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Review

Modern insights into hepatic arterial infusion for liver metastases from colorectal cancer

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ABSTRACT

Hepatic arterial infusion (HAI) selectively achieves high drug exposure of liver metastases from colorectal cancer. Such pharmacologic advantage has doubled the response rate of liver metastases on fluoropyrimidines (FP) delivered as HAI rather than intravenously, in a meta-analysis of randomised clinical trials (RCT). However, the improvement in antitumour efficacy did not consistently translate into any significant survival advantage across all randomised studies. However, the results of this meta-analysis should be cautiously interpreted due to the heterogeneity of the studies, inadequate study designs, obsolete therapy and high rate of early treatment discontinuation due to HAI technical failures or hepato-biliary toxicity. Most studies actually were performed before year 2000 and did not integrate the considerable progresses accomplished in the management of CRC, such as multidrug regimens instead of single agent FP and secondary resection of metastases, a major contributing factor for prolonged survival. Furthermore, the systemic exposure of patients given HAI was low without concomitant IV therapy, facilitating extra-hepatic relapses. The role of HAI in liver metastases from CRC should, therefore, be revisited, using modern multidisciplinary therapeutic approaches and appropriate study designs. Recommendations for the design of future RCTs exploring HAI are provided.

1. Introduction

Metastases are confined to the liver in 30–60% of the patients with metastatic colorectal cancer (mCRC).[1,2] Uncontrolled growth of hepatic metastases is fatal in patients with predominant liver metastases. Thus, most patients whose metastases are not resected die within 5 years of metastatic disease onset.[3,4] Complete surgical resection of metastases is, therefore, the only curative treatment for these patients.[4] Systemic chemotherapy is the standard of care that prolongs overall survival in patients with unresectable metastatic disease. Secondary resection after downstaging of initially unresectable metastases with systemic chemotherapy plays an important role in life prolongation and remains potentially curative.[5] It is, therefore, a primary objective of therapy in fit patients with mCRC.

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Hepatic arterial infusion (HAI) has been an appealing investigational method over the last 3 decades for patients with mCRC confined to the liver, in whom it has reproducibly yielded higher response rates than IV therapy. HAI offers theoretical advantages over standard intravenous (IV) administration of drugs. However, all randomised trials assessing this technique, using fluoropyrimidine (FP) alone, have not consistently improved survival outcomes.[6] Nevertheless the benefit of HAI, which is still giving raise to passionate debates,[7–9] should be revisited in the current era of multiple-drug armamentarium and multidisciplinary strategy against mCRC.

2. Why HAI should work?

Like any locoregional therapy, HAI provides high drug exposure of the tumour at first passage, capable of overcoming some drug resistance mechanisms, such as drug efflux. However, to be clinically relevant, therapy with HAI should preferentially expose tumour cells to high drug concentrations, while both extra-hepatic tissues and healthy hepatocytes are relatively protected.

2.1. *Metastatic spread peculiarity of CRC*

Necropsy studies have shown that liver deposits are a compulsory first visceral step in the metastatic spread of CRC.[2,3,10] Hence there is a therapeutic slot in the CRC natural history, when metastatic disease is still confined to the liver and the disease still at a locoregional stage. This explains why complete resection of liver metastases may be curative, even in the absence of any systemic therapy, when it is performed before further metastatic spread beyond the liver has occurred. Thus, when isolated liver metastases are not resectable, HAI administration of drugs is a logical method of locoregional disease control. Furthermore, even when the disease has spread beyond the liver, e.g. small lung deposits coexisting with large hepatic metastases, the patient's life is immediately threatened by metastatic progression in the liver. Thus, effective locoregional hepatic therapy theoretically could still prolong survival.

2.2. *Anatomic opportunity*

While newly arising, microscopic liver metastases, as well as normal liver, are preferentially irrigated by the portal venous blood flow, established macroscopic metastases are preferentially fed by the hepatic arterial blood supply.[11,12] Delivering drugs via the hepatic artery results in a higher exposure of, and a higher drug clearance by, tumour cells, compared to normal hepatocytes and, consequently, yields a more selective killing of cancer cells.

