



## Review Article

# Rectal carcinoma with synchronous liver metastases



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### ABSTRACT

**Introduction:** Colorectal cancer is amongst the most prevailing malignancies in the world and it is associated with a relatively high mortality rate. Rectal cancer occurs in 20–30% of all colorectal cancer cases, and 25% of this present synchronous metastatic disease. This study aims to review the current treatment approaches for rectal cancer patients with synchronous liver metastases, as there are no specific guidelines for the management of this group of patients.

**Methods:** A systematic literature search was performed on Pubmed database with a 10 year timeline limitation from 2008 to 2018.

**Results:** Currently, the only potentially curative approach remains to be the surgical resection. Conventionally, the classical strategy of these patients involves resection of rectal tumor, followed by liver resection, with chemotherapy sessions between the two procedures. However, recent studies have reported no inferiority, in safety and survival outcomes, when compared with other approaches (liver-first resection or simultaneous resection), except when symptoms of primary tumor are present. Hence, treatment strategy should be individualized based on the assessment of metastatic extent, primary tumor symptoms and the patient's overall clinical status. Chemotherapy and targeted agents have substantially contributed to overall survival improvements, allowing enhanced tumor down staging.

**Conclusion:** Complete resection of liver metastases is considered the major condition for a potential survival outcome in these patients. Management of these patients should include a multidisciplinary team with consideration of each individual specificities. Prospective randomized trials are needed to elucidate the optimal treatment strategy.

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## Carcinoma retal com metástases hepáticas síncronas

### R E S U M O

#### Palavras-chave:

Neoplasias retais  
Metástase neoplásica  
Fígado  
Quimiorradioterapia  
Terapia neoadjuvante

**Introdução:** O câncer colorretal está entre as neoplasias mais prevalentes no mundo, apresentando a uma taxa de mortalidade relativamente alta. Ele corresponde a 20% a 30% de todos os casos de câncer colorretal; 25% dos casos apresentam doença metastática síncrona. Este estudo teve como objetivo revisar as abordagens atuais de tratamento para pacientes com câncer retal com metástases hepáticas síncronas, uma vez que não existem diretrizes específicas para o manejo deste grupo de pacientes.

**Métodos:** Uma busca sistemática da literatura foi realizada no banco de dados PubMed com uma limitação temporal de 10 anos (2008 a 2018).

**Resultados:** Atualmente, a ressecção cirúrgica ainda é a única abordagem potencialmente curativa. Tradicionalmente, a estratégia clássica para o tratamento desses pacientes envolve a ressecção do tumor retal, seguida de ressecção hepática, com sessões de quimioterapia entre os dois procedimentos. No entanto, ao comparar a abordagem tradicional com outras técnicas (ressecção em primeiro plano do fígado ou ressecção simultânea), estudos recentes não relataram inferioridade nos desfechos de segurança e sobrevida, exceto quando sintomas de tumor primário estão presentes. Portanto, a estratégia de tratamento deve ser individualizada com base na avaliação da extensão metastática, nos sintomas primários do tumor e no estado clínico geral do paciente. A quimioterapia e os agentes dirigidos contribuíram substancialmente para as melhorias gerais na sobrevida, permitindo uma maior redução do estadiamento tumoral.

**Conclusão:** A ressecção completa de metástases hepáticas é considerado o principal requisito para um possível resultado de sobrevida nesses pacientes. O manejo desses pacientes deve incluir uma equipe multidisciplinar e considerar as características específicas de cada paciente. Estudos prospectivos randomizados são necessários para elucidar a estratégia de tratamento ideal.

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## Introduction

The incidence of Colorectal Cancer (CRC) remains alarmingly high worldwide, ranking as the third most common malignancy in the world. There was an estimated number of 19.7 new cases per 100,000 (age-standardized rate) in 2018, worldwide for both sexes.<sup>1</sup> CRC accounted for an age-standardized mortality rate of 8.9 per 100,000; making it the third most common cause of cancer-related deaths in the world.<sup>1</sup>

In Europe, CRC has become the second most common form of neoplasm, accounting for 499,667 new cases in 2018.<sup>1</sup> The high mortality rate for both sexes in Europe has led to 242,483 number of deaths in 2018.<sup>1</sup>

Rectal cancer and colon cancer have been explored as an own different subgroup to a minor extent, as they share many similar clinical features and are often referred to as colorectal cancer.<sup>2,3</sup> Nevertheless, in SEER (Surveillance, Epidemiology, and End Results program) database, after adjustment for age, sex and race, in the more advanced later stages, stages IIIC and IV, rectal cancer patients seemed to have longer survival than colon cancer patients and it was more frequently affected in men compared to women.<sup>3</sup> Therefore, these two entities should be explored in different settings.

