

# Modern Approach to Colorectal Liver Metastases

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## Abstract

Colorectal cancer is the third leading cause of death worldwide. Approximately 15-20 % of the patients present synchronous Colorectal Liver Metastases (CRLM) and 60 % will develop them metachronically. Surgical treatment is the only therapy that gives these patients the option of long-term survival. In the 1980s surgical treatment offered a 5-year survival rate of approximately 20 % for patients undergoing liver resection. Recent studies show 5-year overall survival rates ranging between 42 and 58 %. Systemic chemotherapy regimens are based on fluoropyrimidines. These regimens include neoadjuvant, adjuvant or both depending on the disease stage. Adjuvant chemotherapy has shown better overall survival and progression free survival in patients treated surgically for CRLM.

Surgical approach to CRLM has changed dramatically in the last years. There are hardly any contraindications for treating surgically CRLM, as long as the liver remnant is at least 30 % of the total volume for non-cirrhotic non-chemotherapy treated livers. In cirrhotic or chemotherapy-treated livers this amount should reach 40 %.

Aspects concerning synchronous CRLM and irresectable metastases have shown greater advances. The reverse approach or liver-first approach has offered patients with advanced disease a better option for completing total resection. Portal vein embolization, two-stage hepatectomy or ALPPS procedure (associating liver partition and portal vein ligation) are the top developments in this field showing promising results. These developments are widening surgical indications in CRLM. Surgical and systemic treatment, as well as a better understanding of molecular alterations has definitely improved the perspective for patients with CRLM.

**Keywords:** Colorectal liver metastases; Irresectable metastases; Synchronous metastases

## Introduction

Colorectal cancer is the third most common malignancy in the United States with 132,700 new cases in 2015. In Europe 241,621 new cases were diagnosed in 2012 and 113,168 cancer related deaths occurred. Approximately 15-20 % of the patients present with synchronous Colorectal Liver Metastases (CRLM) and 60 % will develop them metachronically [1]. Surgical treatment is the only therapy that gives these patients the option of long-

term survival. Outcomes have improved in the last three decades due to better surgical technique and more effective systemic chemotherapy. In the 1980s surgical treatment offered a 5-year survival rate of approximately 20 % for patients undergoing liver resection. Recent studies show 5-year overall survival rates ranging between 42 and 58 % [2,3].

## Revision

Several authors have studied factors that can presumably influence in survival and predict cancer recurrence. In 1999 Fong, et al. published the experience of Memorial Sloan Kettering with CRLM in 1001 consecutive cases. They created a clinical score based on five parameters. Each parameter had proven to be an independent predictor of poor long-term outcome by multivariate analysis. These parameters were: node-positive primary, disease-free interval from primary to metastases less than 12 months, more than one hepatic tumor, tumor size larger than 5 centimeters, and preoperative level of Carcino Embryonic Antigen (CEA) more than 200 ng/ml. One point was assigned to each of them. The study showed that no patient with a score of five had a long-term survival rate [4].

A recent study from Hallet et al. of the French colorectal liver metastases working group, with 2320 patients, demonstrated that almost half of the patients developed recurrence after hepatectomy for CRLM. 47.4 % of these patients recurred at median of 10.1 months and 89.1 % developed that recurrence within 3 years. Hepatic recurrence was seen in 46.2 % of the patients, 31.8 % was extrahepatic and 22 % for both combined. The factors related to recurrence after initial hepatectomy were very similar to those described by Fong disease free interval less than 12 months, node positive in the primary tumor or more than 3 liver metastases.

In the past few years, tumor biology has gained importance, more specifically KRAS mutational status and BRAF oncogene. KRAS status can be classified as wild type KRAS (wtKRAS) or mutated KRAS (mutKRAS). Mut KRAS as well as BRAF mutations are associated with a more aggressive tumor phenotype thus affecting long-term survival in these patients.

Chemotherapy regimens are also influenced by the tumor biology, RAS mutations are a well-known predictive factor for resistance to anti-EGFR monoclonal antibodies such as cetuximab and panitumomab. In the presence of such mutations we would substitute the anti-EGFR for an anti-angiogenic factor such as bevacizumab. Chemotherapy can be used as neoadjuvant therapy, adjuvant therapy or both.

Regimes are based on fluoropyrimidines and the most frequently used are FOLFIRI (flourouracil, irinotecan, leucovorin), FOLFOX (flourouracil, irinotecan and oxaliplatin) or Cape-ox (capecitabin and oxaliplatin).