2.3. *Pharmacological condition: Drugs with high hepatic clearance*

Drugs to be used via HAI should have a high first-passage hepatic clearance, responsible for a low systemic exposure allowing for dose increment and even higher local exposure.[13] In this respect, floxuridine (FUDR), a prodrug of fluorouracil (5-FU) with a hepatic extraction rate >90% that results in a hepatic/systemic ratio of 100–400 is more suitable for HAI than 5-FU with a hepatic extraction rate <50% and a hepatic/systemic ratio around 10.[7] Similarly, Munck et al. reported very elegant results with pirarubicin (P), a doxorubicin analogue with a much higher cellular uptake than the parent compound.[14] In a rabbit VX2 tumour model, they showed that HAI administration of P resulted in intra-tumour drug concentration 10-fold higher than IV administration, while HAI doxorubicin resulted in intra-tumour concentration only twice that achieved with the IV route. Furthermore, systemic exposure after HAI P, including heart exposure, was much lower than after IV P, HAI or IV doxorubicin. Similar results were reported in the same animal model with oxaliplatin, compared to cisplatin.[15] HAI of oxaliplatin achieved higher tissue concentrations than IV oxaliplatin, HAI or IV cisplatin.

3. Proof of concept

Randomised clinical studies comparing HAI to IV FP have consistently shown a significantly higher response rate with the HAI route. In the meta-analysis of all published randomised trials, the response rate was 42.9% with HAI, versus 18.4% with the IV route. Achieving a response was 2.26-fold more likely with HAI than with IV infusion ($p < 0.0001$).[6,7] This major difference shown in these old studies offers a proof of principle that the theoretical advantages of the HAI route actually translate into a higher clinical activity of fluoropyrimidines.

An advantage in terms of overall survival was shown in only three studies of the meta-analysis.[16–18] This advantage should be interpreted cautiously for the two oldest trials, because many patients in the control arm did not receive systemic chemotherapy. In turn, in the most recent CALGB trial,[18] all patients of the control arm were given systemic chemotherapy and the survival advantage observed is an important argument in favour of HAI.

In clinical studies testing HAI pirarubicin in patients with mCRC to the liver,[19–21] response rates >30% were reported, which are impressive considering the well-established resistance of CRC cells to anthracyclines. In addition the authors confirmed a 4-fold decrease in systemic exposure to P given via the HAI route compared to the IV route in humans. P-glycoprotein-driven drug efflux is probably the clinically predominant mechanism of anthracycline resistance.[22] Clinical responses concomitant to high drug concentration within tumour cells is, therefore, consistent with drug resistance reversal due to drug efflux pump saturation. In the pirarubicin model, clinical data have, therefore, confirmed the relevance of the findings established in animal models.

4. Why has the benefit of HAI not been clearly demonstrated so far?

Despite the accumulation of clues of clinically meaningful activity, HAI of drugs has not been validated yet as a standard therapy in mCRC. In 1996 a first meta-analysis including the first six published randomised studies testing HAI concluded

to significant higher response rate and longer survival of patients given HAI versus those given "no HAI".[23] But patients who did not receive HAI included a high proportion of patients receiving only supportive care. When patients receiving HAI were compared to patients actually receiving IV chemotherapy, only a non-significant trend for a longer survival was observed.[23] In the most recent meta-analysis, including the mature results of the previous studies, plus four additional randomised clinical trials,[6,7] 7 of the 10 studies did not report an improved survival, and the meta-analysis did not show a significant survival advantage, in spite of a significantly higher response rate. However, the results of this meta-analysis should be interpreted with caution due to the heterogeneity of the studies, widely discussed in the publication,[6] but also to inadequate study designs, obsolete therapy or high rate of HAI technical failures.

First, the studies were published between 1987 and 2006 and the majority of patients (in seven studies) were treated before 2000. This explains why fluoropyrimidines alone were used, including in the IV control arms, rather than modern multidrug regimens. At the time when the patients were entered into the studies, resection of metastases after downstaging by chemotherapy, in patients with initially non-resectable disease, was not a common practice in all participating centres, notably because significant tumour shrinkage seldom occurred with single agent FP. The rate of secondary surgical resection is not even mentioned in the published results of most studies. This may be the major reason why most of these randomised studies have failed to show a survival advantage, as the prolongation of survival observed with standard IV irinotecan- or oxaliplatin-based regimens over FP alone is at least partly related to higher resection rate as a consequence of higher response rate. The recent results reported by Kemeny et al., using HAI FUDR plus systemic irinotecan and oxaliplatin, suggest that, when HAI is performed in specialised centres, as many as 47% of patients, even with extensive disease may undergo liver resection.[24]