The major difference when comparing the rectal cancer patients with the colon cancer patients relates to the preoperative local treatment. Combination of preoperative

chemoradiotherapy with surgery is crucial for advanced stage of rectal cancer, whereas treatment with surgery alone is the most common strategy used for colon cancer patients.<sup>2</sup>

Thus, this study aims to assess a multimodal approach treatment specifically for rectal cancer patients with liver metastatic disease upon presentation, as management strategy in this patient setting is not well defined at present.

Approximately 20–30% of all CRC cases have a primary tumor in the rectum and around 25% of these present with synchronous metastatic disease.<sup>3</sup> Liver metastases remains a substantial problem as it has become the most prevailed site of involvement, affecting 40% of the CRC synchronous metastases.<sup>4</sup> Generally, radical surgery is considered to be the most effective and potentially the only curative approach. However, rectal cancer patients with synchronous liver metastases are deemed resectable in only 10–20% of cases with disappointing results and high recurrence rate.<sup>5</sup>

Metastasized rectal cancer had been considered incurable for many years, and treatment was focused largely on prolonging the overall survival and improving the quality of life.<sup>6</sup>

Patients with synchronous liver metastases from rectal cancer have a 5 year survival rates ranging from 30% to 40% for those who undergo successful resection procedures,<sup>7</sup> with mortality of hepatic resection in the range of 5%<sup>8</sup> and is almost nil among those unable to have surgery. Different modalities of treatment have been observed in this field.<sup>5,9–11</sup>

Management of patients who are initially considered as nonoperable has been improved with recent advances of neoadjuvant and/or adjuvant chemotherapy strategies as well as some novel molecular targeted therapies. There has been increased response rates and tumor down staging with these strategies resulting in secondary surgery in 15–30% of the initially non-eligible for resection patients.<sup>12</sup>

In the treatment of Rectal Cancer patients with Synchronous Liver Metastases (RCSLM), not only the appropriate selection of treatment modalities – radiotherapy, chemotherapy and surgery – has shown to substantially improve survival benefits, but also the optimal timing between these strategies is of vital importance.<sup>2</sup> Integration of all existing relevant studies available in concern to this management will be analyzed in this investigation.

## Methods

A systematic literature search was performed to assess the current evidence relevant to the management of patients with the setting of synchronous liver metastatic rectal cancer. A Pubmed database search was performed in September 2018 using the combination of terms – “rectal cancer” AND “liver metastases” AND (“surgery” OR “treatment”). A restriction was made to obtain a selection of articles in Portuguese or English languages, coupled with a time limitation of 2008–2018 (10 year timeline).

All article headings and abstracts of the obtained search results were reviewed, and subsequent full texts of relevant studies were considered for inclusion. In total, 38 publications were included in this study.

In addition, further analysis of the references cited by the articles found was included for relevant work.

## Results

Current evidence hasn't yet determined the most effective overall management of RCSLM. The vast array of different therapeutical strategies available for this group of patients makes the multi-disciplinary approach and an individualized strategy for each patient the uttermost importance for the management.<sup>13</sup> Initial assessment of hepatic metastases resectability is the main determinant as to whether palliative or curative treatment will be suitable.<sup>13</sup> Studies have reported several poor prognostic factors for hepatic surgery, including bilobar disease, presence of more than 4 metastases, presence of extra-hepatic disease, preoperative CEA (Carcinoembryonic Antigen) > 200 ng/mL, primary lymph node involvement, potential resection margin < 1 cm and metastases greater than 5 cm in size.<sup>9</sup> These were traditionally recognized as contraindications to hepatectomy, but they no longer constitute an absolute contraindication.<sup>9,12</sup> Now, only the possibility to achieve a R0 resection (the only major predictor of prognosis) and an estimated remnant hepatic volume of 20–30% of the actual volume remain the core indicators for a potential surgical resection.<sup>9,14</sup>

