

Is There a Chance of Cure for Colorectal Liver Metastases?

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ABSTRACT

The liver is the most common site for metastatic spread from colorectal cancer with up to 50% of patients developing liver metastases during the course of their disease. Liver resection is the most effective treatment to achieve long-term survival and the only approach to obtain a potential cure for patients with colorectal liver metastases. R0 resectability criteria are not well established and these must be decided within a multidisciplinary committee. Unfortunately, only few patients are amenable for surgery. The role of chemotherapy in colorectal liver metastases aims to decrease tumor size, to control micrometastatic disease and to identify groups of patients that might benefit from liver resection. Moreover, chemotherapy can convert some irresectable metastases into resectable ones. We must consider chemotherapy before surgery in patients with resectable colorectal liver metastases and bad prognostic factors and in those cases of

potential resectability. Other liver-directed therapies must be reserved for unresectable disease without curative aims.

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Key words: Liver colorectal metastases; Cure; Surgery; Resection rate; Conversion chemotherapy; Neoadjuvant chemotherapy

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IS THERE A CHANCE OF CURE FOR COLORECTAL LIVER METASTASES?

Colorectal cancer is a major health problem with over 100,000 new cases diagnosed in the United States in 2014, representing the third leading cause of cancer deaths in both genders^[1].

Liver is the most common site of colorectal metastases. Up to 25% of patients present liver metastatic spread at the moment of diagnosis of a colorectal cancer and a 30% of patients will develop metastases during the course of the disease. Up to 60% of the recurrences after resection will be located in the liver and, in between 20 - 30% of the cases, this will be the only site of disease^[2].

Hepatic resection is the treatment of choice for exclusively metastatic liver disease, with 5-years survival rates of 50-60% in recent series, associating low surgical morbidity and mortality rates. Thus, hepatic resection represents the standard of care and the only chance for cure for these patients^[3]. Some authors suggest the definition of cure as a period of 10 years of survival after resection of colorectal liver metastases, based in the plateau reached in survival curves at this time of follow up, concluding that the definition of cure must be considered at the time point after hepatectomy, when disease-specific death becomes an extremely rare event^[4].

The criteria for R0 resectability are not well standardized and are

not limited by size of the metastasis, number or bilobar involvement. The decision must be adopted by a multidisciplinary medical committee. Curative surgery needs a complete surgical resection maintaining sufficient hepatic reserve. Actual surgical consensus allows 1cm free margin obtained after complete resection. Hepatic remnant must be individualized and calculated for each patient. Minimal hepatic remnant allowed for a safe surgery will depend in the underlying liver disease^[5].

Hepatectomy is also indicated in selected patients with a minimal affection of extra-hepatic metastatic disease. Long-term survival is directly related with a complete resection of the extra-hepatic metastases located, reporting morbidity and mortality rates similar to hepatic disease alone. Lung metastases present the best survival rates in this context^[6]. Patients developing synchronous presentation of colorectal cancer and liver metastases present worse outcome than a metachronous scenario. Therapeutic options range from surgical resection of the colon or rectum first, liver first or simultaneous resection of both tumoral locations^[7].

Other liver-directed therapies such as ablative ones (radiofrequency, microwave and cryoablation), hepatic artery infusion, chemoembolization and stereotactic body radiotherapy (SBRT) must be reserved for unresectable disease without curative aims^[8].

Few patients with colorectal liver metastases are amenable for surgery. The European Society of Medical Oncology Guidelines for colorectal cancer define two different types of metastatic colorectal cancer candidates for a curative intent^[9]. Type 0 patients are those with technically R0 resectable liver metastases, where initial resection with curative intention is an option with or without perioperative chemotherapy. Type 1 patients have potentially resectable disease and initial chemotherapy should try to convert these metastases into resectable ones.

Chemotherapy is indicated in both types of disease in order to decrease tumor size, control micrometastatic disease and identify groups of patients who may obtain most benefit from liver resection. In the first group of patients, metastases are initially resectable so that the aim of previous chemotherapy is preventing a relapse after surgery (neoadjuvant chemotherapy). In the second group, the aim of previous chemotherapy and other systemic therapies is to achieve a high response rate in order to convert irresectable into resectable liver disease (conversion chemotherapy).

Neoadjuvant and conversion therapy are two types of treatment with own indications, so the use of either one of the proposals should be individualized.

In patients with resectable colorectal liver metastases, several prognostic factors have been described with significant impact on survival after resection^[10]: Disease-free interval for less than 12 months, number of metastases > 1, preoperative CEA level > 200, primary positive lymph-nodes and tumor size > 5 cm. A scoring system has been performed with 1 point assigned for each one of the proposed items. Patients with 0-1 score have a favorable outcome (60% five-years survival rate), whereas those with 2-5 score have a worse prognosis (14% five-years survival rate) and therefore, resection should be performed only in the context of neoadjuvant chemotherapy.

In this setting, only one clinical trial has demonstrated benefit for the neoadjuvant therapeutic approach. Disease-free survival improved in a 8-9% of patients receiving 3 months of neoadjuvant (preoperative) therapy of oxaliplatin, folinic acid and 5-fluorouracil and 3 months of adjuvant (postoperative) therapy, when compared with surgical resection alone^[11]. Up to date, combination of targeted therapies with cytotoxic therapy has not shown benefit in these patients.

An expert panel of the European Colorectal Metastases Treatment Group^[12], the European Society for Medical Oncology Clinical Practice Guidelines^[9] and the National Comprehensive Cancer Network practice guidelines for colorectal cancer^[13] support the use of neoadjuvant chemotherapy irrespective of the initial resectability status of their metastases, because approximately 70% of resected patients will develop a recurrence in the first two years after surgery and most of them occur in the liver again^[14].

In the scenario of conversion therapy, the most active treatment should be selected because an excellent correlation has been demonstrated between the response rate to therapeutic schedule and resectability rate^[15]. Cytotoxic drugs, such as 5- fluorouracil, oxaliplatin or irinotecan, and the targeted therapies anti-VEGF (bevacizumab) or anti-EGFR (cetuximab and panitumab) constitute the election drugs, but the best regimen in this setting is not yet known.

Drug toxicity effects, patient's performance status and molecular profiles should be considered for individualized treatments. RAS is an intracitoplasmatic protein of the RAS-RAF-MEK-MAPK pathway and its mutation results in an independent abnormal activation of the pathway and the development of tumor proliferation, evasion of apoptosis, migration and aberrant angiogenesis^[16]. Therefore, RAS must be investigated in all metastatic colorectal cancer patients.

Activation mutations in RAS occur approximately in 50% of patients and have been suggested as a negative predictive biomarker for anti-EGFR therapy (cetuximab, panitumumab), while wild-type RAS predicts anti-EGFR monoclonal antibodies efficacy, based on recent results of the head-to-head trials comparing anti-VEGF (bevacizumab) and anti-EGFR in combination with different chemotherapy schedules in first line metastatic colorectal cancer patients^[17,18].

The toxicity of chemotherapy and targeted therapies in the liver is well established. Clinical studies have demonstrated a correlation between the duration of systemic therapies and a higher postoperative morbidity and mortality. Therefore, surgery must be carried out as soon as the metastases become technically resectable. This surgical approach can be done safely 3-4 weeks after the last cycle of chemotherapy plus cetuximab/panitumumab or 6-8 weeks following chemotherapy plus bevacizumab^[19].

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests and received no financial support.

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