

Current treatment options for patients with initially unresectable isolated colorectal liver metastases

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Abstract

The development of liver metastases is a common clinical entity in the clinical course of colorectal cancer. For patients with isolated liver involvement, surgical resection is the only treatment that can provide a chance of prolonged survival and cure. However, most of these patients are not initially eligible for the surgery. Selected patients with initially considered to have unresectable disease may become resectable after systemic (che-

motherapy ± biological therapy) and loco-regional treatment modalities including hepatic arterial infusion. Patients who have colorectal liver metastases ideally should be referred to a multidisciplinary cancer care team in order to identify the most optimal management approach.

Key words: Colorectal cancer; Conversion therapy; Liver metastases; Targeted therapy; Hepatic arterial infusion

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Core tip: A subset of patients presenting with unresectable colorectal liver metastases (CLM) patients may become eligible for resection following systemic (chemotherapy ± biological therapy) and loco-regional treatments, including hepatic arterial infusion. After successful complete (R0) resection of liver lesions, these patients can achieve long-term survival. Therefore, all patients with CLM should be discussed in a multidisciplinary team meeting to identify appropriate treatment options.

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INTRODUCTION

The liver is the one of the most attractive site for colorectal cancer (CRC) metastases. Up to 50% of CRC patients will experience liver metastases at some point during their clinical follow-up, and approximately 20%-30% of these patients will have isolated liver metastases. Complete surgical removal of all liver meta-

stases is the only treatment option providing the best opportunity for long-term survival in these patients^[1-4].

However, most patients with isolated colorectal liver metastases (CLM) are not eligible for surgical resection due to the size, location or number of the lesions and anatomical constraints^[5]. On the other hand, a subset of patients initially considered to have unresectable CLM may become eligible for resection following effective systemic chemotherapy. When the chemotherapy is used for that purpose, it is called conversion chemotherapy. Patients with resected CLM following conversion chemotherapy can achieve similar survival to those with initially resectable tumors^[4]. In a large series reported by Adam *et al*^[6], 1104 patients with unresectable CLM received chronomodulated chemotherapy regimens combining 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin or irinotecan. After an average of 10 cycles of chemotherapy, tumor response that allowed secondary curative hepatic resection was seen in 138 (12.5%) of these patients. The 5- and 10-year overall survival (OS) rates after resection were 33% and 23%, respectively, which are better than those in patients who did not undergo resection, but less than those observed in patients who underwent initial complete metastasectomy at the same institution during the same period of time (48% and 30%, respectively, $P = 0.01$).

According to the new systematic review that looked at ten observational studies, the use of modern chemotherapy regimens including irinotecan and oxaliplatin with or without biological agents permitted secondary curative (R0) resection of CLM in 436 of 1886 patients (23.1%). The median OS following surgery was 45 (range, 36-60) mo and recurrence-free survival rate was 19%^[7].

IS THERE AN OPTIMAL CHEMOTHERAPY REGIMEN FOR CONVERSION THERAPY?

It is clear that the regimens that can produce high response rates with an acceptable toxicity will lead to a higher rate of R0 resections of liver metastases and improved survival rates^[8]. Folprecht *et al*^[9] examined all published or presented trials as well as retrospective studies that report the rate of objective response and the rate of secondary resection following systemic chemotherapy in patients with initially unresectable CLM. They demonstrated a strong relationship between response rates to the regimen used and the liver resection rates in patients who have isolated liver involvement, and also speculated that highly active schedules can provide response rates as high as 70% and complete surgical resection rates as high as 50% in selected cases.