Second, any actual benefit from HAI chemotherapy in terms of locoregional disease control may have been offset by a deleterious effect of lower systemic drug concentration on extra-hepatic disease progression. Patients treated with FP single drug HAI actually had fewer hepatic progressions but more extra-hepatic progressions than patients given IV FP in randomised trials included in the meta-analysis.[25–27] Moreover, in the oldest studies included in the meta-analysis, small lung deposits at baseline were probably not detected in the absence of spiral, or even standard, CT-scan of the lungs. The combination of HAI and IV FP is feasible and was shown to prolong overall survival and even time to hepatic progression over HAI alone in one small randomised study,[28] whereas no difference was found in a retrospective observational study.[29]

Third, FP single agent HAI is likely to be a suboptimal regimen. While IV standard doublet regimens have been proven superior to IV single agent 5-FU and regularly yield similar or higher response rates than the 42.3% reported with HAI fluoropyrimidine,[30–33] it can be reasonably expected that multidrug HAI chemotherapy would be superior to single agent HAI.

Fourth, toxicity of FP HAI was considerable, especially chemical hepatitis, biliary sclerosis and gastroduodenal ulcus/gastroduodenitis[34] often leading to treatment discontinuation and suboptimal treatment duration. Gastrointestinal complications of HAI were responsible for a very variable rate of study treatment discontinuations across studies of the meta-analysis, from 5%[27] to as many as 52%.[35] Sclerosing cholangitis, mainly associated with FUDR use, is the other side of the coin of high hepatic extraction and high biliary concentration of FP metabolites. It can be a very severe and potentially lethal complication of FP HAI.[36–38]

Fifth, placement failures of the intra-arterial catheter or further complications (catheter obstruction, hepatic artery thrombosis or dissection, catheter leakage, bleeding /infection of the pump pocket, and extra-hepatic perfusion, responsible for gastroduodenal ulcus) have also limited the benefit of the technique and adversely influenced the outcome of patients randomised in the HAI arms of the studies. In one negative multicentre randomised study included in the meta-analysis, the rate of initial catheter placement failure was as high as 37%, while further catheter failure leading to early treatment discontinuation occurred in an additional 29% of patients.[39] It is clear that any actual benefit of HAI can be hardly demonstrated using an intent-to-treat analysis with such a high rate of HAI technical failure. In a large literature review among 4580 cases, hepatic artery occlusion occurred in 6%, catheter thrombosis in 5% and catheter displacement in 7% of patients.[34] Nevertheless, the incidence of catheter complications decreases over time, in experienced versus other centres[26] and with surgeon experience.[40]

Sixth, crossover to HAI was allowed after failure of IV therapy in four of the 10 studies and may have erased a slight survival advantage for patients randomised to HAI, though the result of the meta-analysis did not change when only studies not allowing crossover were taken into account.[7]

Last, it is possible that HAI benefits only to some patient subsets. As a matter of example, a study of the benefit of preoperative HAI versus IV chemotherapy suggested that HAI would benefit more to patients with a high liver tumour burden.[41] Although the meta-analysis has not shown a benefit in any subgroup studied, including that with liver replacement $\geqslant$25%, one cannot exclude, as underlined by the authors[7], that a benefit in a subset of patient would have been ignored due to the low power of the meta-analysis.

5. Why is HAI still an exciting experimental approach?

Both the therapeutic approach and the study design of previous randomised studies are now obsolete and the negative results of their meta-analysis should not discourage further assessment of HAI benefit (Table 1).

(1) One positive, but consistent finding in randomised studies having assessed HAI in mCRC, is the higher response rate of liver metastases achieved with HAI, compared to similar chemotherapy, given intravenously. These data are of paramount importance nowadays, while multidisciplinary approach of mCRC

Table 1 – Plea for pursuing clinical assessment of HAI therapy in liver predominant metastatic colorectal cancer.

Facts and consensus: treatment of liver metastases from CRC	Why previous clinical trials failed to validate HAI?	Why forthcoming clinical trials should succeed?
R0/R1 resection = the only chance for cure/prolonged survival in both resectable and unresectable patients	Resection of metastases seldom attempted in older studies	Maximal resection attempt = current SOC for fit patients (generalisation of multidisciplinary team practice in GI oncology)
Standard IV doublet regimens > IV fluoropyrimidine alone (RR, PFS and/or OS)	Suboptimal single agent fluoropyrimidine both IV and HAI	IV combination regimens ± targeted agents = current SOC = reference therapy arm
HAI > IV for single agent fluoropyrimidine (RR and resectability of initially non-resectable disease)		Optimised HAI chemotherapy regimens tolerable and yielding higher RR & greater tumour shrinkage magnitude
	Suboptimal systemic exposure using drugs with high hepatic extraction	Combination of IV SOC + HAI regimen = investigational therapy arm
	Suboptimal treatment duration due to high rate of toxicity-related early treatment discontinuation	Modern HAI regimens better tolerated than FUDR (no biliary sclerosis)
	Catheter placement failures and suboptimal treatment duration due to catheter-related technical issues	Improvement of catheter placement techniques in a growing number of experimented centres. Increasing use of PC catheter placement in non-surgical patients
	Crossover to HAI of patients failing on IV therapy	Prospectively planned subgroup analysis of patients without crossover and simulated analysis of OS without crossover
	Underpowered studies/non-stratified randomisation	Adequately powered studies and randomisation stratification allowing for prognostic subgroup analyses

