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TOPIC HIGHLIGHT

2016 Colorectal Cancer: Global view

Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis

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Abstract

Surgical resection is the only option of cure for patients with metastatic colorectal cancer (CRC). However, the risk of recurrence within 18 mo after metastasectomy is around 75% and the liver is the most frequent site of relapse. The current international guidelines recommend an adjuvant therapy after surgical resection of CRC metastases despite the lower level of evidence (based on the quality of studies in this setting). However, there is still no standard treatment and the effective role of an adjuvant therapy remains controversial. The aim of this review is to report the state-of-art of systemic chemotherapy and regional chemotherapy with hepatic arterial infusion in the management of patients after resection of metastases from CRC, with a literature review and meta-analysis of the relevant randomized controlled trials.

Key words: Liver metastases; Adjuvant chemotherapy; Metastasectomy; Colorectal cancer; Adjuvant hepatic artery infusion

Core tip: Surgical resection is the only option of cure for patients with metastatic colorectal cancer (CRC). The risk of recurrence within 18 mo after metastasectomy is about 75% and the liver is the main organ involved. However, there is still no standard treatment and the effective role of adjuvant therapy remains controversial. The aim of this review is to

summarize current knowledge on the role of systemic chemotherapy and regional chemotherapy with hepatic arterial infusion in the management of patients after resection of metastases from CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and is responsible for 8% of cancer-related deaths in men and 9% in women[1].

About 80% of patients with CRC have localized and resectable disease at diagnosis and, depending on the pathological stage, the 5-year survival rate is 90% in stage Ⅰ, 70%-80% in stage Ⅱ and 40%-65% in stage Ⅲ. The risk of recurrence also depends on the pathological stage of the primary tumor (30% in stage Ⅱ and 50% in stage Ⅲ) and is higher within the first two years after surgery[2]. The most frequent sites of CRC recurrence are liver, abdominal lymph nodes, peritoneum and lung. In 30%-40% of patients with advanced CRC, the liver represents the only site of metastases: 25% of these patients present synchronous liver metastases at diagnosis, while 45%-50% of patients with stage Ⅱ-Ⅲ develop liver metastases within two years after the primary resection[3-5]. The current management of unresectable metastatic CRC consists of systemic chemotherapy involving various agents, alone or in combination. The choice of therapy is based on several factors, namely the performance status (PS) of patients and the goals of treatment.

When feasible, surgical resection is the treatment of choice for patients with liver or lung metastases with a survival rate ranging from 25% to 50%[6]. The management of patients with resectable metastatic CRC is a typical example of a multidisciplinary task involving both oncologists and surgeons. In recent years, the availability of even more effective therapeutic regimens together with the improvement of surgical techniques have significantly improved the chance of survival for patients with resectable stage Ⅳ CRC. However, around 75% of patients undergoing metastasectomy develop recurrence within 18 mo after the surgery and the liver is the most frequent site of relapse[7]. Therefore, effective therapeutic strategies to reduce the risk of relapse in this subgroup of patients are urgently needed.

To date, no standard treatments have been established and the effective role of adjuvant therapy remains controversial. In addition, tumor clonal heterogeneity, a hallmark of most human cancers, may complicate the choice of the best adjuvant treatment for CRC[8]. Indeed, the optimal adjuvant therapy for the primary tumor may not be the best treatment for metastases, given that the biological tumor background may significantly differ between primary and metastastic sites[9,10].

The aim of this review is to report the state-of-art on the role of systemic chemotherapy and regional chemotherapy with hepatic arterial infusion (HAI) in the management of patients after resection of metastases from CRC.

SYSTEMIC CHEMOTHERAPY IN CRC

Strategy of systemic treatment in metastatic disease as the backbone of adjuvant therapy

To date, the systemic treatment of advanced CRC has been based on four main cytotoxic agents: fluoropyrimidine [intravenous 5-fluorouracil/leucovorin (5-FU/LV) and oral fluoropyrimidine capecitabine], oxaliplatin and irinotecan. More recently, new biological targeted agents (bevacizumab, cetuximab, panitumumab, regorafenib and aflibercept) have been added to the chemotherapy armamentarium[3,5].

In patients with good PS and without contra-indications, a combination therapy is recommended, whereas a monotherapy should be preferred for elderly patients or those with significant comorbidities or in poor clinical condition. The efficacy of all these agents, alone or in combination, has been supported by studies showing an improvement in overall survival (OS) and response rate (RR) in patients who received systemic treatment. Based on these results, the current international guidelines (European Society for Medical Oncology-ESMO guidelines and National Comprehensive Cancer Network-NCCN guidelines) have recognized at least three lines of therapy, using these agents in various combinations and schedules[3,5]. Several clinical trials have directly compared these treatments, but the large number of potential combinations makes it impossible to define the best therapeutic strategy. However, some key points can help the oncologist select the best chemotherapy for patients with metastatic CRC.

Treatments with 5-FU/LV, oxaliplatin and irinotecan (used sequentially or together upfront) have demonstrated a better outcome in terms of objective response and survival. Some authors showed an increased median OS and a longer progression-free survival (PFS) in patients treated with combinations of 5-FU/LV plus oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), compared with those who received FU/LV alone[11-13]. Subsequently, Grothey *et al*[14] analyzed data from 11 published phase Ⅲ trials to assess the effectiveness of these three chemotherapeutic agents in advanced

CRC. They found that the median OS reported in these trials was significantly correlated with the percentage of patients receiving all three drugs in the course of their treatment. A similar analysis also comprising the targeted therapy is currently lacking. Finally, a randomized trial has shown that the combination of infusional 5-FU/LV, oxaliplatin and irinotecan (FOLFOXIRI) improves the RR, PFS, and OS compared with FOLFIRI. Due to the greater but manageable toxicity, the use of this chemotherapy regime can be limited to a small group of patients based on their PS and the absence of contraindications[15].