The standard doublet combinations of fluoropyrimidines plus either oxaliplatin (XELOX, FOLFOX) or irinotecan (FOLFIRI) offer conversion rates of between 9 and 33%, and their use remains a reasonable option for patients with unresectable CLM^[8,10-12]. On the other hand,

the administration of intensified triplet chemotherapy regimen of 5-FU, oxaliplatin and irinotecan (FOLFOXIRI) is an attractive strategy that may potentially increase response and resectability rates^[13]. The Gruppo Oncologico Nord Ovest (GONO) performed a phase III clinical study comparing FOLFOXIRI with FOLFIRI in front-line chemotherapy for patients with initially unresectable CRC^[14]. In this trial, response rate (60% vs 34%, $P < 0.0001$) and R0 secondary resection rate was significantly greater in patients treated with FOLFOXIRI (15% vs 6%; $P = 0.033$, among all participants; and 36% vs 12%; $P = 0.017$ among patients with liver-only metastases). Furthermore, patients who received FOLFOXIRI had significantly improved progression-free survival (PFS) and OS than those who received FOLFIRI (median PFS, 6.9 mo vs 9.8 mo, $P = 0.0006$; median OS, 16.7 mo vs 22.6 mo, $P = 0.032$). As expected, FOLFOXIRI was found to be more toxic with regard to peripheral neurotoxicity and neutropenia, but they were manageable.

Masi *et al*^[15] recently performed a retrospective analysis of pooled clinical data from 196 patients who received FOLFOXIRI because of initially unresectable metastatic CRC in phase I -III GONO studies. The primary aim of the investigators was to determine the long-term clinical results of patients undergoing a secondary complete resection and the effects of this regimen on perioperative surgical morbidity and mortality. They demonstrated that administration of this intensified regimen was associated with a high response rate of 70.4%, and a secondary complete (R0) resection was possible in 37 of 196 patients (19%) after a median of 5.5 mo of chemotherapy. In addition, four patients achieved a complete pathologic response. No perioperative mortality was recorded. Although 27% of patients developed perioperative complications, all of them resolved without sequelae. After a median follow-up period of 67 mo, the estimated OS rate at 5 and 8 years were 42% and 33%, respectively for the total patients population. For patients who had liver-only metastatic disease ($n = 25$), however, the median survival was 65 mo, with the estimated 5-year and 8-year survival rate was 43%. In the histopathological examination of chemotherapy-induced hepatic injury, a major cause for concern when treating patients with CLM, neither grade 3 vascular toxicity nor grade 4 steatosis, was detected.

The addition of targeted agents to chemotherapy backbones may further improve resectability rates of CLM^[16-18]. According to the results of an initial phase 3 trial, bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor, only moderately improved resectability rates when added to oxaliplatin-based chemotherapy (8.4% vs 6.1%) in an unselected patient population with metastatic CRC^[19]. Further data on the effects of bevacizumab on resection rates of CLM came from the Bevacizumab Expanded Access Trial investigating the safety of bevacizumab with fluoropyrimidine-based chemotherapy in the

first-line treatment of 1914 patients with metastatic CRC^[20]. In 704 patients with liver-only metastases, 107 patients (15.2%) underwent hepatectomy, which was R0 resection in 85 out of 107 patients (79.4%). The 2-year survival rate was 89% in patients who underwent resection with curative intent and 94% in those who achieved complete R0 resection.

The BOXER (bevacizumab, oxaliplatin, xeloda in unresectable liver metastases) study investigated the efficacy of perioperative chemotherapy with bevacizumab plus capecitabine and oxaliplatin in patients with CLM who were considered ineligible for upfront resection due to following poor-risk features: The presence of more than four metastatic lesions, metastasis diameter > 5 cm, unlikely R0 resection, inadequate viable liver function if undergoing upfront surgical resection, inability to maintain adequate liver vascular perfusion, or the presence of synchronous metastases. After a median number of four cycles (range, 3-9) preoperative chemotherapy, objective tumor response was observed in 78% of patients and 40% of patients were converted from unresectable to resectable disease. Of these patients, 20% achieved an R0 resection^[21].

