

Management of potentially resectable colorectal cancer liver metastases

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Received: February 24, 2013 Revised: March 28, 2013

Accepted: April 27, 2013

Published online: May 27, 2013

Abstract

Colorectal cancer is a very common malignancy worldwide and development of liver metastases, both synchronous or metachronous, is a common event. Of all patients with metastatic colorectal cancer, up to 77% have a liver-only disease and approximately 10%-20% of patients with colorectal liver metastases are considered resectable at the time of diagnosis. Surgical resection of liver metastases remains the best treatment option and it is associated with a survival plateau and a 20%-25% of long-term survivors. Perioperative chemotherapy for resectable liver metastases may improve resectability of liver metastases and disease free survival, but its impact on overall survival is still unclear and more studies are needed. Moreover, preoperative chemotherapy can increase postoperative complications. Further studies are needed to define the role of adjuvant chemotherapy after a R0 resection of liver metastases and to define the criteria for a better selection of patients candidate to hepatectomy. New strategies such as targeted therapies are emerging with promising results. Optimal management requires a multidisciplinary approach, local and systemic, but it is a still pending question. Colorectal liver metastases represent a major challenge for oncologists and surgeons. In this review will be analyzed available data about assessment and

management of the patients with potentially resectable colorectal liver metastases.

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Key words: Colorectal cancer; Liver metastases; Perioperative chemotherapy; Surgical resection; Targeted therapies

Core tip: Colorectal cancer is a very common malignancy and its incidence is rapidly increasing worldwide. Of all patients with metastatic colorectal cancer, up to 77% have a liver-only disease and about 10%-20% of them are considered resectable at the time of diagnosis. Surgery actually still represents the best option of treatment, but new strategies such as perioperative chemotherapy and targeted therapies are emerging with promising results. However, optimal management requires a multidisciplinary approach, both local and systemic. This review aims to critically analyze the management of potentially resectable colorectal liver metastases.

Meriggi F, Bertocchi P, Zaniboni A. Management of potentially resectable colorectal cancer liver metastases. *World J Gastrointest Surg* 2013; 5(5): 138-145 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v5/i5/138.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v5.i5.138>

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality^[1]. The liver is the most common site of CRC metastases and nearly 25% of patients with CRC present with synchronous liver metastases at the time of initial diagnosis and 50%-75% of patients within three years after primary colonic surgery at the time of disease recurrence^[2-5]. Though most of

these patients have a poor prognosis, there is a subset of patients with liver metastases, both synchronous or metachronous, that can benefit from radical surgery and possibly even achieve cure^[6]. In fact, from 25% to 50% of patients with surgically resected colorectal liver metastases (CLM) today can survive five or more years after surgery^[7-11]. Unfortunately, only a small percentage of patients, estimated at 10%-20%, exhibits with initially resectable liver metastases^[12] and up to 2/3 of patients with resected CLM will experience a recurrence in the majority cases just in the same organ^[13,14]. In the last two decades, we have observed remarkable advances in the treatment of CLM, both from a medical point of view with the advent of new chemotherapeutic and biologic agents, and with the improvement of surgical techniques and a better definition of the resectability criteria. However, up to now, strong scientific evidences about what is the best strategy for the treatment of CLM are still debated. One of the obstacles to be addressed is the difficulty in defining “Who is resectable?”. The indications for resection of CLM changed significantly over the years. In the late eighties, Ekberg defined restrictive criteria for resectability: less than four metastases (uni or bilobar), absence of extrahepatic disease, and resection margin of at least 1 cm. Moreover, Steele suggested resection of liver metastases only from colorectal primary, three or less lesions, R0 resections, absence of comorbidities and extrahepatic disease^[5,15]. Starting from the nineties, these criteria were gradually extended, in relation to location and size of tumor, number of lesions, and absence of extrahepatic disease^[16]. Currently, the number or size of hepatic nodules in the hands of trained surgeons and in high-volume liver departments, are no longer considered an absolute contraindication to hepatectomy if the remnant healthy liver is > 25%-30%^[17]. Preoperative liver magnetic resonance imaging and intraoperative ultrasound offer the optimal assessment of the number, size, and proximity of tumors to key vascular and biliary structures. Moreover, recent guidelines from the National Comprehensive Cancer Network (NCCN) (v3.2013) recommend a staging positron emission tomography scan for patients with potentially surgically curable metastatic colorectal cancer. Even the simultaneous presence of potentially resectable extrahepatic disease is no longer an absolute contraindication to surgery of liver metastases, particularly if the extrahepatic disease is surgically resectable lung or ovarian metastases. From 1996 to 2009 were identified at least twelve prognostic scoring-systems, in an attempt to predict survival after resection of CLM as a function of the number of risk factors present in the patient’s medical history^[18]. One of these scoring-systems was tested by Fong *et al*^[3] and assessed five risk factors on approximately 1000 patients: presence of metastatic nodes at the time of the surgery of the primary tumor, disease-free interval < 12 mo, > 1 metastatic lesion; size > 5 cm and a value of Carcinoembryonic Antigen (CEA) > 200 ng/mL. The 5-year OS ranges from 14% in patients with five risk fac-