Among RCSLM patients, an allocation into one of the three different categories can be made, depending on the extent of metastatic disease at diagnosis and subsequently the

potential for radical surgical resection: resectable, potentially resectable and unresectable metastatic disease.<sup>15</sup>

Traditionally, a classical approach to RCSLM patients involves a short-course RT or chemoradiotherapy schedule and resection of primary tumor, followed by adjuvant chemotherapy (combined with radiotherapy when indicated) and then finally resection of liver metastases 3–6 months after the first procedure, with consideration of continuation of adjuvant chemotherapy.<sup>16</sup> Numerous studies have established that Mesorectal Fascia (MRF) involvement, determined by MRI scanning, has a substantial impact on predicting local tumor recurrence and patient survival.<sup>17,18</sup> Thus, a preoperative MRI assessment of MRF status should be performed to induce tumor regression, through long-course RT with chemotherapy that enables an uninvolved MRF. The standard of care of rectal cancer surgery is recognized to be, conventionally, a total mesorectal excision and restoration of the bowel continuity.<sup>19</sup>

However, complications following rectal surgery are relatively frequent and often delay adequate therapy of the synchronous liver metastases in up to 50% of patients.<sup>20</sup> Furthermore, there is currently no evidence that shows any inferiority between the three surgical strategies available (primary-first, i.e. classical strategy, liver-first or simultaneous resection).<sup>21</sup> Thus, all these treatment modalities should be considered.<sup>21</sup>

### Unresectable metastases with primary tumor symptoms

Resection of liver metastases is the current potentially curative treatment for RCSLM and should be undertaken whenever achievable.<sup>12,22</sup> In the recent years, the criteria for resectability in RCSLM has been extended with more patients being eligible for curative hepatectomy due to better preoperative staging as well as improved surgical techniques.<sup>23,24</sup> However, this procedure, when performed with resection of multiple or large lesions, it may lead to a small liver remnant volume (less than 30% functional parenchyma), compromising functional capacity of the underlying liver.<sup>12,25</sup> This may, therefore, produce a significant morbidity and mortality for the patient and would, consequently, preclude surgery.<sup>26,27</sup> Several strategies, including non-surgical alternatives, have been implemented to avoid this outcome, and can increase hepatic resection rate by 15–30%.<sup>12</sup>

Radiofrequency Ablation (RFA) is an effective preoperative modality that can be applied to lesions that have a surgically difficult access and also when there is a maximum of 3 metastases with the largest tumor less than 3 cm in size.<sup>9,28,29</sup> This can further expand the number of patients eligible for curative resections, but its major limitation occurs when lesions are adjacent to vascular structures where its ablative capacity becomes lower due to heat dissipation as a result of blood flow.<sup>9,29</sup>

RFA has a 3 year survival rate of 40%, which is significantly lower than surgical resection; however it is superior to non-surgical treatment. Thus, this procedure should be limited to patients with parenchymatous disease or recurrent metastases who are not deemed to major resections.<sup>30</sup>

In addition to ablative therapies such as RFA and cryosurgery techniques for lesions with challenging surgical approach, portal vein embolization – which may help to

induce hypertrophy of the remnant liver – portal vein ligation and two-stage hepatectomy can effectively overcome the unresectable set of lesions, preventing concurrently the development of liver failure.<sup>12,31–34</sup> However, these alternatives are associated with various limitations of effectiveness and should, hence, only be considered on an individualized basis for each patient.

In patients with a symptomatic rectal primary and metastatic disease that are not deemed to resection due to its extension, the use of a standardized approach that combines high-dose pelvic radiation with oxaplatin/5FU (5-Fluorouracil)-based chemotherapy (FOLFOX+CRT) allows the chance of disease control within the pelvis, without compromising on systemic treatment.<sup>23</sup> Bird et al. showed a very high response rate (90%) with FOLFOX+CRT for the primary rectal tumor.<sup>23</sup> The majority of the patients in this study has achieved a good local symptomatic control and did not undergo further resection of the primary disease, with only 5% requiring future palliative surgery.<sup>23</sup> Nevertheless, this approach has not been demonstrated with an improvement in overall survival for these patients.<sup>20,35,36</sup>

Almost 80% of the patients have unresectable liver disease,<sup>37</sup> and downsizing of the liver metastases with conversion chemotherapy can originate a surgical resection in around 13% of patients, hence improving the 5 year survival rate to 33%, similar to patients with resectable liver disease at diagnosis.<sup>37–42</sup>

