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World J Gastroenterol 2005;11(25):3817-3822
World Journal of Gastroenterology ISSN 1007-9327

• *REVIEW* •

Current preventive treatment for recurrence after curative hepatectomy for liver metastases of colorectal carcinoma: A literature review of randomized control trials

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Received: 2004-09-18 Accepted: 2004-12-21

Abstract

To review the preventive approaches for recurrence after curative resection of hepatic metastases from colorectal carcinoma, we have summarized all available publications reporting randomized control trials (RCTs) covered in PubMed. The treatment approaches presented above include adjuvant intrahepatic arterial infusion chemotherapy, systemic chemotherapy, neoadjuvant chemotherapy, and immunotherapy. Although no standard treatment has been established, several approaches present promising results, which are both effective and tolerable in post-hepatectomy patients. Intrahepatic arterial infusion chemotherapy should be regarded as effective and tolerable and it increases overall survival (OS) and disease-free survival (DFS) of patients, while 5-fluorouracil-based systemic chemotherapy has not shown any significant survival benefit. Fortunately chemotherapy combined with hepatic arterial infusion and intravenous infusion has shown OS and DFS benefit in many researches. Few neoadjuvant RCT studies have been conducted to evaluate its effect on prolonging survivals although many retrospective studies and case reports are published in which unresectable colorectal liver metastases are downstaged and made resectable with neoadjuvant chemotherapy. Liver resection supplemented with immunotherapy is associated with optimal results; however, it is also questioned by others. In conclusion, several adjuvant approaches have been studied for their efficacy on recurrence after hepatectomy for liver metastases from colorectal cancer (CRC), but multi-centric RCT is still needed for further evaluation on their efficacy and systemic or local toxicities. In addition, new adjuvant treatment should be investigated to provide more effective and tolerable methods for the patients with resectable hepatic metastases from CRC.

Key words: Preventive treatment; Recurrence; Hepatectomy; Metastatic colorectal cancer; Randomized control trials

Wang P, Chen Z, Huang WX, Liu LM. Current preventive treatment for recurrence after curative hepatectomy for liver metastases of colorectal carcinoma: A literature review of randomized control trials. *World J Gastroenterol* 2005; 11(25): 3817-3822
http://www.wjgnet.com/1007-9327/11/3817.asp

INTRODUCTION

Although many approaches have been invented for the treatment of liver metastases from colorectal cancer (CRC)[1], resection continues to be the only curative therapeutic option. Liver resection is today a safe procedure, with a low mortality rate of 0.8%[2] and a morbidity of 7.2%[3]. Though the 5- and 10-year overall survival (OS) rates are 37% and 22% respectively[4], recurrence is already evidenced, either in the liver or with extrahepatic disease in about half of all resected patients within 18 mo after resection[5]. Intrahepatic recurrence, alone or with other localization, is common. However, about 60% recurrences are seen in the remnant liver[6]. In the last two decades people have tried a number of approaches to prevent recurrence, but only a few of them were designed as randomized control trials (RCTs), which provide evidence-based results for those treatment modalities. In this paper, we summarized the results from RCTs, attempting to find a more suitable treatment modality for prevention of recurrence.

LITERATURE REVIEWS OF RANDOMIZED CONTROL TRIALS TO PREVENT RECURRENCE AFTER CURATIVE HEPATECTOMY FOR LIVER METASTASES OF COLORECTAL CARCINOMA

Hepatic arterial infusion

Rationale for regional therapy after resection of liver metastases is that hepatic metastases are perfused almost exclusively by the hepatic artery, while normal hepatocytes derive their blood supply from the portal vein, which provides the basis for the use of regional hepatic arterial infusion (HAI) therapy after resection of hepatic metastases. Though favorable long-term results can be achieved after surgery for colorectal metastases to the liver, recurrences both intrahepatic and extrahepatic commonly occur[5,6]. Tumor cells from colorectal carcinoma spread hematogenously

via the pertal circulation, making liver the first site of metastases. The most common site of failure after resection is within the remnant liver. Hence, additional therapy, either regional or systemic or both, has potential as an adjunct treatment after surgery. Extraction of drugs from the hepatic arterial circulation ensures high drug concentrations to residual cancer cells while minimizing systemic toxicity, provided the agent used has a high first-pass extraction. Of the various chemotherapy agents, 5-fluoro-2-deoxyuridine (FUDR) is the most commonly used drug for this purpose, which demonstrates 95% hepatic extraction when given via HAI. FUDR via HAI markedly increases its estimated exposure up to 400-fold. 5-FU is the other agent used in this setting of regional therapy and its response rate can be expected higher when used in combination with concomitant leukovorin[7]. Combining 5-FU with other agents by hepatic artery infusion has been proven to be an effective treatment for liver metastases from CRC.

