consequences. To ensure adequate Future Liver Remnant (**FLR**), preoperative measurement of FLR volume is determinant. Volumetric analysis, made by CT multidetector, helical with 3D reconstruction, is not a simply volume meter but also predict a function of FRL. However, even with a minimum error rates of measuring liver with CT volumetry (error rates <5%), this technique not account for actual functional liver volume when this is pathologic like in situations of biliary dilations or parenchyma compromising [12]. In some cases, functional tests like Indocyanine Green retention can be done, particularly in cases of chronic liver disease [15].

In general, FRL of 20% is considered the minimum safe after hepatic resection in patient with normal liver; in patients submitted to chemotherapy, FRL of 30% is required; in patients with cirrhosis or hepatitis, a threshold volume for safe resection of 40% is necessary. Patients with anticipated FRL volumes below these cutoffs should be selected for Portal Vein Embolization (**PVE**) [16]. Preoperative PVE increases hepatic function of hypertrophied FLR. That was proved biochemically as well as volumetrically in both cirrotic and non cirrotic livers. That was associated with decreased complications, shorter hospital

stays, increased resectability and increased disease free survival in patients with cirrhosis [3].

Patients that is expected that will be need PVE, should undergo CT volumetric analysis immediately before and 3 to 4 weeks after PVE to assess the degree of hypertrophy. In patients with impaired liver regeneration (ex.: diabetics and cirrhotics), this time cannot be sufficient and additional 3 to 4 weeks can be required before decision [12]. Data shows that is expected that 2 to 20 % of patients with cirrhosis have no significant increase in FLR after a technically successful PVE [3].

So, being the only potential curable treatment for LM, resection seems to be useful even at later line of therapy. MDT is fundamental being consulted at each stage of patient's treatment. If necessary, repeat resection can be performed, safely and effectively, with survival races that seems to be similar to those following first resection [2].

Chemotherapy Treatment

Chemotherapy can be considered, nowadays, for both unresectable and resectable LM.

In unresectable cases, conversion to resectable LM by "conversion therapy", often represents the initial treatment choice. Most commonly used chemotherapy regimens in CRCLM are FOLFOX (leucovorin-LV, 5-fluorouracil-5-FU, oxaliplatin), FOLFIRI (LV, 5-FU, irinotecan) and FOLFOXIRI/FOLFIRINOX (LV, 5-FU, irinotecan and oxaliplatin). They are now achieving high response rates (>50%) and long median survival (~30months) [2,17].

Studies with FOLFOX and FOLFIRI showed resection of LM in 38% of patients initially unresectable [12]. Using FOLFFOXIRI, being intensified chemotherapy regimen, seems to be stronger than other regimens with conversion to resectable lesions >60% [18].

Even when LM are resectable, chemotherapy is gaining space as first line of treatment to reduce the incidence of cancer relapse. However, in a 2015 in a multidisciplinary international consensus, it was verified that more evidence is needed to support non-surgical initial strategy on resectable synchronous LM [4]. In fact, even with resection in best conditions, relapse seems to occur in up to 50-70%.2 In CRC, micrometastases are separated from LM by a thin rim of normal parenchyma, usually located within 1 cm of CRCLM. It is known that micrometastases have a negative impact on outcomes and that they are less frequently detected in patients receiving preoperative chemotherapy [4,17]. On the other hand, ESMO consensus guidelines 2016 refer that, in patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified (Level of evidence "I" and Grade of recommendation "C"); in case where the prognosis is unclear or probably unfavourable, preoperative chemotherapy should be administered ("I,B"). Patients must be re-evaluated regularly (~every 2monts) in order to prevent overtreatment of resectable LM, as the maximal response expected to be achieved after 12-16 weeks of the beginning the treatment [1,4].

The way that tumor respond to chemotherapy is important marker of chemotherapy efficacy, biological behavior of tumor and survival outcomes. Unfortunately, complete pathological response is reported only about 10% of cases [4].