A wide variety of other options are available for palliation of rectal symptoms (rectal bleeding, perforation), including laser recanalization, colostomy and self-expanding metallic stenting (the latter being applicable only for superior and middle rectum disease), likewise the chemo-radiation and primary resection therapies.<sup>43</sup> However, these treatment options are generally associated with various technical and anatomical contraindications and have limited effectiveness.<sup>44</sup> Accordingly, careful selection of individual patients for different alternatives is crucial to prevent high rates of post-operative mortality.<sup>45</sup>

More recent biological and molecular targeting therapies, including bevacizumab (anti-VEGF) and cetuximab (anti-EGFR), have been implemented in the current management of all RCLSM patients, including resectable RCLSM,<sup>46</sup> allowing response rates for unresectable liver disease to approximately 60%,<sup>47</sup> when in association to chemotherapy.

### **Unresectable metastases with asymptomatic primary tumor**

Although management of the two distinct groups of unresectable metastatic disease – with symptomatic and asymptomatic rectal disease – may include certain particularities, the mainstay of treatment of both remains the systemic chemotherapy with or without radiation.<sup>13,48</sup> Their median overall survival rates stand close to 2 years.<sup>48</sup> Conventionally, rectal surgery should follow chemo-radiation for both sets of patients – in asymptomatic rectal cancer patients the benefit subsists on the prevention of the development of symptoms or complications (e.g. obstruction).<sup>44,49</sup> Recent studies showed that this approach may be questioned due to the fact that the primary resection may induce metastatic

tumor progression,<sup>50</sup> moreover there is also a demonstrated effectiveness of palliation with systemic chemo-radiation for asymptomatic rectal cancers, associated with a lower risk of morbidity and mortality compared to primary resection.<sup>13,51</sup>

Hence, in asymptomatic rectal cancers with progressing hepatic disease it is reasonable to preclude primary resection and proceed to other palliative alternatives.<sup>49</sup> Systemic chemotherapy stands as the recommended first-line treatment for asymptomatic rectal cancer, according to NCCN guidelines.<sup>43</sup>

Presently, there is poor evidence supporting either a primary resection or a non-surgical intervention in unresectable metastases of rectal cancers, so individualized approach of each patient is fundamental for the consideration of all alternatives available, depending on patient's comorbidities, symptoms, performance status, expected survival and its own wishes.<sup>45</sup>

### **Resectable metastases**

Whereas resection of the primary tumor remains the standard indication for patients with symptoms of primary tumor,<sup>52</sup> in the setting of an asymptomatic primary disease (i.e., without obstruction or perforation that renders urgent rectal surgical management) and resectable liver metastases, rectal resection does not provide short-term palliative benefit, and has been associated with a considerable mortality (6–10%) and morbidity (20–25%).<sup>52–55</sup> The “liver first” approach in this scenario enables optimal management of the resectable liver metastases and adequate neoadjuvant treatment for the primary tumor permits a delay of rectal surgery.<sup>56</sup> Patients with a resectable metastatic disease must preserve an adequate remnant liver tissue after surgery because the insufficient postoperative remnant liver tissue is related to the major cause of surgery-related death.<sup>57</sup> In a healthy patient, 20% of the liver tissue is appropriate for survival, conversely for patients who undergo chemotherapy treatment pre- or post-operatively, 30–40% of the liver is required.<sup>58,59</sup> These patients may achieve a 5 year disease free survival and overall survival rates of 21.5 and 50.9%, respectively.<sup>60,61</sup>

There is still debate in the literature about the role of upfront chemotherapy prior to liver surgery, but some studies have determined that using a standardized upfront treatment with combination of oxaliplatin/5FU-based chemotherapy with high-dose pelvic radiation (FOLFOX+CRT) can be considered an effective and tolerable treatment option.<sup>23</sup>

In summary, following at least 3 weeks of upfront systemic neoadjuvant chemotherapy in these patients, if no progression of the disease occurs, surgery can be performed to remove the liver metastases. After successful liver surgery, patients are treated with a 8–10 week neoadjuvant radiotherapy, combined or not with chemotherapy, for the primary rectal tumor. Imaging re-staging after 4 weeks of neoadjuvant radiotherapy with thoracic CT and abdomino-pelvic MRI may determine whether rectal resection can be performed, after the last 8 week radiotherapy dose, based on the manifestation of unresectable metastases.<sup>56</sup> This allows the prevention of redundant rectal surgery in patients with incurable metastatic disease.<sup>56</sup>