Table 1 summarizes the randomized series of adjuvant intrahepatic therapy (with or without systemic therapy) after potentially curative hepatic resection of metastatic CRC.

A small study by Lygidakis *et al*.[8], prospectively randomized 40 patients to hepatic surgery alone or surgery combined with post-operative regional chemoimmunotherapy via implanted splenic and gastroduodenal arterial catheters, and found that liver resection supplemented with postoperative targeted transarterial locoregional immunotherapy-chemotherapy is associated with optimal results.

Asahara *et al*.[9], conducted a study to evaluate the efficacy of postoperative transarterial infusion chemotherapy for the prevention of recurrence after hepatectomy following curative surgery for colorectal carcinoma. The result showed that the 3- and 4-year survival rates are 100% in the experimental group, and 60% and 47% respectively in the control group.

Kemeny *et al*.[12], tried to improve the outcomes by treating patients with HAI of floxuridine plus systemic fluorouracil after liver resection, and found that a 2-year OS and DFS benefit in HAI group is 86% *vs* 72%, 57% *vs* 42%. After 2 years, the rate of survival free of hepatic recurrence is 90% in the HAI group and 60% in the monotherapy group, suggesting that for patients who undergo resection of liver metastases from CRC, postoperative treatment with a combination of HAI of floxuridine and intravenous fluorouracil improves the outcome.

Tono *et al*.[13], divided 19 patients who underwent curative hepatectomy for metastatic colorectal carcinoma into HAI group and control group. Patients in HAI group received continuous intra-arterial infusion of 5-FU (500 mg/d), 4 d a week for 6 wk. The study showed a significant 1-, 2-, 3-year prolongation of DFS in the HAI group (77.8% *vs* 50.0%, 77.8% *vs* 30.0%, 66.7% *vs* 20.0%, $P = 0.045$). The 1-, 3-, and 5-year cumulative survival rates for the HAI group were 88.9%, 77.8%, and 77.8%, respectively, whereas those of the control group were 100.0%, 50.0%, and 50.0%, respectively. This randomized study reveals that short-term HAI of 5-FU after curative resection of colorectal hepatic metastases is effective in preventing the recurrence of disease and has no serious complications.

Kemeny *et al*.[14], studied the effect of postoperative hepatic arterial floxuridine combined with intravenous continuous infusion of fluorouracil on the OS and DFS of patients, and found that the 4-year recurrence-free rate is 25% in the control group and 46% in the chemotherapy group, the median survival time of the 75 assessable patients is 49 mo in the control group and 63.7 mo in the chemotherapy group, demonstrating that adjuvant intra-arterial and intravenous chemotherapy is beneficial to the prevention of hepatic recurrence after hepatic resection of CRC.

However, in a German co-operative multicenter study[11], patients were randomized to resection only or resection plus 6 mo of HAI of 5-FU/LV given as a 5-d continuous

Table 1 Randomized series of adjuvant intrahepatic arterial chemotherapy after surgical resection of hepatic metastases