In a phase 2 study, Masi *et al*^[22] assessed the feasibility of FOLFOXIRI and bevacizumab combination in 57 patients with metastatic CRC. Among the 30 patients with liver-only metastatic disease, this regimen yielded an 80% objective response rate and 40% of these patients could undergo a curative (R0) resection. No perioperative mortality was recorded. Subsequently, the GONO reported the results of the phase 3 TRIBE (combination chemotherapy and bevacizumab as first-line therapy in treating patients with metastatic CRC) study comparing FOLFOXIRI plus bevacizumab with FOLFIRI plus bevacizumab in metastatic CRC patients^[23]. FOLFOXIRI plus bevacizumab provided a significant increase in response rates (65% vs 53%) and PFS (median 12.1 mo vs 9.7 mo) compared with FOLFIRI plus bevacizumab. However, FOLFOXIRI plus bevacizumab did not improve the secondary curative R0 resection rate in the liver-only patient subgroup (28% vs 32%, $P = 0.823$).

In the OLIVIA randomized phase II trial, 80 patients with initially unresectable CLM were randomized to receive bevacizumab plus modified FOLFOX6 or bevacizumab plus FOLFOXIRI^[24]. The results showed that the combination of bevacizumab plus FOLFOXIRI improved overall resection rate (61% vs 49%) and R0 resection rate (49% vs 23%), and PFS (18.6 mo vs 11.5 mo) compared with bevacizumab plus FOLFOX6.

The results of phase III CRYSTAL (cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer) trial and phase II OPUS (oxaliplatin and cetuximab in first-line treatment of metastatic colorectal cancer) trial have showed that the integration of cetuximab, a chimeric immunoglobulin G1 anti-epidermal growth factor receptor (EGFR) monoclonal antibody, to irinotecan or oxaliplatin-based first-line chemotherapy significantly improved response

rates, R0 resection rates, PFS, and OS compared with chemotherapy alone in patients with metastatic CRC whose tumors did not harbor a KRAS mutation^[25,26]. In the CRYSTAL trial, combined administration cetuximab and FOLFIRI resulted in an increase in the resection rate from 4.5% to 9.8% in the subgroup of patients with disease confined to the liver at presentation^[25]. Similarly, in the OPUS study, the R0 resection rate for hepatic metastases doubled from 2.4% to 4.7% when cetuximab was added to FOLFOX4 regimen^[26].

The CELIM randomized phase II study was designed to assess the effect of cetuximab combined with chemotherapy (FOLFOX6 or FOLFIRI) on tumor response and secondary resectability of CLM^[27]. A retrospective analysis of the study revealed that 70% of patients with KRAS wild-type disease achieved either a complete or partial or complete response after chemotherapy-biologic therapy, and the resectability rates increased from 32% (at baseline) to 60% (after treatment).

In the study by Ye *et al*^[28], patients with KRAS wild-type unresectable colorectal liver-limited metastases were randomly assigned to receive chemotherapy (FOLFIRI or FOLFOX6) plus cetuximab or chemotherapy alone. Patients who received cetuximab plus chemotherapy had improved objective response rates (57.1% vs 29.4%; $P < 0.01$), and the R0 hepatic resection rates (25.7% vs 7.4%, $P < 0.01$) compared to patients who received chemotherapy alone.

Preliminary reports have suggested that response rates can be increased further by combining cetuximab with FOLFOXIRI regimen. The POCHER study investigated secondary liver resection rates following neoadjuvant treatment with cetuximab plus chronomodulated FOLFOXIRI in patients who were considered unsuitable for resection of their CLM at presentation^[29]. After a median of six cycles of chemotherapy, a partial response was obtained in 79% of patients and R0 liver resection was possible in 60% of patients.

The MetaPan study evaluated the activity of adding panitumumab, a fully human monoclonal anti-EGFR antibody, to the capecitabine plus oxaliplatin (XELOX) combination as perioperative conversion treatment in CRC patients with unresectable liver-only metastases^[30]. After conversion therapy, the overall response rate in the unselected patient population was 54%. However, in 35 patients with KRAS wild-type, response rate reached to 65%, which allowed for liver resection in 15 of these patients.

Petrelli *et al*^[31] have performed a literature-based meta-analysis to determine the effects of cetuximab and panitumumab on objective response rate, the conversion rate, and survival outcome in patients with KRAS wild-type unresectable colorectal liver-limited metastases. They found that compared to chemotherapy alone, the addition of anti-EGFR agents significantly increased the response rate of liver metastases from 43% to 72% ($P = 0.0001$), and the curative (R0) resection rate of liver metastases from 11% to 18% ($P = 0.04$). Although anti-EGFR agents significantly reduced the risk of progression

by 32% ($P = 0.002$), they did not show any significant favorable effect on OS ($P = 0.42$).