It has been proven that the response to chemotherapy after 8 week treatment is a good prognostic feature to assess tumor biology, predictive to patient's potential for cure.<sup>2,62</sup> Studies have reported a high response rate (over 50%) and an increased rate of resectability from 10% to 30%,<sup>63,64</sup> however significantly higher rates of postoperative complications occur due to chemotherapy-associated liver injury. Development of steatosis may be predisposed with the use of 5-FU, leucovorin and irinotecan, and sinusoidal obstruction syndrome may be caused by oxaliplatin.<sup>65</sup> Thus, a limited duration and number of chemotherapy cycles should be preferred to prevent additional morbidity and mortality after liver surgery.<sup>46</sup>

The major value of the “liver first” approach is the fact that it removes the main indicator of poor prognosis first and prevents the delay of chemotherapy initiation, with subsequent lower metastatic liver progression, when compared to staged primary resection.<sup>66</sup> A concern regarding the “liver first” approach is the absence of response to chemotherapy or progression after initial response in patients with resectable disease, alongside its high recurrence rates.<sup>56</sup> Also, an increase in complexity of liver surgery due to neoadjuvant-induced parenchymal injury and increased risk of hemorrhage during rectal resection as a result of the portal hypertension, secondary to prior liver operation, may occur.<sup>67</sup> Conversely, there are findings that demonstrated no significant difference in postoperative morbidity or mortality when comparing “liver first” or reverse strategy with either staged and simultaneous resections.<sup>68</sup> Therefore, the safety of the reverse strategy is still not possible to determine because of the few studies available for locally advanced rectal cancers, though there is evidence that supports that such a strategy should merely be applied for primary tumors without symptoms.<sup>45</sup>

### Simultaneous resection

With a staged rectal resection followed by liver resection, it enables the assessment of the liver metastases response to chemotherapy, allowing the exclusion of patients with unfavorable prognosis from further unnecessary surgery.<sup>9,24,28,69,70</sup> However, due to the associated postoperative immunodeficiency following primary surgery, staged resections may result in increased rate of liver metastatic growth.<sup>9,71</sup> In the recent few years, there has been a shift toward simultaneous resections, which has the main advantage of avoiding additional progression of hepatic metastatic disease as adjuvant therapy can be initiated without delay as opposed to staged resections.<sup>28,70,72</sup> Nevertheless, with this approach, there is risk of leaving behind occult micro-metastases in the remnant liver.<sup>73</sup> Therefore, this strategy should be potentially complemented with neoadjuvant chemotherapy and followed by adjuvant chemotherapy.<sup>74,75</sup>

There are some additional favorable short-term results regarding the simultaneous resections – because a second operation is avoided, a significant decrease in morbidity and length of hospital stay, as well as lower adverse psychological effects from 2 separate operations and blood transfusion requirements, improves short-term outcomes for patients, without compromising curability or increasing mortality with this strategy.<sup>76,77</sup> It is of paramount importance a careful patient selection, according primarily to the indices of

patients' preoperative physiological function, but also to the pathological features of the primary tumor for this simultaneous approach.<sup>78</sup> In fact, one study has reported a lower morbidity rate with 8% of postoperative complications in the simultaneous resection, when compared with staged resection 31%.<sup>71</sup> Despite that, disease recurrence was greater within the first year after simultaneous strategy occurring in 62% of patients, as opposed to staged surgery with 19% of patients.<sup>71</sup> Three-year overall survival rates did not significantly change according to the surgical strategy – 67% in simultaneous group versus 76% in staged group ( $p=0.780$ ).<sup>71</sup>

Regardless the promising short-term results, they are mostly based on small studies with low levels of evidence, hence more studies with larger scale and randomized controlled trials assessing short- and long-term outcomes compared with the multi-staged conventional treatment are needed to confirm the indication for this method. The majority of the available evidence demonstrated no differences in overall survival rates and post-operative morbidities, making the ideal approach presently difficult to define.<sup>45</sup> Nonetheless, there are several low levels of evidence, mostly from retrospective studies and expert opinions, that favors staged resection over a simultaneous resection, including patients with age greater than 70, requirement for major hepatectomies (more than 3 metastases), hepatic damage following neoadjuvant therapy and complex rectal surgery.<sup>28,71,79,80</sup> Simultaneous resection with a major or extended hepatectomy has a reported mortality rate of up to 36%.<sup>72</sup>

