Review

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The progress in adjuvant therapy after curative resection of liver metastasis from colorectal cancer

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Summary **Colorectal cancer liver metastases (CRLM) are common and found in almost 50% of patients with colorectal cancer. Surgical resection has proved to be the most effective therapy for metastatic colorectal cancer isolated to the liver and has yielded long term survival. However, recurrence frequently occurs within the remaining liver as well as at extra-hepatic sites. The role of adjuvant therapy has been investigated in many studies but has still been controversial until now. This review examines the incorporation of adjuvant systemic chemotherapy, regional chemotherapy with hepatic arterial infusion and molecular targeted therapy following liver resection for patients with CRLM, and summarized the advantage and adverse effects for these treatments. Finally, we propose the prospective of future adjuvant treatments to further improve prognosis.**

Keywords: Colorectal cancer liver metastases (CRLM), adjuvant treatment, systemic chemotherapy, molecular-targeted therapy, hepatic arterial infusion (HAI)

1. Introduction

The liver is the most common site of colorectal cancer metastasis, with 15% of patients presenting with liver metastases at the time of diagnosis and up to 60% of patients developing liver metastases during the course of their disease (*1*). Surgical resection has proved to be the most effective therapy for metastatic colorectal cancer isolated to the liver and has yielded 5-year overall survival (OS) rates of 28% to 44% (*2-7*) and 10-year survival of over 20% (*5,6,8*) (Table 1). However, the risk of postoperative recurrence, especially in the remnant liver, remains high, occurring in approximately 75% of patients. Furthermore, there is the view that it is the liver metastatic disease, rather than the primary cancer, that gives rise to systemic metastatic disease (*9*). So it is of great importance to achieve long-term survival by suppressing the liver metastasis after resection for liver metastasis from colorectal cancer (CRLM).

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Chemotherapy and molecular targeted therapy have made great progress in treatment of advanced colorectal cancer, and adjuvant chemotherapy has proved to prolong survival after resection of primary colon cancer, especially with the development of modern chemotherapeutic medications (*10-13*). However, there is no standard treatment in the adjuvant setting after resection of liver metastasis from colorectal cancer. In the current review, we summarize chemotherapy, molecular targeted therapy as well as regional chemotherapy with hepatic arterial infusion (HAI) for patients with curatively resected liver metastasis from colorectal cancer in an adjuvant setting. We propose a future perspective potential strategy of adjuvant therapy for patients with CRLM.

2. Systemic chemotherapy after curative resection of colorectal cancer liver metastasis.

The efficacy of adjuvant chemotherapy for liver metastasis of CRLM is still controversial. A retrospective review of 792 patients supported the importance of adjuvant chemotherapy in terms of significantly prolonging overall survival (*8*). Two phase III trials (Federation Francophone de Cancerologie Digestive (FFCD) Trial 9002 and the European Organization for

Table 1. Long-term survival after liver resection for colorectal cancer liver metastasis

Author	Year	Ref.	No. cases	5-year OS	10-year OS
Nordlinger-France	1996	*4*	1,568	28%	n.a.
Fong-US-MSKCC	1999	*5*	1,001	37%	22%
Rees-UK	2008	*6*	929	36%*	23%*
Mayo-US-John-Hopkins	2013	*7*	1,004#	44%	n.a.

* Cancer-specific overall survival; # Synchronous liver metastasis with multi-institutional data. n.a., not available.