The second key point is that oral capecitabine can be used as an alternative to intravenous 5-FU/LV, as demonstrated in some randomized trials[16]. The combination of capecitabine and oxaliplatin (XELOX) may be used as an alternative to 5-FU/LV/oxaliplatin, with similar efficacy and safety[17,18]. The association of capecitabine and irinotecan (XELIRI) has also demonstrated similar results, but it is burdened with greater toxicity than 5-FU/LV/irinotecan and therefore is less used[19].

For biological targeted agents, the presence of activating mutations of KRAS/NRAS/BRAF genes is now considered the main predictor of response to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab, because these mutations confer resistance to these drugs and in some cases may also be associated with a detrimental effect[20-22]. Therefore, mutational analysis of the KRAS/NRAS/BRAF line is important in patients with advanced CRC and the use of cetuximab and panitumumab should be limited to patients in whom a RAS gene mutation is excluded. A recent meta-analysis and the TRIBE trial showed that the association of bevacizumab with different chemotherapy regimens in patients with advanced CRC (compared with patients receiving systemic chemotherapy alone) leads to an improved PFS and OS that could exceed 30 mo[23,24]. Therefore, in the absence of contraindications, bevacizumab plus chemotherapy can be used in both first line and second line regimens in patients not previously treated with anti-angiogenic drugs.

Another key point is that the anti-EGFR drugs should not be combined with bevacizumab, as shown by two randomized trials in which the concomitant use of bevacizumab and cetuximab resulted in a detrimental effect in the combination arm[25,26].

Finally, the treatment strategy for patients with advanced CRC should consider if the disease is potentially curable with a combination of chemotherapy and surgery or merely defensive when the goal of the treatment is only increased survival. In the first case, a combination of multiple drugs (chemotherapy +/- target therapy), referred to as "conversion therapy", is needed to shrink the metastatic tumor mass until it is resectable.

Adjuvant chemotherapy in resectable primary CRC

About 80% of patients with CRC have resectable disease at diagnosis and surgery is the main treatment option with curative intent in these patients[2]. As the risk of recurrence depends on the pathological stage of the primary tumor (30% in stage Ⅱ and 50% in stage Ⅲ), the rationale of adjuvant therapy is generally to reduce this risk, improving the survival rate[2].

Adjuvant systemic chemotherapy is currently recommended for stage Ⅲ CRC patients and for high risk stage Ⅱ, who present at least one of the following negative prognostic factors: contiguity infiltration of neighboring organs (T4b), grading G3, inadequate number of lymph nodes analyzed (12), vascular, lymphatic and/or perineural invasion, clinical presentation with perforation or occlusion[5,27]. In these patients, adjuvant treatment reduces the risk of recurrence by 5% (78.2% *vs* 72.9% of 3-year DFS), with a total gain of 1% survival (87.7% *vs* 86.6% of 3-year OS)[2,28]. The adjuvant chemotherapy regimens are based on therapies that have proven their effectiveness in the advanced setting (Table 1). Conversely, not all treatments commonly used in metastatic disease have maintained their effectiveness when used in the adjuvant setting.

The combination of fluoropyrimidine (5-FU/LV or capecitabine) and oxaliplatin is the adjuvant treatment recommended by the current international guidelines[5,27]. The MOSAIC study randomly assigned 1123 patients to receive 5-FU/LV or FOLFOX4 in the post-operative adjuvant setting[28]. After a 6-year follow-up, the advantage in DFS for patients treated with FOLFOX4 was 73.3% (*vs* 67.4%) with an improvement of OS for patients in stage Ⅲ (72.9% *vs* 68.7%, compared with 5-FU/LV alone treatment)[29]. Similar results were observed in a phase Ⅲ trial (NSABP C-07) evaluating FLOX (bolus of 5-FU/LV plus oxaliplatin) *vs* 5-FU/LV alone[30]. The XELOXA phase Ⅲ study compared XELOX (capecitabine plus oxaliplatin) with bolus 5-FU/LV in stage Ⅲ patients: the 3-year DFS rates were 70.9% and 66.5%, respectively, but after 5 years of follow-up the OS had not yet reached statistical significance (P = 0.14)[31]. In patients with non-optimal PS, monotherapy with fluoropyrimidine can be considered a viable alternative to the doublet chemotherapy and capecitabine has shown a similar efficacy and a better tolerability than intravenous 5-FU/LV[32]. Recently, two Japanese phase Ⅲ trials (JCOG0205, ACTS-CC) showed the safety and efficacy of other oral fluoropyrimidines as adjuvant treatments for patients with resectable CRC[33,34]. The authors demonstrated the non-inferiority of tegafur-uracil/leucovorin (UFT/LV) and S-1 (tegafur-gimeracil-oteracil) to 5-FU/LV in terms of DFS.

According to the efficacy demonstrated in patients with metastatic CRC, the irinotecan-based regimes were also assessed in the adjuvant setting, but

Table 1 Adjuvant systemic chemotherapy after primary resectable colorectal cancer