tors to 60% in those without risk factors^[19]. In an attempt to confirm these results, Tomlinson *et al* have validated the reliability of this “score”, recording a 10-year OS of 21% in resected patients with a low score (0-2) and of 10% in those with a high-risk score (3-5)^[20]. On the other hand, Nordlinger score included seven risk factors: age \geq 60 year, extension into the serosa of the primary cancer, lymphatic spread of the primary cancer, interval less than 2 years from primary tumor to metastases, number of metastases \geq 4, largest size of liver metastasis \geq 5, defining three risk groups (low, intermediate, high) with different 2-years survival rates^[21]. Finally, there are increasing clinical evidences that medical perioperative treatment may improve the outcome of these patients^[22,23].

NEOADJUVANT CHEMOTHERAPY

Surgery remains the treatment of choice for cure or prolonged survival if it is possible to obtain a radical resection (R0) and with the preservation of a residual functioning liver of 25%-30% of the original liver volume. The term “neoadjuvant chemotherapy” is reserved for chemotherapy for resectable and potentially resectable liver metastases prior to surgery. The role of neoadjuvant chemotherapy in the management of potentially resectable CLM is still controversial and debated^[24]. In fact, not infrequently, in patients with favorable prognostic factors, “upfront” surgery of liver metastases is the preferred strategy. An argument in favor of the use of preoperative chemotherapy is that this may be a good test *in vivo* to evaluate the chemosensitivity of the tumor. Tumor progression while on preoperative treatment is almost always associated with a poor prognosis, even if the metastases will be resected^[25]. Perioperative treatment of resectable liver metastases is supported by the phase III European Organization for Research and Treatment of Cancer (EORTC) 40983 trial (Table 1). This study randomized 364 patients with 1-4 resectable CLM to 6 cycles of preoperative and 6 cycles of postoperative 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX4) compared with surgery alone. The primary endpoint was progression free survival (PFS). If we consider all of the 364 enrolled patients (182 per arm), the gain in PFS at 3 years was 7.3% in the perioperative chemotherapy arm compared with surgery alone, although this difference was not statistically significant ($P = 0.058$). If you take into account only the patients who underwent a surgical resection of CLM, then the increase in favor of the perioperative treatment reaches the statistical significance (difference in PFS between the two arms of 9.2%, $P = 0.025$)^[22]. In a recent update of the study after a median follow-up of 8.5 years, the 5-years OS (secondary endpoint) was found of 7 mo longer in the experimental arm (an increase of 3.4%, HR = 0.88; 95%CI: 0.68-1.14, $P = 0.339$), but also in this case not such to reach a statistical significance. Note that in the experimental arm only 2/3 of resected patients has been able to receive the programmed postoperative

Table 1 European Organization for Research and Treatment of Cancer 40983 Trial

	<i>n</i>	Treatment	HR for progression	3-yr PFS	5-yr PFS	Postoperative OS complications
All pts	364	CHT	0.79	35.4	51.2	-
		Surgery alone	<i>P</i> = 0.058	28.1	47.8 (<i>P</i> = 0.339)	-
Elegible pts	342	CHT	0.77	36.2	52.4	-
		Surgery alone	<i>P</i> = 0.041	28.1	48.3 (<i>P</i> = 0.303)	-
Resected pts	329	CHT	0.73	42.4		25%
		Surgery alone	<i>P</i> = 0.025	33.2		16%

Reproduced from reference Nordlinger *et al*^[22] and Sorbye *et al*^[23]. pts: Patients; CHT: Chemotherapy; HR: Hazard ratio; PFS: Progression free survival; OS: Overall survival.