CRC: colorectal cancer; R0/R1: micoscopically/macroscopically complete resection; RR: response rate; PFS: progression-free survival; OS: overall survival; HAI: hepatic arterial infusion; IV: intravenous; SOC: standard of care; PC: percutaneous.

therapy is the rule. Given that complete resection of the metastases is the only hope for cure, or more humbly, for prolonged survival, even in patients with initially unresectable disease, the current primary objective in these patients is to achieve not only the highest response rate, that has been shown to be correlated with the resection rate with systemic chemotherapy,[42] but also the highest magnitude of individual tumour shrinkage. Furthermore, HAI chemotherapy has been associated with a 6-fold increased probability of pathological complete response in patients with liver metastases that had disappeared on therapy.[43] HAI of drugs remains a very attractive technique in this respect, especially in patients with large tumour burden. HAI allows the resection of up to 50% of adequately selected first-line patients with initially unresectable metastases[24,42] and could be an effective salvage regimen in patients having failed previous IV chemotherapy.[44,45] Thus, forthcoming clinical trials should include resection rate as a major study end-point in patients with unresectable disease.

(2) Suboptimal systemic exposure with higher rate of extra-hepatic progression is probably the major drawback of exclusive HAI therapy. Comparing HAI to IV therapy or supportive care, was an inappropriate study design. Future study should ideally compare standard IV therapy to the same IV regimen plus HAI therapy. However, the optimal regimen and sequence remains to be defined, either concomitant HAI and IV chemotherapy, or sequential administration. In the former option, the HAI regimen should ideally be highly extracted by first hepatic passage, such as pirarubicin, to avoid cumulative systemic toxicity,[21] while in the latter option, the same regimen could be sequentially delivered via the HAI and IV routes. Studies have shown that the concomitant combination of FUDR HAI plus IV irinotecan single agent[46,47] or IV oxaliplatin and 5-FU or oxaliplatin and irinotecan[24,48] or oxaliplatin HAI plus IV 5-FU/leucovorin,[44,49,50] or 5-FU HAI plus IV irinotecan and UFT/leucovorin[51] are feasible and yield high response rates and resection rates in selected patients.

(3) More effective drugs than FP can actually be safely administered via HAI, as single agents or in combination, including irinotecan[52–56] and oxaliplatin.[44,49,50,56–60] The HAI of irinotecan increases its conversion rate to its active metabolite SN38, resulting in similar SN38 systemic exposure, but a significantly lower irinotecan exposure[52], as compared to the IV route. Consistently, the safety profile of irinotecan HAI was similar to that of the conventional IV route, but no hepato-biliary toxicity was observed. In addition, increased carboxylesterase activity, responsible for the metabolic conversion of irinotecan into SN38, as well as increased topoisomerase 1 activity, the target of SN38, have been reported in 25–50% colorectal cancers,