Trials	No. of patients	Schedules	DFS	*P* value	OS	*P* value
Oxaliplatin-based regimes						
X-ACT	1987	CAPECITABINE (1004)	64.2%	0.12	81.3%	0.07
(Twelves *et al*[32], 2005)		5FU/LV (983)	60.6%		77.6%	
NSABP C-07	2407	5FU/LV (1207)	67.0%	0.0034	-	-
(Kuebler *et al*[30], 2007)		FLOX (1200)	73.2%			
MOSAIC	2246	5FU/LV (1123)	67.4%	0.003	68.7%	0.46
(André *et al*[29], 2009)		FOLFOX4 (1123)	73.3%		78.5%	
XELOXA	1886	XELOX (944)	70.9%	0.045	77.6%	0.15
(Haller *et al*[31], 2011)		5FU/LV (942)	66.5%		74.2%	
Irinotecan-based regimes						
CALGB-89803	1264	Irinotecan + 5FU/LV (635)	59.0%	0.85	64.0%	0.74
(Saltz *et al*[35], 2007)		5FU/LV (629)	61.0%		67.0%	
PETACC-3	2982	Irinotecan + 5FU/LV (1485)	56.7%	0.106	73.6%	0.094
(Van Cutsem *et al*[36], 2009)		5FU/LV (1497)	54.3%		71.3%	
Bevacizumab + chemotherapy						
NSABP C-08	2710	FOLFOX6 + Bevacizumab (1354)	77.4%	0.15	-	-
(Allegra *et al*[37], 2011)		FOLFOX6 (1356)	75.5%			
AVANT	2867	FOLFOX4 + Bevacizumab (960)	73.0%	0.07	81.0%	0.02
(de Gramont *et al*[38], 2012)		FOLFOX4 (955)	76.0%		85.0%	
		XELOX + Bevacizumab (952)	75.0%	0.44	82.0%	0.21
Cetuximab + chemotherapy						
NCCTG NO147	2686	FOLFOX6 + Cetuximab (1349)	71.5%	0.08	72.5%	0.03
(Alberts *et al*[41], 2012)		FOLFOX6 (1337)	74.6%		86.2%	
PETACC-8	337	FOLFOX4 + Cetuximab (169)	60.45	0.60	46.0%	0.064
(Taieb *et al*[42], 2012)		FOLFOX4 (168)	60.7%		36.0%	
Oral flupropyrimidine in monotherapy						
JCOG02051	1092	5-FU/LV (550)	74.3%	0.0236	-	-
(Shimada *et al*[33], 2014)		UFT/LV (551)	73.6%			
ACT-CC[1]	1518	S-1 (758)	75.5%	< 0.01	-	-
(Yoshida *et al*[34], 2014)		UFT/LV (760)	72.5%			

[1]These trials were randomized, controlled non-inferiority studies. 5-FU/LV: 5-fluorouracil/leucovorin; FOLFOX: 5-FU/LV plus oxaliplatin; DFS: Disease-free survival; OS: Overall survival; UFT: Tegafur-uracil.

the results failed to demonstrate any advantage. Two randomized trials (CALGB-89803, PETACC-3) comparing bolus 5-FU/LV plus irinotecan to only 5-FU/LV did not find differences in terms of DFS and OS[35,36].

Bevacizumab has also reached negative results in the adjuvant setting as in the NSABP C-08 trial in which 2710 patients were randomized to receive FOLFOX6 plus Bevacizumab or FOLFOX6 alone[37]. The AVANT study also showed the negative effect of bevacizumab in the adjuvant setting, comparing the outcome of patients treated with FOLFOX4, FOLFOX4 plus bevacizumab and bevacizumab plus XELOX after surgery[38].

Similarly, while cetuximab plus FOLFOX are associated with an increased objective response rate and an improvement of PFS in metastatic CRC compared with the cytotoxic doublets alone[39,40], both NCCTG NO147[41] and PETACC-8 trials[42] demonstrated a detrimental effect of cetuximab in the adjuvant setting. Therefore, both irinotecan-based regime combinations and biological targeted agents should be ruled out in the adjuvant setting of primary CRC.

SURGICAL RESECTION OF METASTASES

Radical surgical resection (R0) is the only option of cure for patients with isolated liver or lung metastases[7]. The median OS of patients after radical surgical resection of liver metastases, upfront or previously treated with a preoperative chemotherapy, ranges from 22 mo to 5 years, with a survival rate of 70% at one year, 36% in 3 years and 25% at 5 years[4,43-48]. However, around 75% of patients develop recurrence within 18 mo after the first resection of CRC metastases and the liver is the most frequent site of relapse[7]. Recent studies have shown that the survival of patients undergoing repeated hepatic resections is comparable to that of the first metastasectomy[49,50], and, in a small case series, the survival benefit of a third hepatectomy seems to be similar to that achieved by the first and second surgery[51,52]. Finally, it has been shown that highly selected metastatic CRC patients can achieve longer survival even after third metastasectomy, compared with patients treated with medical therapy alone[53].

Therefore, over the years, the gain in OS of metastatic CRC patients has been mainly thanks to the improvement of surgical techniques that have revised the definition of respectability, no longer limited by number or size of metastases, improvements to imaging techniques and the integration of pre- and post-operative chemotherapy with more active agents. In recent years, several prognostic scores have been

proposed for a better selection of those patients who may benefit most from the integration of surgery with systemic treatments[54-59].

Some prognostic factors are shared by all scoring scales. In particular, extrahepatic disease, node-positive primary disease, the size and number of hepatic metastases, an interval less than 2 years from primary tumor to metastases and high pre-operative CEA levels have proved unfavorable prognostic factors. However, the predictive value of all these scores has not been assessed in the specific group of patients receiving neoadjuvant chemotherapy before resection of metastases, and recent studies have shown that none of these factors are reliable prognostic tools[60-62]. Even in the era of modern chemotherapy, negative surgical margins remain an important determinant of survival for patients undergoing hepatectomy for CRC liver metastases, but most reports claim the width of a negative surgical margin does not affect outcome[63]. Although there is still no consensus on the definition of R1, the width of surgical margins has been gradually reduced to 0.1 mm. A recent French study showed that in multivariate analysis positive surgical margins (R1 defined as resection below 1 mm) did not constitute a negative prognostic factor of survival *per se*, but may be related to more aggressive disease[64]. Conversely, other studies confirmed the role of resection margin status as an important determinant of OS. Angelsen *et al*[65] reported that resection margins below 5 mm may increase the risk for local recurrence and shorten the time to recurrence. A United States study showed a better 5-year OS in patients who underwent R0 liver resection (tumor-free margin $\geqslant$ 1 mm) compared with R1 resection (< 1 mm)[66]. A more recent analysis by Sadot *et al*[67] compared 2368 patients who underwent R1 (0 mm) or R0 hepatic resection (divided into three groups: 0.1-0.9 mm, 1-9 mm, $\geqslant$ 10 mm) for CRC liver metastases and demonstrated that all margin widths, including sub-mm, correlated with improved OS compared with R1 resection (P = 0.05), whereas there was no significant difference in OS between 1-9 mm and $\geqslant$ 10 mm groups.