Authors	Treatment protocol	Sample size (Tx / Ctl)	Observation time	DFS Tx *vs* Ctl	OS Tx *vs* Ctl	Conclusions
Lygidakis *et al*.[8]	Surgery+HAI chemoimmunotherapy *vs* surgery alone	40 (20 / 20)	3 yr	NA	Median 20 *vs* 11 (mo) ($P<0.05$)	Beneficial
Asahara *et al*.[9]	Surgery+HAI chemotherapy *vs* surgery alone	38 (10 / 28)	NA	NA	3-yr 100% *vs* 60% 4-yr 100% *vs* 47%, respectively ($P<0.05$)	Beneficial
Rudroff *et al*.[10]	Surgery+HAI 5-FU / MMC *vs* surgery alone	30 (14 / 16)	5 yr	5-yr 15% *vs* 23% ($P>0.05$)	5-yr 25% *vs* 31% ($P>0.05$)	Not beneficial
Lorenz *et al*.[11]	Surgery+HAI 5-FU / LV *vs* surgery alone	226 (113 / 113)	NA	Median 14.2 *vs* 13.7 (mo) ($P>0.05$)	Median 34.5 *vs* 40.8 (mo) ($P>0.05$)	Not beneficial
Kemeny *et al*.[12]	Surgery+HAI FUDR / DEXA+IV 5-FU / LV *vs* surgery+IV 5-FU / LV	156 (74 / 82)	2 yr	2-yr 57% *vs* 42% ($P = 0.07$)	2-yr 86% *vs* 72% ($P = 0.03$)	Beneficial
Tono *et al*.[13]	Surgery+HAI 5-FU+oral 5-FU *vs* surgery+oral 5-FU	19 (9 / 10)	62.2 (mo) (mean)	1-, 2-, 3-yr 77.8%, 77.8%, 66.7% *vs* 50.0%, 30.0%, 20.0% respectively ($P = 0.045$)	1-, 2-, 3-yr 88.9%, 77.8%, 77.8% *vs* 100.0%, 50.0%, and 50.0% respectively ($P = 0.2686$)	Beneficial
Kemeny *et al*.[14]	Surgery+HAI FUDR+IV 5-FU vs surgery	109 (53 / 56)	NA	4-yr 46% *vs* 25% ($P = 0.04$)	Median 63.7 *vs* 49 (mo) ($P = 0.60$)	Beneficial

Tx: treatment; Ctl: control; DFS: disease-free survival; OS: overall survival; NA: not available.

infusion every 28 d. No differences in time-to-progression, time-to-hepatic progression, or median OS are noted in this study.

Rudroff *et al*.[10], evaluated the preventive effect of adjuvant intra-arterial chemotherapy after R0 liver resection and found that there is no significant difference in either 5-year survival or long-term disease-free status between the two groups. They concluded that routine application of adjuvant regional chemotherapy after R0 liver resection is not warranted.

A recent meta-analysis[15] also showed that hepatic artery chemotherapy after curative hepatectomy metastases cannot improve the OS.

The above data suggest that adjuvant intrahepatic arterial chemotherapy combined with or without intravenous chemotherapy can inhibit the recurrence, and that the toxicity and side effects are tolerable.

At present, the superior rates of response and survival reported with irinotecan- and oxaliplatin-based regimens[16-19] provide a new standard first-line treatment of metastatic CRC, which have led to more clinical trials to re-evaluate the efficiency of HAI combining irinotecan or oxaliplatin on recurrence after curative hepatectomy for CRC. At the Memorial Sloan-Kettering Cancer Center (MSKCC), a phase I/II study used HAI with floxuridine and dexamethasone in combination with systemic irinotecan as adjuvant therapy following curative hepatectomy in 90 CRC patients. The maximum tolerable dose of combined HAI+systemic irinotecan is 0.12 mg/kg FUDR with systemic CPT-11 at 200 mg/m^2 every other week, the 2-year survival rate is 87%[20-22]. Oxaliplatin, a new cytotoxic agent, when used in combination with 5-FU/LV (FOLFOX), can achieve more than 50% clinical response and a median survival time of 16.2 mo in untreated patients with metastatic CRC[18,19], suggesting that oxaliplatin-based regimens combined with HAI of FUDR have a promising result.

HAI of FUDR plus systemic 5-FU/LV following resection of hepatic metastases decreases local recurrence and improves OS. It is necessary to further study the effect of HAI combing newer systemic agents, such as irinotecan and oxaliplatin and to make it clear which combination of regimens are the most effective and well-tolerated.

Systemic chemotherapy

While patients who undergo resection of liver metastases from CRC can prolong their survival time, the majority will have relapse not only intrahepatically but also extrahepatically. Therefore, the investigation of adjuvant therapies designed to decrease relapse is warranted. Adjuvant chemotherapy via HAI after resection of liver metastases has shown its efficacy in terms of both disease-free survival (DFS) and OS. On the contrary, the role of "adjuvant" chemotherapy following liver resection for hepatic colorectal metastases remains unclear. Some retrospective trials about adjuvant 5-FU-based systemic chemotherapy have not shown any significant survival benefit[18,19]. Few prospective randomized studies have been performed to answer the question whether postoperative chemotherapy improves survival in comparison to liver resection alone. However, the effects on survival of postoperative systemic chemotherapy are currently under evaluation. The following are recent RCT studies on systemic chemotherapy (Table 2).