Neither study found a significant increase in surgical complications with the use of biological agents in this setting^[16-18]. There are currently no specific recommendations regarding the use of anti-EGFR antibodies in the preoperative period^[16,17]. However, bevacizumab should be stopped at least 6-8 wk before surgery to reduce the risk of specific postoperative complications, including wound healing or bleeding problems^[18,32].

HEPATIC ARTERIAL INFUSION

Since CLMs predominantly receive their blood supply from the hepatic artery, infusion of chemotherapeutic agents that have a high hepatic extraction rate [such as 5-fluorouridine (FUDR)] *via* the hepatic artery results higher drug concentrations in liver metastases compared with tumor-free liver parenchyma, which is supplied mainly by portals vein^[33]. This can be achieved through a biocompatible pump that is implanted under the subcutaneous tissue of the abdomen and attached to a catheter placed in the hepatic artery, which delivers the chemotherapeutic drugs at a slow fixed rate.

Currently hepatic arterial infusion (HAI) chemotherapy is primarily recommended for the treatment of patients with unresectable liver confined metastatic CRC who had disease progression after first-line systemic chemotherapy^[34]. However, available data suggest that HAI in combination with systemic chemotherapy or chemo-biologic therapy offer a chance for curative rescue resection to a substantial proportion of patients presenting with liver-limited metastatic CRC^[34,35]. With this approach, down-staging to resectability occurs in 25%-50% of patients; the percentage can reach up to 57% in chemotherapy-naïve patients^[10,11,35,36]. Importantly, the long-term overall survival can be obtained^[10,11,35-37]. In the series reported by Goere *et al*^[37], 87 patients with isolated unresectable CLM were treated with HAI of oxaliplatin with systemic 5-FU and LV. Seventy-nine percent of patients had previously received systemic chemotherapy. After the treatment, a curative resection was possible in 26% of patients, and the 5-year survival for these patients was 56% vs 0% for non-resected patients.

Ammori *et al*^[38] reported the largest institutional series of 373 patients with unresectable CLM who were treated with HAI FUDR and systemic chemotherapy. Two hundred and ninety-six patients (79%) had been treated with systemic chemotherapy before HAI, and 43 of these patients received multiple lines of chemotherapy. Sixty patients (16%) had also extrahepatic disease at the time of HAI pump placement. Despite these unfavorable features, 25% of patients responded sufficiently to treatment and subsequently underwent complete resection and/or radiofrequency/microwave ablation. The median and the estimated 5-year survival for this conversion group were 59 mo and 47%, respectively, which were comparable to reports in the literature of patients initially

presenting with resectable disease.

HAI can be associated with technical and liver-related complications. Technical complications including arterial thrombosis, catheter occlusion or dislodgement, extra-hepatic perfusion, pump pocket infections or hematoma, have been reported up to 22% of patients^[39]. However, most of these complications are manageable and overall rate of pump failure is around 9% at 1 year^[39]. The most limiting hepatic toxicity related to HAI is biliary sclerosis, which has been reported in 4.6% of patients receiving HAI FUDR for unresectable CLM, and it can often be effectively managed, if detected early^[40].

CONCLUSION

Surgical resection is currently the only curative approach for patients with isolated CRC liver metastases. Conversion chemotherapy may offer a chance for secondary resection in about one-third of these patients. Although, the optimal regimen for this is still unclear, a doublet combination of 5-FU plus either oxaliplatin or irinotecan remain the standard first-line option. The FOLFOXIRI triplet is a very attractive treatment option especially for patients who can tolerate this regimen. Despite lacking specifically designed randomized trials, available data suggest that the integration of targeted biological agents into chemotherapy may further improve tumor response and resectability. HAI should be considered in patients with extensive liver tumor burden and chemotherapy-refractory disease.

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