Table 2. Systemic chemotherapy after resection of CRLM

Author	*Ref.*	Study types	No. cases	Regimen for chemotherapy	Survival benefic for chemotherapy
Parks (2007)	*8*	Large cohort	792 (374 *vs*. 518)	5-FU-based adjuvant chemotherapy	Improved survival (p = 0.007, log-rank test)
Mitry (2008)	*14*	Pooled analysis of two phase III RCTs	278, CT: 138, S: 140	FU 400 mg/m^2 administered *i.v*. once daily plus DL-LV 200 mg/m^2 [FFCD] for 5 days or FU 370 mg/m^2 plus L-LV 100 mg/m^2 IV for 5 days [ENG] for six cycles at 28-day intervals	Benefit was statistically marginal, with median DFS: 27.9 *vs.* 18.8 (p = 0.058) and median OS: 62.2 *vs*. 49.3 (p = 0.095).
Nordlinger (2008)	*15*	Phase III	364(171 *vs.* 152)	Perioperative FOLFOX4 (EORTC 40983; short-tern results)	3-year PFS improved in eligible patients (p = 0.041) and resected patients (p = 0.025).
Nordlinger (2013)	*16*	Phase III	364(171 *vs.* 152)	Perioperative FOLFOX4 (EORTC 40983; long-term results)	No benefit in 5 year OS: 51.2% (95% CI: 43.6-58.3) *vs.* 47.8% (95% CI: 40.3-55.0).
Sorbye (2012)	*17*	Phase III	342	Perioperative FOLFOX4 (EORTC 40983 inter-group study)	3-year PFS (35% *vs*. 20%) better for patients with moderately (5.1-30 ng/mL, p = 0.018) and highly (>30 ng/mL, p = 0.0075) elevated CEA.
Ychou (2009)	*18*	Phase III	306	FOLFIRI *vs*. LV5FUs	For DFS, FOLFIRI not better than LV5FUs.
Kim (2011)	*19*	Single armed	60	mFOLFOX6 (oxaliplatin 130 mg/m^2 d1) or 5-FU (1,000 mg/m^2 d1–3, continuous infusion) for 6 months.	Increased OS and RFS (compared to historical control).
Hirokawa (2014)	*20*	Retrospective	110	77 patients (70%) received chemo-therapy (5-FU ± LV, tegafur/uracil ± folinate, oteracil (TS-1), *etc*.). 25 patients received FOLFOX, FOLFIRI or HAI with 5-FU/cisplatin.	Risk factors: H2-classification, pT4 and LN+. < 2 factors: no benefit for OS and RFS; ≥ 2 factors: OS better.

Notes: IV, intravenously; FU, fluorouracil; FOLFOX; FOLFIRI, CEA, carcinogen embryo antigen, OS, overall survival, PFS, progression-free survival; CT, chemotherapy, S, surgery alone.

Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia (ENG) trial) used a similar design and showed a trend favoring adjuvant chemotherapy with a fluorouracil (FU) bolus-based regimen, but both trials had to close prematurely because of slow accrual, thus lacking the statistical power to demonstrate the predefined difference in survival. A pooled analysis of individual data from these two trials shows a marginal statistical significance in favor of adjuvant chemotherapy after complete resection of colorectal cancer metastases (*14*) (Table 2).

The most convincing evidence comes from a phase III trial, EORTC trial 40983. The EORTC intergroup trial 40983 showed that perioperative chemotherapy with FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) increases progression-free survival (PFS) compared with surgery alone for patients with initially resectable liver metastases from colorectal cancer (*15*), with 3-year PFS improved in eligible patients (p = 0.041) and resected patients (p = 0.025). However, at a median follow-up of 8.5 years (*16*), there is still no difference in overall survival with the addition of perioperative FOLFOX4 compared with surgery alone (5 year OS: 51.2% *vs.* 47.8%). It showed that 107 (59%) patients in the perioperative chemotherapy group had died versus 114 (63%) in the surgery-only group (HR 0.88, p = 0.34), and median overall survival was 61.3 months in the

perioperative chemotherapy group and 54.3 months in the surgery alone group.

Some scholars made comments about the results. First, the PFS increase in resected patients suggested that FOLFOX delays progression of disease but does not improve long term survival compared with surgery alone. Second, the chemotherapy in EORTC trial 40983 perioperative rather than adjuvant, because chemotherapy was given for 6 cycles before and 6 cycles after surgery, so the perioperative chemotherapy may select patients most likely to benefit from hepatic resection.

Interestingly, Sorbye *et al*. (*17*) analyzed the predictive factors for the benefit of a subgroup of patients in the EORTC 40983 study and found that for patients with moderately or highly elevated CEA (> 5 ng/mL), the 3-year PFS was 35% with perioperative chemotherapy compared to 20% with surgery alone, and performance status (PS) 0 and BMI lower than 30 were also predictive for the benefit of perioperative chemotherapy (interaction $p = 0.04$ and $p = 0.02$), suggesting that application of adjuvant FOLFOX4 maybe only be justified in subgroup patients with specific features.

Chemotherapy with Irinotecan is not justified in the adjuvant setting. A phase III clinical trail conduced by Ychou *et al*. (*18*) showed that FOLFIRI in the adjuvant treatment of CRLM showed no significant improvement in DFS compared with LV5FUs.

Many retrospective studies with small sample sizes provided insufficient evidence (Table 2). Kim *et al*. (*19*) showed that oxaliplatin-based adjuvant chemotherapy (mFOLFOX6) after radical resection resulted in increased OS and RFS compared to historical controls. Hirokawa *et al.* (*20*) found benefit for OS and RFS only in patients with more than 2 risk factors (including H2-classification, invasion depth pT4, and lymph node positive).