Interestingly, wedge resection and anatomic resection yield similar positive surgical margin and recurrence rates, recurrence patterns, and 5-year OS rates, therefore both approaches are considered equivalent for patients with CRC liver metastases[68,69].

In recent years, accumulating evidence on the role of surgery also for lung CRC metastases has shown that, in well-selected patients, resection of solitary liver and lung metastases may provide long-term survival[70,71]. A recent Japanese retrospective study evaluated the clinical outcome of patients undergoing surgical resection of lung metastases, showing a 5-year OS of 65.7% and a 5-year DFS of 35.3%[72]. The main prognostic factors affecting the long-term outcome were negative surgical margins, the absence of mediastinal and hilar lymph node involvement, and a solitary metastasis. Moreover, the 5-year OS may be influenced by the histologic characteristics of the primary tumor or metastases[73-75]. Taken together all these results show that resection of lung metastases may improve the survival rate in well-selected patients with metastatic CRC.

On the basis of all the results outlined above, it is well established that the selection of patients with metastastic CRC eligible for surgery is mandatory to identify those patients with limited and resectable or potentially resectable disease representing the subset of patients who could really benefit from surgery. In the case of patients with upfront resectable disease, the indication for neo-adjuvant chemotherapy is still debated as no OS difference has been found with the addition of peri-operative chemotherapy compared with surgery alone for patients with resectable CRC liver metastases[76]. Patients with potentially resectable disease should be referred to intensive systemic treatments, defined as "conversion therapies", associated with a higher disease RR. However, the impact of pre-operative chemotherapy on the long-term outcome of radically resected metastatic CRC patients is still undefined and neither the type of conventional regimen nor the combined use of targeted agents seems to independently influence outcome following resection[77]. It is noteworthy that pre-operative chemotherapy can induce regimen-specific liver damage, increasing the risk of mortality after liver resection. A retrospective study by Vauthey *et al*[78] evaluated the postoperative outcome of 406 patients after metastasectomy with or without pre-operative chemotherapy (5-FU/LV alone, oxaliplatin + 5-FU/LV, or irinotecan + 5-FU/LV). In pre-operative chemotherapy group, oxaliplatin was associated with sinusoidal injury and irinotecan with steatohepatitis, but only irinotecan-based regimes also increased the 90-d mortality rate compared with surgery alone. These data were confirmed by Pawlik *et al*[79], who found regimen-specific hepatic injury in about 20%-30% of their patients treated with pre-operative chemotherapy.

New surgical techniques have recently been considered to treat patients with a small future liver remnant. Portal vein embolization and two-stage hepatectomy is based on hypertrophy of the future liver remnant caused by contra-lateral portal vein occlusion. The functional reserve of the liver grows within 2-4 wk and the patients may be subjected to subsequent metastasectomy[80,81]. Instead, associating liver partition and portal vein occlusion for staged hepatectomy (ALPPS) combined portal vein ligation with *in situ* parenchymal transaction, reducing the risk of tumor progression during the period of liver regeneration and increasing the resectability rate[82]. A multicenter Italian study showed no significant difference in feasibility between these two surgical techniques, but the overall complication rate was

higher in the ALPPS group[83]. Consequently, ALPPS should be proposed with caution in patients with CRC liver metastases and small functional liver reserve.

In addition to surgical techniques, ablative therapies [such as radiofrequency ablation (RFA), cryosurgery or microwave] can be used as potentially curative treatments for CRC liver metastases. In several studies, the 5-year OS ranged between 20%-30% in patients with advanced CRC who underwent RFA[84,85]. Pawlik *et al*[86]'s study was the first to evaluate the outcome of a large series of patients treated with combined hepatic resection and RFA. More recently, Eltawil *et al*[87] estimated the recurrence rate of 174 patients with CRC liver metastases (24 undergoing liver resection with RFA and 150 undergoing surgery alone). The median OS were 38 mo *vs* 52 mo and the median RFS were 7.4 and 13 mo, without statistically significant differences (P = 0.95 and P = 0.08, respectively). These studies suggested that RFA combined with liver resection may enhance long-term survival in a select group of patients.

To date, no randomized trials have compared RFA and surgery. A recent Cochrane review included 18 studies comparing RFA and any other treatment (10 observational, 7 clinical controlled trials and 1 randomized clinical trial)[88]. These data did not allow any definitive conclusion to be reached and are insufficient to recommend RFA as a radical treatment for CRC liver metastases.

Cryotherapy (in which liquid nitrogen or argon gas is delivered to the liver tumor) is another local ablative technique used to treat patients unsuitable for liver resection, alone or in combination with surgery. A retrospective United States study analyzed 158 patients with CRC liver metastases treated with surgery and/or ablation treatment. The ablation techniques were performed by radiofrequency ablation, cryotherapy and microwave ablation (total: 315 treated tumors). The local recurrence rate in the cryotherapy group was statistically significantly higher than in the RFA group both in univariate and multivariate analysis (P = 0.03 and P = 0.018, respectively)[89].

POST-METASTASECTOMY ADJUVANT SYSTEMIC CHEMOTHERAPY AND META-ANALYSIS

Adjuvant systemic chemotherapy after metastasectomy

The management of CRC patients after surgical resection of metastases is still debated. In these patients, the current international guidelines recommend an adjuvant strategy for 6 mo: postoperative adjuvant chemotherapy or peri-operative chemotherapy (3 mo before surgery and 3 mo after surgery)[3,5]. However, there is no standard treatment and the effective role of systemic adjuvant chemotherapy remains controversial.