It seems logical to treat unresectable CRLM with neoadjuvant chemotherapy in order to make them resectable and downstage patients' status. It has still not been clarified whether neoadjuvant chemotherapy regimens should also be used in resectable CRLM. According to EORTC 40,983, a phase III trial published in 2013 all patients should be treated with perioperative chemotherapy independently of their resectable status [5]. Although it has not been established as the gold standard it is already included as an alternative to initial resection in the NCCN guidelines. A possible benefit could be testing the sensitivity of the tumor to chemotherapy enabling the choice of the best postoperative treatment. Prospective studies should determine the risks and benefits of preoperative chemotherapy in resectable liver metastases.

Potential disadvantages of preoperative chemotherapy like liver damage or complete radiological response to the treatment without pathological confirmation should be considered in these patients.

There is more consensus when we are using chemotherapy following surgery. Adjuvant chemotherapy has showed better overall survival and progression free survival in patients treated surgically for CRLM.

As mentioned above, surgical approach to CRLM has changed dramatically in the last years. There are no contraindications nowadays in relation to the number of metastases or the size of them. Synchronic liver and lung metastases are neither a contraindication of resection as long as they are both resectable. The goal is to achieve an R0 resection leaving enough functional liver remnant. That means at least 30 % of the total volume for non-cirrotic non-chemotherapy treated livers. In cirrhotic or chemotherapy-treated livers this amount should reach 40 %.

This concept is also being modified, instead of measuring volumes we are now measuring quality of liver parenchyma with the indocyanine green test. The idea is that metabolic capacity of the parenchyma is more important than volume.

Synchronic CRLM have been managed differently along the years. There are three approaches to asses this matter: classic, synchronic treatment and the reverse approach popularized by Mentha.

When the primary tumor is symptomatic either by bleeding or obstructive symptoms there is little discussion that this problem

should be treated first. There are a few groups in high-volume centers that perform synchronic treatment for both primary and metastatic disease obtaining results with no increase in morbidity or mortality. Other authors propose the synchronic approach in cases of minor hepatic resection, in these cases no morbidity or mortality is added to the procedure. If the hepatic resection is major then they defend that the primary and the metastases should be treated in a staged approach because of an increase in mortality and sever morbidity.

The liver-first approach also known as the reverse approach is based on the idea that treating the metastases first instead of the primary avoids the risk of progression of the metastatic disease. Initial data showed that up to 80 % could undergo complete resection treatment if performing a reverse approach [6]. Survival rates are similar in both approaches if the treatment is totally completed.

New strategies have recently been defined for previously considered irresectable liver metastases. In 1980s Makuuchi introduced the concept of Portal Vein Embolization (PVE) of the right portal branch to allow the left lobe to hypertrophy before surgery. It was performed mostly to enable removal of large tumors located in the right hemiliver. In 2000 the Paul Bousse Hospital team published the results for two-stage hepatectomy. The first surgery intention is to remove the highest possible number of tumors while the second resects the remaining after a period of liver regeneration. This procedure was modified a few years later associating right portal vein ligation and wedge resection of the left lobe tumors in the first surgery followed by right extended hepatectomy in the second. Portal vein ligation allows shorter periods of time to allow liver hypertrophy than PVE. This solved the problem of drawback patients between both procedures that could initially be of more than two months and after portal vein ligation was reduced to about four weeks. In 2011 a novel approach was reported and in 2012 this technique was labeled as Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS). It is also a two-stage surgical technique. In the first procedure a right portal ligation associated to an in situ split of the liver and wedge resection of left tumor charge is performed. The second step consists of resection of the diseased right hemiliver. Initial reports of rapid increase of volume between both surgeries were promising. Schnitzbauer et al. reported a 74 % volume increase in 9 days. On the other hand, morbidity and mortality (3 patients out of 25) rates were significant [7]. In order to improve the outcomes and search for a better selection criterion an international registry and modified approaches to the ALPPS procedure such as partial ALPPS (50-80 % of liver partition) were developed. In 2014 the international ALPPS registry including 202 patients revealed an in-hospital mortality rate of 9 % [8].

## Conclusion

All these developments are widening surgical indications in CRLM. Surgical and systemic treatment as well as a better understanding of molecular alterations have changed the approach of liver metastases. The development of predictive

scores has helped us make a better patient selection. It is thanks to these efforts that the outcomes are improving daily and more and more patients can benefit from this year's experience with CRLM.

### **Declaration**

**All the mentioned authors in the cover letter declare:**

- That have contributed in the design of the article
- Having revised and edited the paper
- Provide consent to the final version of the manuscript to be published

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