as compared to normal liver. This may provide an even improved pharmacodynamic selectivity of HAI, compared to IV irinotecan.[61,62] Irinotecan drug-elutig beads (DEBIRI) may be a promising delivery approach of irinotecan HAI.[63] Oxaliplatin HAI displays the same toxicity as the IV route plus abdominal pain, which is the dose-limiting toxicity. The decreased systemic exposure may explain a lower incidence of severe chronic sensory neuropathy reported in initial studies with oxaliplatin HAI.[57–60] However, this better neurological tolerance remains to be confirmed with longer treatment duration.[44,49,50] Finally, since IV doublet regimens yield higher response rates than single IV agent, IV three-drug than IV doublet regimens[64] and HAI of single agent than IV single agent, it is reasonably anticipated that multidrug HAI regimens would yield the highest response rates. Combination regimens may actually be safely administered via HAI.[65] In order to maximise efficacy and tolerance we administered a 3-drug chronomodulated HAI regimen to 29 heavily pretreated patients (median of three previous chemotherapy regimens) with a very good tolerance and a promising activity in heavily pretreated patients, including a 14% rate of macroscopically complete resections of liver metastases.[66] This 3-drug (5-FU, irinotecan and oxaliplatin) HAI regimen – chronomodulated or not – is currently tested in a prospective European multicentre trial (OPTILIV07) in combination with IV cetuximab in patients with tumours harbouring a wild type KRAS gene who failed one to three prior regimens to further potentiate its activity.[67] Thus, a wide range of potential candidate drugs and schedules have recently become available for HAI combination regimens to be tested in randomised clinical trials, including FP, irinotecan, oxaliplatin and pirarubicin, as well as infusions of various durations, including circadian chronomodulation. In turn, mitomycin C HAI should be avoided, due to a possibly increased biliary toxicity.[68] Table 2 shows the feasibility and antitumour activity on non-FP drugs via the HAI route in small non-randomised studies. Efficacy data are hardly comparable across studies, because the selection criteria were variable, especially those regarding previous therapy and chemoresistance. Nevertheless, the vast majority of patients treated in the studies shown in Table 2 were heavily pretreated and these preliminary results compare favourably with the 43% response rate reported with FP HAI in first-line patients.[6,7] Interestingly, combination therapy (either multidrug HAI regimen, or combination of single drug HAI and IV chemotherapy) seems to produce the highest response rates. Of note, hepatic resections were feasible in a considerable proportion of these pretreated patients. Combination of HAI with systemic therapy including cetuximab or bevacizumab should be considered. A recent trial in the adjuvant setting assessing the addition of bevacizumab to HAI plus systemic chemotherapy did not suggeste a superiority of the bevacizumab containing regimen, but suggested an increased biliary toxicity.[69]

(4) New HAI regimens are now safe enough to avoid a high rate of early treatment discontinuation due to toxicity. FUDR is probably too toxic, due principally to the possible occurrence of severe sclerosing cholangitis even though this adverse event is less frequent with the concomitant use of dexamethasone and a careful follow-up of liver function tests.[70] However, the risk of this toxicity is no longer justified in our opinion, whilst HAI of other drugs are effective and better tolerated and FUDR no longer available in several countries. While systemic oxaliplatin administration can give rise to severe sinusoid obstruction syndrome (SOS),[71] which may be life-threatening or even fatal[72] and both IV FP and irinotecan are responsible for non-alcoholic steato-hepatitis that could increase post-operative morbidity,[73] it is concerning that HAI of these drugs could lead to aggravated hepatic toxicity, including increased post-operative morbidity.[74] Nevertheless, no increase in surgical complications has been observed when resection is performed after HAI of FP, compared to patients without prior HAI.[75] In addition, pathological examination of healthy liver after HAI of irinotecan and oxaliplatin did not show evidence of increased hepatic toxicity.[66] Nevertheless, this good hepatic tolerance warrants to be confirmed in large prospective studies.

(5) Technical progresses and increasing experience of the multidisciplinary teams taking care of patients with mCRC should markedly decrease the incidence of catheter-related issues. The impressive rate of catheter failures reported in some studies[39] is not consistent with our current daily practice and suggests that the experience of the centre is essential[26,40] and that technical issues are now better controlled. Nevertheless, the need for highly experienced centres has been and remains a major limitation for this approach. The most frequent problems are catheter placement failures and thrombosis of the hepatic artery. One retrospective study strongly suggested that the technique of catheter placement could significantly influence not only the complication rate and treatment duration, but the time to hepatic progression and the overall survival of patients treated with HAI chemotherapy.[76] One of the major issues is whether the catheter should be implanted surgically or percutaneously. In most previous studies, all patients had their catheter surgically implanted during exploratory laparotomy performed to ensure the absence of extrahepatic disease and/or to remove the primary tumour in case of synchronous metastases. Nowadays, while we have at our disposal more effective systemic chemotherapy, the initial resection of the primary tumour in case of synchronous metastases, is seldom indicated. Furthermore, the progresses of medical imaging make it less necessary to perform an exploratory laparotomy. Thus, some teams are reluctant to operate patients mainly for catheter placement purpose and this could lead to the non -easibility of the HAI strategy in the neoadjuvant setting. At the same time, important progresses have been accomplished with interventional radiology, permitting the safe percutaneous (PC) placement of an indwelling catheter in the hepatic artery with a subcutaneously implanted port, through either an axillary or a femoral access.[77] Retrospective studies having compared series of

Table 2 – Activity of drugs other than fluoropyrimidines delivered via HAI in pretreated patients with liver predominant unresectable metastatic colorectal cancer.