Following preoperative chemotherapy and resection, adjuvant chemotherapy should be considered [4]. According to ESMO guidelines, patients who have not received any previous chemotherapy, adjuvant treatment with FOLFOX can be recommended [1].

In terms of time, a total duration of 6 months perioperative chemotherapy (neoadjuvant plus adjuvant) is recommended [4].

Targeted Agents

Nowadays, increased knowledge of biology tumors, namely CRC, allowed specific identification of biomarkers and development of targeted therapies. These, based in tumour biology and behavior, allows estimating the prognosis and response to treatment. Biologic therapies can be targeted to two different biomarkers such as Epidermal Growth Factor Receptor (**EGFR**) like bevacizumab and Vascular Endothelial Growth Factor (**VEGF**) like cetuximab or panitumumab [2,4]. Unless contraindicated, biologicals are indicated in the first line treatment of mCRC [1].

Towards synchronous CRCLM, optimal therapies can include: doublets (FOLFOX/FOLFIRI) in addition with targeted therapies, triplets (FOLFOXIRI) or triplets combined with targeted therapies [4].

In resectable LM, chemotherapy without biologicals could be used once the absence of evidence for biological agents being useful in this setting [1,4].

In patients not responding to first-line therapy (ex.: FOLFOX/FOLFIRI + VEGF antibody like bevacizumab) should be considered for second-line combination (ex.: FOLFOX/FOLFIRI + another VEGF antibody different from bevacizumab or EGFR antibody in patients RAS wild type).1 Data from GERCOR database suggest that response to second-line therapy does not depend on response to first-line [4].

Bevacizumab associated to first and second-line therapy seems to improve Progression Free Survival (**PFS**) and OS however, the handling of this drug has to be careful primarily about potential wound healing complication. In terms of associations, data supports that treatment association of bevacizumab with FOLFOX was better in resection rates (16.1%) than those associated with FOLFIRI (9.7%) [2].

Anti-EGFR agents like cetuximab or panitumumab can be used as single agents or associated with chemotherapy agents with their activity exclusive for patients with RAS (KRAS and NRAS) wild type tumors [2]. Retrospective analyses of pivotal clinical trials for EGFR monoclonal antibodies shows that tumors with KRAS mutations do not drive a benefit from this therapy in addition to having a detrimental effect in those patients, mainly when combined with oxaliplatin [18,19,20]. Since the presence of RAS mutation seems to be a negative predictive marker of treatment outcome with EGFR monoclonal antibodies, cetuximab and panitumumab should only be considered in patients with RAS wild type. This reinforces the importance for detecting RAS mutations in all patients that eligible/being considered for EGFR antibody therapy [1].

Many randomizes trials evaluated the effects of cetuximab in addition to chemotherapy in patients with unresectable LM (ex. OPUS, CRYSTAL, CELIM and POCHER) and all of them showed significants improvements of R0 resection rates with this preoperative association [21-24].

Trials have also showed resection rates with association of

chemotherapy with panitumumab in first-line treatment, also with more R0 resections in association with FOLFOX than FOLFOX alone (32% vs 28%, respectively) [25].

ASPECCT trial was the first randomized multicenter trial comparing the two EGFR antibodies (cetuximab and panitumumab) when used in monotherapy for refractory mCRC. This study revealed no difference between the two drugs with OS ~10months in both [26].

A recent retrospective analysis investigated different clinical outcomes and predictive influence of location of primary tumour (left vs right) in patients with unresectable CRCLM RAS wild type, comparing the use of chemotherapy plus EGFR antibodies therapy with chemotherapy or chemotherapy plus bevacizumab. This retrospective analysis based in six randomized trials shows a significantly worse prognosis for patients with right-sided tumours with those with left-sided. Benefit of associating EGFR antibodies to chemotherapy was verified in left-sided tumour, effect that did not occur on right side. So, a worse prognosis for PFS and OS was showed on right colon tumours wih a greater effect of association of chemotherapy and EGFR antibodies on left-sided tumours [27].