In conclusion, the application of adjuvant systemic chemotherapy in CRLM is still controversial but promising, with FOLFOX as the main regimen for chemotherapy. FOLFIRI should not be recommended as adjuvant chemotherapy because of a negative phase III trial. Further studies are urgently needed to clarify the effectiveness of adjuvant systemic chemotherapy by stratification of patients with risk factors that are more predictive of advanced disease, and by identification of patients who will more probably benefit from systemic chemotherapy.

3. Molecular targeted therapy

Although molecular targeted therapy has been widely used for advanced colorectal cancer, bevacizumab (BV), cetuximad, and panitumumab were not allowed to be used in the adjuvant setting for patients with stage II or III colon cancer outside the setting of a clinical trial as suggested by the National Comprehensive Cancer Network (NCCN) guideline. As for stage IV colorectal cancer with liver metastasis, there is no evidence supporting the rationale of using adjuvant molecular targeted therapy. For bevacizumab, Kemeny *et al.* (*21*) conducted a randomized phase II trial of adjuvant hepatic arterial infusion and systemic chemotherapy with or without bevacizumab in patients with resected hepatic metastases from colorectal cancer. With a median follow-up of 30 months, 4-year survival was 85% and 81% ($p = 0.5$), 4-year RFS was 46% versus 37% and 1-year RFS was 83% and 71% ($p = 0.4$) for No BEV versus BEV arms. So it was obvious that the addition of BEV to adjuvant HAI plus systemic therapy after liver resection did not increase RFS or survival. Furthermore, the combination with BEV appeared to increase biliary toxicity. Meanwhile, Turan *et al.* (*22*) also showed that addition of BEV to chemotherapy had no impact on both RFS and OS, with median RFS ($p = 0.375$) and OS ($p = 0.251$) similar in BEV and NoBEV arms. Until now, the evidence level of combination of bevacizumab with systemic therapy was not high; the only randomized two-arm phase III study (*23*) is ongoing in patients after radical resection of CRLM to investigate bevacizumab in combination with capecitabine plus oxaliplatin (CAPOX) versus CAPOX alone as adjuvant treatment (Table 3).

The story with cetuximab was even worse, in a newly released result from a randomised phase-III clinical trial (New EPOC study) (*24*), addition of cetuximab to chemotherapy and surgery for operable colorectal liver metastases in KRAS exon 2 wild-type patients results in shorter progression-free survival. However, resectable hepatic metastases have been identified as an ideal setting for the development of such targeted approaches because of the availability of pre- and post-treatment tumor tissue for the identification of molecular biomarkers. In addition, resected stage IV disease could serve as a model for micro-metastatic disease for the development of novel adjuvant therapies for earlier stage colorectal cancer (CRC).

In conclusion, there is no evidence supporting the combination of BEV and chemotherapy to benefit patients with resected CRLM, and a randomized phase III study is ongoing to reveal the answer more thoroughly. The addition of cetuximab to chemotherapy after surgery should not be recommended. Other molecular targeted therapy should be tested in phase III clinical trails.

4. Hepatic artery infusion (HAI) in combination with systemic chemotherapy

The most common site of recurrence develops in the remnant liver or other organs after hepatic resection for patients with CRLM. Recognition of differences in the blood supply to metastases compared to normal liver parenchyma has allowed for the development of hepatic arterial delivery of systemic chemotherapeutic

Table 3. Adjuvant molecular targeted therapy after curative resection of synchronous/metachronous CRLM

Author	*Ref.*	Study types	No. cases	Regimen	Survival benefic
Kemeny (2011)	*21*	Phase II (two-armed) (MSKCC)	156	HAI + systemic chemotherapy (fluorodeoxyuridine/DXM) with or without BEV. Systemic therapy and BEV 5 mg/kg was delivered on days 15 and 29: oxaliplatin 85 mg/m^2 (or irinotecan 150 mg/ m^2), LV 400 mg/m^2, and fluorouracil 2,000 mg/m^2 infusion for 2 days	BV-no additive benefit to chemotherapy. 4-year OS: 85% *vs*. 81% (p = 0.5). 4-year RFS: 46% *vs.* 37%. 1-year RFS: 83% *vs*. 71% (p = 0.4) for no BEV versus BEV arms)
Turan (2013)	*22*	Cohort study. (Turkey)	204	Chemotherapy with fluoropyrimidine-based (n = 27), irinotecan-based (n = 84) and oxaliplatin-based (n = 93) combinations. 87 received BEV while 117 did not (No BEV).	Chemotherapy type and addition of BEV have no impact on both RFS and OS; Median RFS (p = 0.375) and OS (p = 0.251) were similar.
Primrose (2014)	*24*	Phase III RCT (New EPOC study) (Southampton, UK)	236 (117 *vs*. 119)	CapeOx regimen and Cetuximab (regimen one:500 mg/m^2 every 2 weeks; regimen two: a loading dose of 400 mg/m^2 followed by a weekly infusion of 250 mg/m^2)	PFS significantly shorter in chemotherapy plus cetuximab group than chemotherapy group (14.1 *vs*. 20.5 months, HR 1.48, p = 0.030).
Snoeren (2010)	*23*	Phase III RCT	n.a.	Bevacizumab in combination with capecitabine plus oxaliplatin (CapeOx) *vs*. CapeOx alone	ongoing