The rationale for adjuvant chemotherapy post-metastasectomy is based on several studies (Table 2). The first studies comparing treatment with only controls had several dropouts and low accrual ratios. Langer *et al*[90] studied a group of CRC patients who underwent surgical resection of liver metastases and for the first time they compared metastasectomy alone *vs* metastasectomy followed by systemic 5-FU/LV treatment. DFS and OS were better in the adjuvant chemotherapy arm *vs* the surgery alone arm (4-year DFS was 45%, *vs* 35%, and 4-year OS was 57%, *vs* 47%) but the trial was prematurely closed due to slow accrual and statistical significance was not reached either for OS or PFS (P = 0.35 and P = 0.39, respectively). In another multicenter trial, Portier *et al*[91] randomized 171 patients after hepatic resection of metastases from CRC to control alone or to adjuvant systemic chemotherapy with 5-FU/LV. The authors observed an improvement in DFS for patients treated with 5-FU/LV compared with the control group (24.4 mo *vs* 17.6 mo, respectively, P = 0.028) but no statistically significant difference in OS was observed (P = 0.13). This trial was also stopped because of the slow accrual. A pooled analyses of these two trials showed a marginal statistical significance in favor of adjuvant chemotherapy 5-FU/LV-based regime, independently associated with both PFS and OS[92].

Cytotoxic doublets have also been studied in the adjuvant setting. Nordlinger *et al*[76] randomized 364 patients with resectable liver metastases from CRC. Comparing the combination of surgery and perioperative FOLFOX-4 treatment (6 cycles before and 6 cycles after surgery) with liver resection alone, they showed that the 3-year PFS was better in the chemotherapy group compared with controls. However, the gain in PFS did not affect the long-term OS: at a follow-up of 8.5 years, the median 5-year OS was 51.2% in the peri-operative chemotherapy group *vs* 47.8% in the surgery only group, without a significant difference between the two[93]. Several Japanese studies have examined the efficacy and safety of oxaliplatin-based adjuvant treatments. In a randomized, controlled phase Ⅱ/Ⅲ trial, Kanemitsu *et al*[94] compared hepatectomy followed by m-FOLFOX-6 adjuvant chemotherapy with surgery alone, but the final results are not yet available. Another two studies (a retrospective cohort study and a phase Ⅱ non-controlled clinical trial) suggested that adjuvant chemotherapy after metastasectomy provides a benefit in DFS[95,96]. The same comparison was evaluated by Kim *et al*[97] in an uncontrolled study analyzing 60 patients who underwent oxaliplatin-regimen postoperative chemotherapy. In another study, the same authors compared the clinical outcomes of 156 patients treated with different chemotherapeutic regimes after metastasectomy from CRC: oxaliplatin/fluoropyrimidine (group Ⅰ), irinotecan/fluoropyrimidine (group Ⅱ) and fluoropyrimidine alone (group Ⅲ). The median DFS was 23.4 mo in group Ⅰ, 14.1 mo in group Ⅱ and 16.3 mo in group Ⅲ (P = 0.03).

Table 2 Systemic adjuvant chemotherapy studies after metastasectomy

Ref.	No. of patients	Setting	Randomized study	Regimes of chemotherapy	Outcomes		
					DFS	PFS	OS
Controlled studies							
Langer *et al*[90], 2002	arm2 = 55 *vs* arm1 = 52	Phase Ⅲ	YES	5-FU/LV *vs* surgery + 5-FU/LV (arm2 *vs* arm1)	4-yr DFS: 35% *vs* 45% (*P* = 0.35) HR = 1.28 (95%CI: 0.76-2.14)	-	4-yr OS: 47% *vs* 57% (*P* = 0.39) HR = 1.30 (95%CI: 0.71-2.36)
Portier *et al*[91], 2006	171 (86 *vs* 85)	Phase Ⅲ	YES	5-FU/LV *vs* surgery alone	5-yr DFS: 33.5% *vs* 26.7% (*P* = 0.028) HR = 0.66 (95%CI: 0.46-0.96)	-	5-yr OS: 51.1% *vs* 41.9% (*P* = 0.13) HR = 0.73 (95%CI: 0.48-1.10)
Mitry *et al*[92], 2008	278 (138 *vs* 140)	Pooled analysis of two phase Ⅲ studies	YES	5-FU/LV *vs* surgery alone	Median DFS: 27.9 mo *vs* 18.8 mo (*P* = 0.058) 5-yr DFS: 36.7% *vs* 27.7% HR = 0.76 (95%CI: 0.57-1.01)	-	Median OS: 62.2 *vs* 47.3 mo (*P* = 0.095) 5-yr OS: 52.8% 39.6% HR = 0.76 (95%CI: 0.55-1.05)
Kanemitsu *et al*[94], 2009	300	Phase Ⅱ/Ⅲ	YES	FOLFOX6 *vs* surgery alone	In progress (results not yet available)		
Ychou *et al*[99], 2009	306 (153 *vs* 153)	Phase Ⅲ	YES	FOLFIRI *vs* 5-FU/LV	2-yr DFS: 50.7% *vs* 46.2% (*P* = 0.44) HR = 0.89 (95%CI: 0.66-1.19)	-	3-yr OS: 72.7% *vs* 71.6% (*P* = 0.69) HR = 1.09 (95%CI: 0.72-1.64)
Kim *et al*[98], 2009	156 [58 + 48 + 50]	Retrospective	NO	Oxaliplatin regimes (group Ⅰ); Irinotecanregimes (group Ⅱ) or Fluoropyrimidine alone (group Ⅲ)	Median DFS: 23.4, 14.1 and 16.3 mo (respectively, *P* = 0.088) HR group1 *vs* 3: 0.63 (95%CI: 0.39-1.03) HR group2 *vs* 3: 0.98 (95%CI: 0.61-1.56)	-	Median OS: 51.2, 47.9 and 60 mo (respectively, *P* = 0.219)
Liu *et al*[100], 2010	50 [31 (17 + 14) *vs* 19]	Retrospective	NO	FOLFOX/FOLFIRI *vs* 5-FU/LV	3-yr DFS: 50.8% *vs* 21.1% (*P* = 0.022) HR = 0.37 (95%CI: 0.15-0.94)	-	3-yr OS: 85.7% *vs* 51.8% (*P* = 0.027) 5-yr OS: 54.0% *vs* 34.6% (*P* = 0.027) HR = 0.27 (95%CI: 0.083-0.86)
Snoeren *et al*[106], 2010				CAPOX + Bevacizumab *vs* CAPOX alone	In progress (results not yet available)		
Kemeny *et al*[104], 2011	73 (35 *vs* 38)	Phase Ⅱ	YES	HAI/systemic therapy + BEVA *vs* HAI/ systemic therapy alone	4-yr DFS: 71% *vs* 83% (*P* = 0.4)	-	4-yr OS: 81% *vs* 85% (*P* = 0.5)
Brandi *et al*[101], 2013	151 (78 *vs* 73)	Cohort study	NO	Oxaliplatinregimes or Irinotecan regimes *vs* surgery alone	Median DFS: 16 *vs* 9.7 mo (*P* = 0.014) 5-yr DFS: 17.4% *vs* 10.5% (*P* = 0.82) HR = 0.64 (95%CI: 0.46-0.90)	-	Median OS: 42 *vs* 39 mo (*P* = 0.8)
Turan *et al*[105], 2013	204 (87 *vs* 117)	Cohort study	NO	Irinotecan regimes or oxaliplatin regimes + bevacizumab *vs* chemotherapy alone	Median DFS: 14 *vs* 18 mo (*P* = 0.37)	-	Median OS: 43 *vs* 54 mo (*P* = 0.25)
Nordlinger *et al*[93], 2013[1]	364 (171 *vs* 152)	Phase Ⅲ study	YES	Peri-operative FOLFOX4 *vs* surgery alone	-	3-yr PFS: 38.2% *vs* 30.3% (*P* = 0.0068) HR = 0.81 (95%CI: 0.64-1.02)	5-yr OS: 51.2% *vs* 47.8% (*P* = 0.3) HR = 0.88 (95%CI: 0.68-1.14)
Primrose *et al*[107], 2014[1]	236 (119 *vs* 117)	Phase Ⅲ	YES	FOLFOX/CAPOX + cetuximab *vs* FOLFOX/CAPOX alone	-	Median PFS: 14.1 *vs* 20.5 mo (*P* = 0.03) HR = 1.48 (95%CI: 1.04-2.12)	Median OS: 39.1 *vs* 32 mo (*P* = 0.16) HR = 1.49 (95%CI: 0.86-2.60)