About prognosis, it's seems to be poorer for synchronously detected LM on CRC than for metachronous with 5-year survival rates shorter for synchronous LM (3.3%) than for metachronous (6.1%) [28]. Despite all these advances, there is no biological marker to distinguishes synchronous to metachronous metastases [4].

After resection, there are no evidence based data to support the use of targeted therapies nevertheless, if a regimen is effective in preoperative, many teams tends to use the same regimen postoperatively [4].

So, molecular evaluation of LM has been fundamental in the evaluation of the biology of LM. It is known that RAS mutations (NRAS and KRAS) have been associated with poor prognosis after LM resection, independent of anti-EGFR therapy [4].

Locoregional Therapies

The management of patients of LM is complex and can involve multiple treatment modalities including Locoregional Therapies (**LRT**) [3].

Despite optimal treatment of LM is surgery, not all patients are candidates for hepatic resection. Patients with uncontrolled extra-hepatic disease, insufficient FLR, significant comorbidities, among others, may not be able to have benefit with an invasive procedure. In those cases, LRT can be performed for local disease control improving symptoms concomitantly [3,6].

There are many options for LRT. That can be transarterial procedures like: Transarterial Embolization (**TAE**) and Transar-Terial Chemoembolization (**TACE**) that use a variety of chemotherapeutic agents, and Transarterial Radioembolization (**TARE**) with Yttrium-90 (Y-90); or Percutaneous ablative options like Radiofrequency Ablation (**RFA**), microwave ablation, cryoablation, irreversible electroporation, conventional Radiotherapy (**RT**) and Stereotactic Body Radiotherapy **(SBRT)** [6,3].

About Conventional Radiotherapy, vast improvements allowed a more focal treatment with limited toxicity, particularly when compared with schemas of the past. LM can take with important symptoms like: pain, nausea, vomiting, anorexia or fatigue. Palliation of symptoms is important component in the management of patients with metastatic disease and RT has an important role by alleviating tumor symptoms, improving quality of life. Despite this, there is no randomized trial that shows that the efficacy and toxicity profile of RT is superior to other LRT [6].

SBRT resulted from the emergence of more sophisticated treatment-plannig software and methods of image guidance allowing deliver higher doses in fewer fractions to discrete individual liver lesions while sparing the uninvolved liver. Therefore SBRT allowed the possibility to achieve high rates of tumor control with a minimum radiation for wealthy liver, reducing the risk of radiation-induced liver disease [29].

According to ESMO guidelines, in patients with LM only or with Oligometastatic Disease (**OMD**), LRT can be considered (IV, B). RFA can be used in addition to surgery with the goal of eradicating all visible metastatic sites (II, B).1

Liver-directed therapy is probably the best established of the LRT nevertheless however, the increasing use of this techniques as well as the increasing options makes that the use of this treatments needing to be applied to each case depending on disease location, treatment goal (curative? local/complete control?), patient-related factors like comorbidities and age [1].

Conclusion

Resection of metastatic disease of CRC is the only potentially curative strategy. In clinical practice, principal difficulties remain in deciding who is resectable. Recent perioperative therapeutic schemes are in expansion to convert unresectable LM to resectable and potential curative lesions [2].

Many strategies allowed the advance in CRCLM treatment like surgical and perioperative management, effective chemotherapy many times in combination with target therapies and new local treatments approaches (ex.: SBRT, TARE, TACE, RFA,…) [2].

Patients with cancer have many aspects to take into account so, their care, never could be addressed optimally by a single specialty or professional [2]. A MDT is imperative to ensure the optimal management of patients with CRCLM, properly selecting the treatments to be applied in each case, reducing the risk of complications and providing the best cure rates possible [2,5].

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