Notes: DFS, disease-free survival; OS, overall survival; PFS, progression-free survival; DXM, dexamethasone; HAI, hepatic arterial infusion; BV, bevacizumab; CapeOX, Capecitabin and Oxaliplatin; RCT, randomized clinical trial; HR, hazard ratio.

agents. Roughly, 20-25% of blood entering the liver is supplied by the hepatic arteries, and 75-80% is supplied by the portal vein. However, experimental studies have demonstrated that hepatic tumors 0.5-3.0 cm or greater in diameter are fed mainly from the hepatic arteries. Hepatic arterial administration can therefore deliver high concentrations of drugs to metastatic tumors in the liver. Furthermore, drugs used for HAI have a short half-life and are primarily metabolized in the liver, allowing extremely low drug concentrations to be maintained in the peripheral blood, thereby minimizing the risk of systemic adverse events. HAI chemotherapy provides much better local control of liver metastases from colorectal cancer than systemic chemotherapy (*25*). The most commonly used agent in HAI is floxuridine (FUDR), a pyrimidine antimetabolite that is converted to 5-fluorouracil in the liver. Floxuridine has a very high rate of hepatic extraction and a short half-life, making it optimal for hepatic infusion (*26*). Other chemotherapeutic drugs have also been used in HAI, Kemeny was the first to apply HAI with oxaliplatin in 2001 (*27*), and HAI with iriticon in 2005 (*28*).

HAI with FU/DXM in combination with intravenous FU, with or without LV has yielded clinical benefits in CRLM (Table 4). Kemeny *et al.* (*29*) from MSKCC conducted a randomized controlled phase-III clinical trial; 74 patients were randomized to combined HAI and systemic chemotherapy and 82 to systemic chemotherapy alone. A significant benefit was seen in patients receiving combined therapy. The median survival in the group receiving combined therapy was 68.4 months compared with 58.8 months for those receiving systemic chemotherapy alone. At 2 years the rate of survival free of hepatic recurrence was 90% in the combined-therapy group compared with 60% in the systemic chemotherapy-only group ($p < 0.001$). However recurrence outside the liver appeared similar in both groups. Recently, Kemeny *et al.* (*30*) re-analyzed patients in the same trial with a median follow-up of 10.3 years and found that overall PFS is significantly greater in the combined-therapy group than in the monotherapy group (31.3 *vs.* 17.2 months, p = 0.02). The median survival free of hepatic progression has not yet been reached in the combined therapy group, whereas it has reached 32.5 months in the monotherapy group ($p < 0.01$). However, the benefic of overall survival was only marginally significant, with a median OS of 68.4 months versus 58.8 months in the combined and monotherapy group, respectively (p = 0.10). Furthermore, patients with a high risk of recurrence (a score of 3 to 5) as evaluated by a clinical risk score had a median survival of 60.0 months in the combined therapy group and 38.3 months in the monotherapy group (p = 0.13), while patients with a lower risk of recurrence (a score of 0-2) had a similar median survival (83.3 months *vs*. 82.8 months), indicating that the effect of postoperative HAI may be more potent in patients with residual disease.

Three cohort studies (*31-33*) showed a significant PFS benefit with HAI therapy but a significant OS