Another group of authors states that simultaneous resection should only be considered in the presence of either early rectal cancers with extensive metastatic liver disease or locally advanced rectal cancers with a limited metastatic burden; a staged resection is recommended when there is both a locally advanced rectal cancer and extensive liver metastatic disease.<sup>45</sup>

Conversely, numerous studies have demonstrated no significant difference in either complications or survival rate between the two approaches, bringing conflicting results as which strategy should be implemented.<sup>45</sup> Consequently, criterious selection of individual patients for simultaneous resection should be the primary attitude for these patients.

## Discussion

There is consensus that resection of liver metastasis in rectal cancer provides clear survival benefits for RCSLM patients.<sup>22</sup> In the recent years, there has been an improvement of survival of stage IV rectal cancer patients.<sup>81</sup>

Treatment strategy should be individualized based on the assessment of metastatic extent, primary tumor symptoms and the patient's overall clinical status. Multimodal intervention subsists with either a surgical approach or with a systemic or local chemotherapy and radiotherapy, as well as other minimally invasive procedures. However, currently the optimal management of patients with RCSLM, with establishment of the ideal timing and integration of the complex combination of these modalities, including the surgical management of two distinct sites, remains debatable.<sup>23</sup>

Presently, there are no randomized controlled trials that assess the ideal management of RCSLM patients, and all the published studies are primarily retrospective observational, often non-comparative. Hence, current clinical practice often stands based on (1) trials evaluating chemotherapy regimens in metastases predominantly from colonic primary tumor; (2) radiotherapy trials on non-metastatic tumor; (3) evidence about the role of hepatic resection mostly from metachronous disease.<sup>23</sup>

There is a small proportion of patients that can be treated with curative intent, mostly when resectable or potentially resectable liver-only metastases are present.<sup>12</sup> This is achieved through an integrated approach with complete excision of all visible disease complemented with adequate peri-operative therapy.<sup>23</sup> Studies have reported a 5 year overall survival rate of approximately 40% in patients who were treated with complete resection of liver metastasis.<sup>7</sup>

In contrast, most patients end up being treated with palliative intent, where efforts are mainly focused on controlling symptoms from both the primary and metastatic disease, but also for a better overall survival improvement. Patients, who fall into the palliative intent treatment, usually receive both radiation and surgery to effectively control symptoms from their primary pelvic disease. Nonetheless, it remains debate concerning the optimal sequencing of treatment modalities for palliation.

Survival improvement has been achieved primarily through the development of more effective chemotherapy regimens – which helps downstaging the tumor, hence converting 10–30% of tumors into a potentially curative resection<sup>63,64</sup> – but also due to novel molecular targeted therapies that may further increase the curability rates for initially nonoperable patients with reserved prognosis.<sup>46,47</sup>

Current evidence indicates that all three surgical strategies (primary-first, liver-first or simultaneous resection) are effective and there was no inferiority between them.<sup>21</sup> Therefore, all approaches should be considered for RCSLM, except when there are symptoms of primary tumor, where the liver-first approach becomes not suitable.<sup>21</sup> For RCSLM patients with resectable liver metastases, a combination of chemotherapy with targeted agents, followed by staged or synchronous resection of metastatic and primary lesions, is a well-established treatment strategy.

According to the existing evidence available, management of RCSLM patients is optimally achieved through a multidisciplinary integration, with continuous team discussion between medical oncologists and surgeons.

Clinical trials are needed to further investigate the best specific treatment strategy algorithms for different subgroup of RCSLM patients.

## Conclusion

Current investigations support a clear survival benefit, with potentially curative effect, of complete resection of liver metastases of RCSLM.

Present management of RCSLM patients has been achieved by multidisciplinary integration, including various therapeutically modalities, on an individual basis. However, there are no

specific guidelines for the appropriate combination or timing of these.

More studies with better levels of evidence, through randomized controlled trials, are necessary to adequately determine the optimal management of particular subgroups of RCSLM patients.

## Conflicts of interest

The authors declare no conflicts of interest.

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