Kobayashi *et al*[102], 2014	177 (88 *vs* 89)	Phase Ⅲ	YES	UFT/LV *vs* surgery alone	-	3-yr PFS: 38.6% *vs* 32.3% (*P* = 0.003) HR = 0.56 (95%CI: 0.38-0.83)	3-yr OS: 82.8% *vs* 81.6% (*P* = 0.41) HR = 0.80 (95%CI: 0.48-1.35)
Non controlled studies							
Kim *et al*[97], 2011	60	Single armed	NO	FOLFOX6	Median DFS: 32.8 mo (95%CI: 5.8-59.6) 5-yr DFS: 39.20%	-	Median OS: 62.8 mo (95%CI: 44.1-81.3) 5-yr OS: 55.5%
Kato *et al*[103], 2015	60	Single armed	NO	S-1	1-yr DFS: 68.30% 3-yr DFS: 47.40%	-	1-yr OS: 96.70% 3-yr OS: 80%
Nakayama *et al*[95], 2015	88	Single armed	NO	Oxaliplatin regimes	3-yr DFS: 54%	-	-
Katayose *et al*[96], 2015	49	Phase Ⅱ single armed	NO	mFOLFOX6	2-yr DFS: 59.20%	-	-

[1]The primary end-point was PFS because these studies evaluated the role of peri-operative chemotherapy, but some patients became ineligible for surgical treatment during the study. 5-FU/LV: 5-fluorouracil/leucovorin; FOLFOX: 5-FU/LV plus oxaliplatin; DFS: Disease-free survival; PFS: Progression-free survival; OS: Overall survival; UFT: Tegafur-uracil.

Therefore, oxaliplatin-based adjuvant chemotherapy seems to show a better DFS than the other two chemotherapeutic regimes, confirming the inefficacy or detrimental effect of irinotecan in the adjuvant setting post-metastasectomy, as already observed in the adjuvant setting after primary resection[98].

Other studies have evaluated the use of adjuvant irinotecan-based chemotherapy after hepatic resection of liver metastases from CRC. In a phase Ⅲ study, Ychou *et al*[99] studied 306 patients treated with two different adjuvant chemotherapy regimens: FOLFIRI *vs* 5-FU/LV. Although the median DFS was 24.7 mo in the FOLFIRI group (*vs* 21.6 mo), this difference was not statistically significant (*P* = 0.44). Their study showed that the use of FOLFIRI after R0 resection added no benefit compared with only 5-FU/LV. Conversely, a retrospective study by Liu *et al*[100] showed that FOLFOX/FOLFIRI chemotherapy was associated with an improvement in DFS and OS compared with 5-FU/LV treatment alone. The median DFS was 34.3 mo and the median OS was 57.7 mo for patients treated with FOLFOX/FOLFIRI, *vs* 14.2 mo and 49 mo in the control group.

A recent study by our group analyzed 151 patients from two Italian centers, who underwent R0 resection of CRC liver or lung metastases (131 and 20 patients respectively): 78 patients received adjuvant chemotherapy for 6 mo after surgery and 73 underwent observation alone. The median DFS was 16 mo for patients treated with adjuvant chemotherapy, *vs* 9.7 mo for patients who underwent observation alone (*P* = 0.014). However, there were no differences in OS between the two groups of patients, probably due to the small sample size of the study[101].