Table 4. Hepatic artery infusion (HAI) in combination with systemic chemotherapy

Author	*Ref.*	Study types	No. cases	Regimen for chemotherapy	Survival benefic for chemotherapy
Kemeny (1999)	*29*	Phase III (MSKCC, US)	156 (74 *vs.* 82)	6 Cycles of HAI with floxuridine/DXM + intravenous FU, with or without LV, or six weeks of similar systemic therapy alone	The median OS: 72.1 m *vs.* 59.3 m; 2-year hepatic RFS 90% *vs*. 60%; 2-year RFS rate 57% *vs*. 42% (p = 0.07).
Kemeny (2005)	*30*	Sam as above	156 (74 *vs.* 82)	Sam as above	Overall PFS is greater in the combined-therapy group (31.3 *vs*. 17.2 months, p = 0.02). Median hepatic RFS is greater (not reached *vs.* 32.5 months (p < 0.01). Clinical-risk scoring system predicted survival. Patients with score 3-5 had OS of 60 m to 38.3 m, and patients with score 0-2 had of 83.3 m *vs.* 82.8 m.
Go´er´e (2013)	*31*	Cohort study (France)	98 (44 *vs.* 54)	HAI: oxaliplatin 100 mg/m^2; IV: modified LV5-FU2 or the de Gramont regimen.	3-Year DFS significantly longer for HAI-OXA + IV than IV (33% *vs*. 5%, p < 0.0001). 3-year OS slightly higher for HAI + IV group (75% *vs*. 62%, p = 0.17).
House (2011)	*32*	Cohort study (MSKCC, US)	250 (125 *vs.* 125)	HAI-FUDR/DXM + systemic chemotherapy. Systemic chemotherapy: FU/LV plus oxaliplatin or irinotecan.	Combination of HAI-FUDR improved 5-year liver RFS, overall RFS, and DSS compared to systemic chemotherapy alone.
Ota (2004)	*33*	Cohort study (Yokohama, Japan)	84 (37 *vs.* 47)	HAIC: 1,500 mg of 5-FU, 24-h continuous infusion once a week for 8 weeks.	5-Year liver RFS were 72.6% in the HAIC group and 29.8% in the control group (p = 0.0005). 5-year OS: 61.4% *vs.* 28.0% (p = 0.0069).
Alberts (2010)	*41*	PHASE-II single armed (Mayo Clinic, US)	76	HAI-FUDR/DXM/Heparin Systemic: CapeOX (OXA:130mg/m^2 + Cape 1,700 mg/m^2/d)	2-Year survival rate 86%. 88% alive at 2 years after operation. 30 patients had disease recurrence.

DFS, disease-free survival; OS, overall survival; DSS, disease-specific survival; RFS, recurrence-free survival; FU/LV, 5-fluorouracil/leucovorin; OXA, oxaliplatin; HAI-FUDR: hepatic arterial infusion with FUDR; DXM, dexamethasone

benefit was only reported in one study (*33*), the other two studies only revealed a marginal survival benefit (*31,32*) (Table 4). So in conclusion, HAI therapy has shown better improvement of PFS but to a less extent in prolonging OS, suggesting a better local control of liver metastasis after resection of CRLM. There is a clue that HAI may be more effective in patients with higher risk scores for recurrence, indicating that HAI may be applied to patients with residual disease in the era of individualized medicine.

5. Adverse effect

Pathologic lesions of the background liver may be encountered among patients who undergo chemotherapy, with sinusoidal dilatation tending to occur if oxaliplatin is used in combination chemotherapy (*34*), and steatohepatitis if CPT-11 (irinotecan) is used (*35*), neurotoxicity is also very common from oxaliplatin (*36*). A phase II study which compared systemic chemotherapy without BV or with BV showed that the combination of systemic chemotherapy with BV resulted in incidences of biliary complications, in which 4 out of 5 patients with an elevated total bilirubin level received a biliary stent due to chemotherapy and BV (*21*).

For HAI, biliary sclerosis after hepatic arterial infusion pump chemotherapy for patients with colorectal cancer liver metastasis should be kept in mind (*37*). In patients who received a combination of mitomycin (MMC), the biliary sclerosis happened in 4.6%-13.4% of patients and the adverse effect was more likely to happen in patients with adjuvant therapy than in patients with an advanced stage (5.5% *vs.* 2.0%) (*26*). It has been reported that the incidence of biliary sclerosis can be reduced by DXM and be effectively managed if detected early. Even though, the implantation and maintenance of HAI pumps is challenging and only a few large-volume centers have the expertise, and complication rates specifically attributable to HAI pumps have ranged from 22-41% (*38,39*). The liver injury of preoperative chemotherapy with modern chemotherapeutic medications and major liver resection also adds more risk for adjuvant HAI (*40*).

6. Conclusions

In conclusion, CRLM with resectable liver metastasis benefits from adjuvant chemotherapy either with systemic chemotherapy to control systemic metastasis or hepatic arterial infusion to control liver-specific recurrence. The combination of molecular targeted therapy should be withdrawn except in the settings of clinical trials, as it not only has no benefit but also may impair survival. Further studies should be emphasized on personalized therapy by identifying patients with residual disease and with higher-risk of distant metastasis; molecular targeted therapy should be given to patients with residual disease and with activation of specific pathways.

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