Lopez-Ladron *et al*.[24], studied the outcome of 38 patients with resection of liver metastases from CRC, and found that the median OS time of patients who did not receive CT is 15 mo, while patients who received CT after hepatic surgery have a median survival time of 30 mo. The actual OS of patients who received adjuvant CT seems to be higher, suggesting that these results should be confirmed in phase III studies.

An intergroup multicentric randomized study[23] was performed to evaluate the value of FU/FA after complete resection of liver metastases compared to surgery alone. The result is in favor of patients who received systemic chemotherapy after resection of liver metastases.

At present, more studies are focused on the effect of HAI combined with systemic chemotherapy on the OS and DFS[12,14] (Table 1).

In general, systemic chemotherapy alone cannot inhibit recurrence in patients after resection of hepatic colorectal metastases, although systemic 5-FU/LV and HAI of FUDR following resection of hepatic metastases decrease local recurrence and improve 2-year survival. Both hepatic and extrahepatic relapses remain a problem. Studies on newer systemic agents such as irinotecan and oxaliplatin are under way.

Neoadjuvant therapy

The application of neoadjuvant chemotherapy has a number of potential advantages in patients with resectable liver metastases. Firstly, it helps the selection of chemotherapeutic agents after resection. The degree of response gives information on the *in vivo* chemosensitivity of the tumor. In patients with fewer responses or severe toxicity, the same agents should be avoided and alternative agents should

Table 2 RCT studies on efficacy of systemic chemotherapy on prevention of recurrence

Authors	Treatment protocol	Sample size (Tx/Ctl)	Observation time	DFS Tx *vs* Ctl	OS Tx *vs* Ctl	Conclusions
Lopez-Ladron *et al*.[24]	Surgery+post-operative chemotherapy vs surgery alone	38 (28/10)	Median 15 (mo)	Median 15 *vs* 9 (mo) (P = 0.352)	Median 30*vs*15 (mo) (P = 0.066)	Not beneficial, needing further study
Portier *et al*.[23]	Surgery+post-operative chemotherapy (FU/FA) vs surgery alone	162 (81/81)	5 yr	5-yr 33% *vs* 24% (P>0.05)	5-yr 51% *vs* 44% (P>0.05)	Not beneficial

Tx: treatment; Ctl: control; DFS: disease-free survival; OS: overall survival; NA: not available.

Table 3 RCTs on efficacy of neoadjuvant chemotherapy

Authors	Treatment protocol	Sample size (Tx / Ctl)	Observation time	DFS Tx *vs* Ctl	OS Tx *vs* Ctl	Conclusions
Lorenz *et al*.[29]	Biweekly FOLFOX regimen×6 cycles *vs* biweekly FOLFOX regimen×3 cycles	40 (20 / 20)	NA	NA	NA	Induced significant remissions without increasing morbidity
Bathe *et al*.[30]	5-FU+leukovorin+CPT-11					Ongoing

Tx: treatment; Ctl: control; DFS: disease-free survival; OS: overall survival; NA: not available.

be considered after resection. Secondly, neoadjuvant chemotherapy may also help the selection of candidates for resection, which means patients who develop extrahepatic disease during a short course of chemotherapy are unsuitable for resection in the first place. Finally, neoadjuvant chemotherapy enhances resectability in some instances[25-27]. Reduction of tumor volume may limit the amount of liver that needs to be removed to accomplish eradication of the tumor and preserve more normal hepatic tissues.

Most reports on neoadjuvant chemotherapy for liver metastasis focus on the strategies for unresectable tumors[25,28]. The reported resectability rate ranges from 10% to 40% for unresectable colorectal liver metastases after preoperative chemotherapy.

Recently, Lorenz *et al*.[29], conducted a prospective pilot study of neoadjuvant chemotherapy with 5-fluorouracil, folinic acid and oxaliplatin for resectable liver metastases of CRC, and found that neoadjuvant chemotherapy for resectable liver metastases induces significant remissions without increasing morbidity (Table 3).

Due to the potential advantage in patients with resectable liver metastases and new regimens using either oxaliplatin or irinotecan in combination with 5-FU, one phase II study[30] of neoadjuvant 5-FU+leukovorin+CPT-11 in patients with resectable liver metastases from colorectal adenocarcinoma is under investigation. The general aim of this study is to determine the efficacy of neoadjuvant chemotherapy for patients with ablatable liver metastases from CRC in reducing recurrence rate. Response to the chemotherapy regimen will constitute an *in vivo* chemosensitivity test, and this will guide adjuvant chemotherapy following resection of liver metastases from CRC.