chemotherapy and that the post-surgery morbidity was more significant (25% *vs* 16%, *P* = 0.04), although reversible, in patients treated with preoperative chemotherapy. Operative mortality was 1% in both treatments group^[23]. It remains unresolved the question whether the benefit in PFS observed in this study is mainly due to the perioperative treatment in toto or primarily to adjuvant post-resection treatment, in favor of which there are several studies that confirm its effectiveness^[26-31]. Two other small phase II trials support the use of a preoperative treatment with FOLFOX/XELOX (Capecitabine plus Oxaliplatin) and XELOX with bevacizumab^[32,33], but before we could say a definitive word on the best approach to the treatment of potentially resectable CLM we still need further dedicated studies, with or without new biological agents. Another aspect to consider in these challenging economic times is cost-effectiveness: according to literature, the use of neo-adjuvant chemotherapy could be convenient because it could possibly avoid hepatic resection in those patients who do not respond to this treatment. Nevertheless this analysis is controversial for synchronous resectable metastases^[34,35]. Neoadjuvant chemotherapy can induce damage to the remnant liver and the risk of hepatic toxicity and surgical complications increase with the duration of pre-operative treatment^[36,37]. Steatosis has been associated with both fluoropyrimidines and irinotecan. Vauthey *et al*^[38] reported 20% patients receiving irinotecan having steatohepatitis and this was associated with increased 90-d mortality and morbidity after hepatectomy. Hepatic sinusoidal obstruction syndrome can emerge in patients treated with oxaliplatin but does not seem to be strongly associated with increased postoperative mortality^[37,39]. A recent retrospective study evaluated histological specimens from 366 resected patients for CLM after preoperative chemotherapy and found that the two independent prognostic factors for OS after hepatectomy were the overall pathologic response > 75% and, surprisingly, fibrosis > 40% and not necrosis as expected^[40]. Another problem with preoperative chemotherapy includes the shrinkage of viable disease, known as “vanishing metastases”, so it is not visible and therefore not resected at laparotomy. However, in many cases, this clinical complete response does not match with pathologic complete response. According to Adam *et al*^[41], the

predictive factors for a complete pathologic response are: age ≤ 60 year, size of metastases ≤ 3 cm, CEA levels at diagnosis ≤ 30 ng/mL, and objective response following chemotherapy. Patients who achieved a complete pathologic response after neoadjuvant chemotherapy had high survival rates (76% at 5 year). Patients should be carefully monitored during chemotherapy and receive surgery before metastases disappear. Therefore, response to neoadjuvant therapy must be closely monitored and it is recommended to reevaluate disease after no more than 2 mo of treatment^[42]. The duration of treatment *in toto* (preoperative and adjuvant) should not exceed 6 mo^[43]. In summary, many oncologists feel that perioperative therapy is the best current option of treatment for resectable CLM and the recent European Society for Medical Oncology guidelines define this subset of patients with clearly R0-resectable CLM as “Group 0”. The treatment aims of patients placed in “Group 0” is cure and decrease risk of relapse. Hence, the intensity of neoadjuvant treatment will be “nothing” (upfront surgery) or “moderate” (FOLFOX)^[44].

ADJUVANT THERAPY AFTER RESECTION OF LIVER METASTASES

Nearly 70% of patients relapse after an hepatic resection for CLM and most of them just in the liver and within the first two years after surgery^[13,14,45]. In an attempt to improve the outcome of these patients was thus adopted the rationale of adjuvant therapy. Two randomized phase III studies and a subsequent meta-analysis of data extracted by them, have evaluated the role of the combination of bolus fluorouracil and leucovorin (5-FU/LV) for 6 mo after R0 surgery of CLM *vs* surgery alone^[26-28]. The results of these studies, although showing a trend in favor of adjuvant chemotherapy both in PFS and OS, do not provide a strong evidence in favor of postoperative treatment, probably due to their limited statistical power and the use of a chemotherapy regimen that actually does not represent the best combination to be administered in patients considered as metastatic patients. There are two additional meta-analyses that support the use of an adjuvant fluoropyrimidine-based treatment^[29,30]. In the study of Ychou *et al*^[31], the regimen FOLFIRI, as expected, has

Table 2 Phase III trials of adjuvant chemotherapy after resection of colorectal liver metastases