Some recent studies have suggested the potential efficacy of other oral fluoropyrimidines also in the adjuvant setting post-metastasectomy. A phase Ⅲ trial (UFT/LV trial) randomized 180 patients after metastasectomy to receive adjuvant UFT/LV chemotherapy or surgery alone. The 3-year DFS was 38.6% in UFT/LV group and 32.3% in surgery group (*P* = 0.003), while a not yet significant difference in the 3-year OS was observed (82.8% *vs* 81.6% respectively, *P* = 0.41)[102]. N-SOG 01 was an uncontrolled single-arm study reporting the outcome of 60 patients treated with adjuvant S-1 chemotherapy after resection of CRC liver metastases: the 1-year and 3-year DFS were 68.3% and 47.4%, respectively, and 1-year and 3-year OS were 96.7% and 80%[103].

A combination of biological targeted agents and chemotherapy improved the outcomes of metastatic CRC, whereas there is no evidence supporting their use in the adjuvant setting after metastasectomy. Kemeny *et al*[104] randomized 73 patients who underwent liver resection to adjuvant HAI plus systemic therapy with bevacizumab (BEV) or without bevacizumab (NoBEV). With a median follow-up of 30 mo, 4-year survival was 81% in patients treated with BEV *vs* 85% in the NoBEV group (*P* = 0.5). Therefore, the addition of BEV to HAI plus systemic chemotherapy does not improve survival, while the combination seems to be associated with an increased biliary toxicity. In a retrospective analysis by Turan *et al*[105], 204 patients who underwent resection of liver metastases were treated with fluoropyrimidine-based, irinotecan-based or oxaliplatin-based regimes, combined with or without BEV. The median OS and the median recurrence-free survival rates were similar in the BEV and NoBEV groups (*P* = 0.25 and *P* = 0.37, respectively). This study showed that there was no survival benefit of adding BEV to chemotherapy, and no difference between the various chemotherapy regimens. More recently, a randomized (still in progress) phase Ⅲ trial compared the combination of BEV plus capecitabine + oxaliplatin (CAPOX) *vs* CAPOX alone as adjuvant treatment post-radical resection of liver metastases[106].

Finally, a phase Ⅲ clinical trial randomized 236 WT-KRAS patients to receive chemotherapy with or

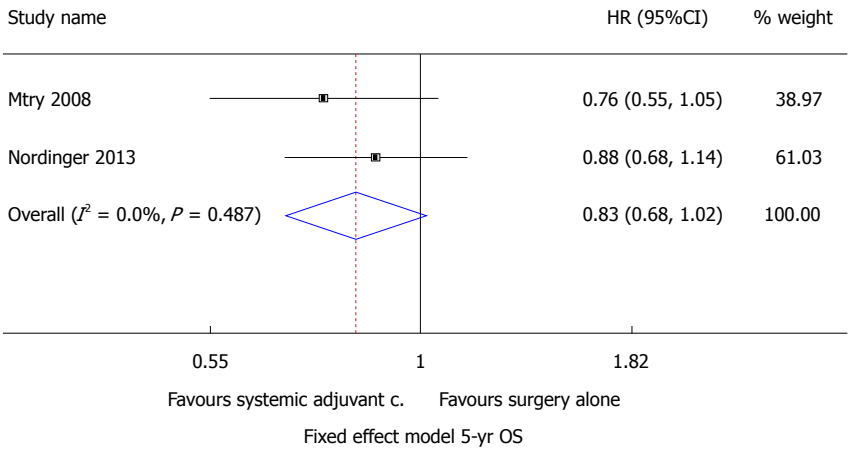

Figure 1 Meta-analysis of the effects of systemic adjuvant chemotherapy studies after metastasectomy *vs* surgery alone (outcome, 5-year OS). The tegafur-uracil/leucovorin trial is not included in the meta-analysis because the follow-up period is not yet completed. Fixed effect model.

without cetuximab before and after liver resection. PFS was 14.1 mo in the chemotherapy plus cetuximab group and 20.5 mo in the chemotherapy alone group, similarly to what happens in the adjuvant setting of primary CRC surgery. These results confirm the detrimental effect of cetuximab in the adjuvant post-metastasectomy setting, being associated with a shorter PFS[107].

Meta-analysis of randomized controlled studies

To better understand the role of adjuvant systemic therapy, we used Stata 12 SE (Stata Corporation, Texas, TX, United States) to perform a meta-analysis based on the only three randomized controlled trials. We pooled data judged to be homogeneous based on type of treatment, type of study, regime of chemotherapy and control group. The results were presented separately for types of outcome. In addition, we tested for statistical heterogeneity by means of the χ^2 test. We considered a *P*-value less than 0.10 to indicate whether there was a problem with heterogeneity. Moreover, we quantified the degree of heterogeneity using the I^2 statistic, where an I^2 value of 25% to 50% indicated a low degree of heterogeneity, 50%-75% a moderate degree of heterogeneity, and $\geqslant$ 75% a high degree of heterogeneity[108]. Individual studies were pooled if sufficient data were available. When studies were statistically heterogeneous, they were combined using a random-effects model; otherwise, a fixed-effect model was used. The effect size was expressed as HR along with the 95%CI for all estimates (Figure 1). Although the analysis did not reach statistical significance (HR = 0.83: 95%CI: 0.68-1.02, P = 0.07), these data demonstrated a benefit of adjuvant therapy post-metastasectomy compared to surgery alone. Further studies are needed to confirm these findings.

POST-METASTASECTOMY ADJUVANT HAI

Several studies have evaluated the role of HAI in the adjuvant treatment of liver metastases from CRC after curative resections. The rationale for HAI is that the normal liver parenchyma receives blood from the hepatic vein, while the blood flow to tumors derives from the branches of the hepatic artery. Moreover, the direct infusion of chemotherapy into the liver minimizes the side-effects of the chemotherapy and allows high doses to be administered[109]. Floxuridine (FUDR), a derivate of 5-FU, plus dexamethasone are the chemotherapeutic agents most frequently used in HAI and different systemic chemotherapies have been administered with HAI in the adjuvant setting (Table 3)[110].