Immunotherapy

Since early 1990s, immunotherapy has become a very attractive cancer treatment modality. However, it is not so effective as expected in a number of clinical trials[31,32]. Recently a series of clinical trials have begun to investigate the effect immunotherapy on recurrence of cancer after surgery. The summary of these RCTs are as follows (Table 4).

Lygidakis *et al*.[8], compared the effect of liver resection combined with post-operative locoregional immunotherapy +chemotherapy on recurrence after curative hepatectomy of hepatic colorectal metastases, and found that the survival time of control group ranges from 4 to 25 mo (mean 11 mo), suggesting that liver resection in combination with postoperative targeted transarterial locoregional immunotherapy -chemotherapy is associated with good results. It is highly recommended as the procedure of choice for patients with liver metastasis of colorectal carcinoma.

Lygidakis *et al*.[33], showed the same results, which support post-operatively locoregional chemotherapy for hepatic metastases of CRC. Lygidakis *et al*.[34], reported that regional immunochemotherapy combined with systemic chemotherapy leads to a lower incidence of disease recurrence and a significant prolongation of the OS and DFS time.

Table 4 RCTs of immunotherapy

Authors	Treatment protocol	Sample size (Tx / Ctl)	Observation time	DFS Tx *vs* Ctl	OS Tx *vs* Ctl	Conclusions
Lygidakis *et al*.[8]	Surgery+post-operative HAI immunochemotherapy *vs* surgery alone	40 (20 / 20)	3 yr	NA	Median 20 *vs* 11 (mo) (P<0.05)	Beneficial
Lygidakis *et al*.[33]	Post-operatively locoregional immunochemotherapy *vs* post-operatively locoregional chemotherapy	45 (33 / 15)	NA	NA	Median 20.3 *vs* 9.9 (mo)	Beneficial
Lygidakis *et al*.[34]	Locoregional chemoimmunotherapy with systemic chemotherapy *vs* systemic immunochemotherapy	122 (62 / 60)	NA	2-yr 66% *vs* 48%	2-yr 92% *vs* 75% 5-yr 73% *vs* 60%	Beneficial
Elias *et al*.[35]	Preoperative rIL-2 continuous intravenous infusion	19 (12 / 7)	NA	NA	NA	Beneficial (well tolerated and reverse postoperative immunodepression)
Gardini *et al*.[36]	Post-operative TIL+IL-2 *vs* post-operative+chemotherapy	45 (25 / 22)	NA	1-, 3-, and 5- yr No difference	1-, 3-, and 5-yr No difference	Not beneficial

Tx: treatment; Ctl: control; DFS: disease-free survival; OS: overall survival; NA: not available.

Elias *et al*.[35], investigated prehepatectomy immunostimulation with recombinant interleukin-2 (rIL-2) and evaluated the tolerance of rIL-2 in association with major hepatectomy to verify the effect of preoperative immunostimulation (neoadjuvant immunotherapy), and found that toxicity during rIL-2 infusion is acceptable, suggesting that infusion of rIL-2 before major hepatectomy for liver metastases of CRC is well tolerated and reverses postoperative immunodepression.

Gardini *et al*.[36], also studied immunotherapy with tumor infiltrating lymphocytes (TIL) plus interleukin-2 (IL-2) as adjuvant treatment, and found that there are no significant differences in the actual and DFS rates after 1, 3, and 5 years, suggesting that whether TIL+IL-2 treatment is an effective adjuvant therapy needs to be further studied.

SUMMARY

Number of preventive treatment protocols for inhibiting recurrence after curative resection of liver metastases from colorectal origin have been evaluated by RCT. Although no standard treatment has been proven to be effective in all patients, several approaches present promising results, which are both effective and tolerable in post-operative patients. Generally intrahepatic arterial infusion chemotherapy is effective in preventing the recurrence of disease without serious complications, while systemic chemotherapy is not in favor of patients who receive systemic chemotherapy after liver metastases resection. Neoadjuvant chemotherapy has shown an advantage in patients with resectable liver metastases. Immunotherapy approaches can achieve a better outcome, but need more evidence before wide acceptance.

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Science Editor Wang XL and Guo SY **Language Editor** Elsevier HK