Ref	n	CHT	Median PFS (mo)	Median OS (mo)
Langer <i>et al</i> ^[26]	129	5-FU/LV	No difference	No difference
Portier <i>et al</i> ^[27]	173	5-FU/LV	24.4 vs 16.6 (<i>P</i> = 0.028)	62.1 vs 46.4 (<i>P</i> = 0.13)
Mitry <i>et al</i> ^[28]	278	5-FU/LV	27.9 vs 18.8 (<i>P</i> = 0.059)	61.1 vs 46.9 (<i>P</i> = 0.125)
Ychou <i>et al</i> ^[31]	306	FOLFIRI vs 5-FU/LV	24.7 vs 21.6 (<i>P</i> = 0.44)	No difference

CHT: Chemotherapy; PFS: Progression free survival; OS: Overall survival; 5-FU/LV: 5-fluorouracil/Leucovorin; FOLFIRI: 5-FU/LV/Irinotecan.

failed to show advantage in disease free survival (DFS) compared to 5-FU/LV (Table 2). It was argued, as in the classical adjuvant therapy after surgery of the primary tumor, that an oxaliplatin-based regimen^[46] may be more effective, but there are no definitive data and studies with the FOLFOX or XELOX regimens with or without biologic agents, are currently ongoing. Several interesting experiences, but difficult to reproduce on a large scale especially for technical difficulties and specific toxicities (*i.e.*, sclerosing cholangitis), were obtained with the administration of a derivate of fluorouracil (floxuridine, FUDR) plus high-dose dexamethasone in the hepatic artery (HAI), using the rationale of the prevalent arterial vascularization of liver metastases and of lower risk of systemic toxicities despite higher doses of chemotherapy^[47-53].

In conclusion, it is common practice to administer a postoperative chemotherapy in patients with resected CLM due to the high-relapse rate expectations and the positive impact on PFS, but unfortunately definitive data in favor of adjuvant therapy after R0 resection of CLM are still lacking. Nevertheless, actually the preferred regimen to be administered in these patients are empirically an oxaliplatin-based regimen.

Hence, it will be crucial to identify subsets of patients at increased risk of relapse and candidate to receive adjuvant treatment.

TARGETED THERAPIES

More recently, the introduction of new biological drugs in the available arsenal of the oncologist has improved the results obtained in the treatment of metastatic colorectal cancer. In particular, anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab in patients with *K-RAS* wild-type^[54-60] and anti-vascular endothelial growth factor (VEGF) antibody bevacizumab^[61-64] have shown a synergistic action when associated to classical chemotherapy regimens with two or three drugs, thus increasing significantly the PFS, the overall response rate and hence also the rate of hepatic resection for CLM if compared with chemotherapy alone, especially when used as “conversion” treatment for unresectable liver metastases. Whether these results provide a real OS advantage, it still remains unclear. Unfortunately, data about targeted therapies in the perioperative or neoadjuvant setting of resectable CLM are lacking.

Gruenberger *et al*^[32] reported their experience of a phase II study with oxaliplatin, capecitabine and bevacizumab in 56 curable CLM patients. This regimen showed a high response rate (73%) with R0 hepatic resections in 52 out of 56 patients and 5 complete pathologic responses. Actually, phase III studies with anti-EGFR antibody cetuximab and with anti-VEGF antibody bevacizumab are ongoing to better define the role of these biological agents in the treatment of potentially resectable CLM.

CONCLUSION

CLM are a common problem, but many patients are able to undergo R0 liver resection, and a significant proportion of those patients may achieve cure or at least obtain prolonged DFS^[65]. A multidisciplinary team approach is important for coordinating care of patients with CLM. Surgery is the treatment of choice for resectable CLM and requires that an adequate liver remnant remains after surgery. Perioperative chemotherapy with FOLFOX regimen for six mo according to the results of the EORTC 40983 randomized trial improves the outcome of these patients and it is actually recommended for most patients^[66-69]. When it an upfront surgery of CLM is performed, then adjuvant chemotherapy with an oxaliplatin-based regimen is a reasonable option. Based on our experience we suggest a close follow up schedule for patients who underwent CLM resection. The role of targeted therapies in neoadjuvant setting of potentially resectable CLM remains to be defined and needs further studies. Finally, where a local approach to CLM is indicated and surgery is contraindicated, the radiofrequency ablation of liver metastases is often considered a good alternative, although generally less effective than surgery in terms of relapse rate and OS^[70-76].

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