In a randomized phase Ⅱ trial, Kemeny *et al*[111] studied 156 patients who underwent resection of hepatic metastases: 72 received HAI-FUDR plus systemic chemotherapy (5-FU with or without LV) and 82 received systemic chemotherapy alone. The median OS was 72.2 mo in the HAI group *vs* 59.3 mo in monotherapy group, with survival rates at 2 years of 86% and 72% respectively. The 2-year actuarial rates of overall PFS were 57% in the combined therapy group and 42% in the chemotherapy alone group. Recently, the same authors re-analyzed these results after a median follow-up of 10 years and showed that the PFS of patients treated with combined-therapy was 31.3 mo compared with 17.2 mo in the group treated with systemic chemotherapy alone. However, no statistically significant difference was observed for median OS (68.4 mo *vs* 58.8 mo respectively, P = 0.10)[112]. A retrospective study compared the outcome in patients receiving oxaliplatin-based or irinotecan-based chemotherapy (5-FU/LV + oxaliplatin

Table 3 Hepatic arterial infusion plus systemic chemotherapy in the adjuvant setting

Ref.	Numbers of patients	Setting	Randomized study	Regimes of therapy	Outcomes		
					DFS	PFS	OS/DSS
Controlled studies							
Ota *et al*[115], 1999	84 (37 *vs* 47)	Cohort study	NO	HAI/5-FU *vs* control group	5-yr DFS: 72.6% *vs* 29.8% (P = 0.0005)	-	5-yr OS: 61.4% *vs* 28% (P = 0.0069)
Kemeny *et al*[112], 2005	156 (74 *vs* 82)	Phase Ⅲ	YES	HAI/FUDR plus systemic 5-FU ± LV *vs* systemic 5-FU ± LV alone	-	Median PFS: 31.3 *vs* 17.2 mo (P = 0.02)	Median OS: 68.4 *vs* 58.8 mo (P = 0.10)
House *et al*[113], 2011	250 (125 *vs* 125)	Cohort study	NO	HAI/FUDR plus systemic chemotherapy (5FU/LV + irinotecan or oxaliplatin) *vs* systemic chemotherapy alone	5-yr DFS: 48% *vs* 25% (P < 0.01) HR = 0.71 (95%CI: 0.48-0.96)	-	5-yr DSS: 75% *vs* 55% (P < 0.01) HR = 0.39 (95%CI: 0.23-0.68)
Goéré *et al*[116], 2013	98 (44 *vs* 54)	Cohort study	NO	HAI/oxaliplatin plus systemic 5-FU/LV *vs* systemic irinotecan regimes or oxaliplatin regimes alone	3-yr DFS: 33% *vs* 5% (P < 0.0001) HR = 0.37 (95%CI: 0.23-0.60)	-	3-yr OS: 75% *vs* 62% (P = 0.17) 5-yr OS: 54% *vs* 52% (P = 0.34)
Non controlled studies							
Alberts *et al*[114], 2010	55	Phase Ⅱ single armed	NO	HAI/FUDR plus systemic capecitabine + oxaliplatin	2-yr DFS: 59.7% Median DFS: 32.7 mo	-	2-yr OS: 89.10%

DFS: Disease-free survival; PFS: Progression-free survival; OS: Overall survival; DSS: Disease-specific survival.

or 5-FU/LV + irinotecan) with or without HAI-FUDR after metastasectomy. The findings showed that HAI plus systemic chemotherapy was associated with an improvement in both DFS and disease-specific survival (DSS) rates: 5-year DFS was 48% (*vs* 25% in chemotherapy alone group) and DSS was 76% (*vs* 55%)[113]. Moreover, a recent phase Ⅱ trial assessed the potential benefit of HAI-FUDR combined with systemic oxaliplatin and capecitabine, showing a median DFS of 32.7 mo[114], but these findings need to be confirmed by phase Ⅲ studies.

Besides FUDR, other chemotherapeutic agents have been used in the context of HAI. Ota *et al*[115] studied 84 patients who underwent surgical resection of liver metastasis and were then treated with arterial infusion of 5-FU. The 5-year liver DFS was 72.6% in the HAI group (*vs* 29.8% in the control group; P = 0.0005) and the 5-year survival ratio was 61.4% (*vs* 28.0%; P = 0.0069). More recently, Goéré *et al*[116] demonstrated a better 3-year DFS in patients who received postoperative HAI with oxaliplatin plus systemic 5-FU therapy in comparison with patients who received systemic chemotherapy alone (33% *vs* 5%, respectively). After a median follow-up of 60 mo, 3-year OS was also higher in the HAI group, but no statistically significant difference was observed (75% *vs* 62%, P = 0.17). A Cochrane review of 7 randomized controlled trials showed no significant advantage for adjuvant HAI compared with systemic therapy alone in a pool of 592 patients who underwent metastasectomy[2].

To date, the use of HAI in the adjuvant setting has not demonstrated a significant difference in term of OS, also due to the increasing efficacy of the new systemic chemotherapy regimens. HAI, however, could be employed only to achieve a better DFS.

CONCLUSION

The decision to implement an adjuvant treatment after resection of metastases from CRC is becoming a major challenge in oncology because the positive role of metastasectomy has been definitely ascertained in patients with advanced CRC in the last decade and the number of these patients is increasing. An ideal study would compare the putative most effective adjuvant therapy post-metastasectomy *vs* surgery alone, stratifying resected patients also on the basis of the risk of recurrence. However, this study is currently unlikely due to the high dropout rate it would incur.

Nonetheless, the data obtained from controlled studies (cohort or randomized studies) on systemic treatment allow us to draw some important conclusions: (1) a systemic chemotherapy with 5-FU +/- oxaliplatin seems to confer an advantage in terms of survival, also supported by the meta-analysis presented in this paper; and (2) not all active drugs in advanced disease appear to be effective in the adjuvant setting. In particular, studies that have used irinotecan-based regimes were negative. However, this aspect should be confirmed in larger series, taking into account the biological heterogeneity between primary tumors and their metastases.

Ultimately, on the basis of all the available data, adjuvant chemotherapy post-metastasectomy should be recommended.

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