Author (year) [Refs.]	HAI delivered drug(s)	Associated IV therapy	No. of patients	Response rate	Complete resection/ ablation rate	Median PFS/TTP (months)
Rougier (1990) [19]	Pirarubicin	NO	18	33% (1CR + 5PR)	NA	NA
Fallik (2003) [21]	Pirarubicin	Fluorouracil/leucovorin	61	39%	NA	11 (hepatic) 18 (extra-hepatic)
Fiorentini (2003) [55]	Irinotecan	NO	12	33% (4PR)	NA	NA
Van Riel (2004) [53]	Irinotecan	NO	22	14% (3PR)	NA	2.8
Mancuso (2003) [58]	Oxaliplatin	NO	15	47% (7PR)	7%	10.0[a]
Fiorentini (2004) [60]	Oxaliplatin	NO	12	33% (4PR)	NA	3.2
Boige (2008) [44]	Oxaliplatin	Fluorouracil/leucovorin	39	62% (24PR)	18%	7.0
Ducreux (2005) [49]	Oxaliplatin	Fluorouracil/leucovorin	28[b]	64% (2CR + 16PR)	18%	27.0
Goéré (2010) [50]	Oxaliplatin	Fluorouracil/leucovorin	87[c]	NA	24%	NA[d]
Kern (2001) [57]	Oxaliplatin + fluorouracil/leucovorin	NO	18[b]	56% (4CR + 6PR)	NA	Not reached
Del Freo (2006) [65]	Oxaliplatin + fluorouracil/leucovorin	NO	21	24% (1CR + 4PR)	10%	5.9
Bouchahda (2009) [66]	Oxaliplatin + irinotecan + fluorouracil	±Cetuximab	29	34% (10 PR)	14%	4.5
Chen (2010) [56]	Oxaliplatin + irinotecan + doxifluridine[e]	NO	32	46.9% (15 PR)	NA	NA
Martin (2011) [63]	Drug-eluting bead, irinotecan (DEBIRI)	YES (30% of patients)	55	66% (6 months) 75% (12 months	NA	11

PFS: progression free survival; TTP: time to progression; CR: complete response; PR: partial response; NA: not available.

[a] Time to hepatic progression.

[b] No previous exposure to oxaliplatin.

[c] 21% previously untreated.

[d] 28% one-year disease-free survival in the 23 operated patients.

[e] +Chemoembolisation with irinotecan.

patients treated with HAI chemotherapy using either PC or surgically implanted catheters either have shown similar tolerance and efficacy,[78] or even have suggested a significantly lower failure rate and longer life duration of PC-implanted catheters.[79] However, the surgical route retains several advantages, such as performing cholecystectomy and ligation of gastroduodenal branches of the hepatic artery to prevent biliary and gastroduodenal complications, though highly experienced radiologists can realise specific embolisation of the gastroduodenal branches.[80,81] Thus, in the absence of standard technique of hepatic arterial catheter placement established so far, this technique should be left at the investigators' discretion in future trials according to local skills.

(6) Beyond neoadjuvant therapy of initially unresectable metastases, which could be a major indication, the role of the HAI technique should also be assessed as a neoadjuvant approach in initially resectable metastases and an adjuvant strategy after their complete resection/ablation.[82]

(7) Results of the European Organization for Research and Treatment of Cancer (EORTC) study 40983 have shown that neoadjuvant IV standard chemotherapy could reduce by 25% the risk of relapse of completely resected, initially resectable metastases.[83] Front-line systemic therapy is, therefore, recommended in Europe even in resectable disease.[84] Thus, HAI neoadjuvant chemotherapy could have a stronger eradication potential and warrants to be tested in this setting. About one half of patients who relapse after complete resection of liver metastases have recurrence in the liver.[85] Hence local adjuvant chemotherapy is still logical. One randomised trial showed a significant prolongation of PFS and over all survival for patients given HAI FUDR plus systemic 5-FU/leucovorin, compared to systemic therapy alone.[85] Reviews of all randomised clinical trials assessing the benefit of adjuvant chemotherapy after complete resection of initially resectable liver metastases showed that HAI was one of the most effective methods showing a prolongation of time to hepatic progression, but, similarly to studies testing neoadjuvant HAI in non-resectable metastases, without a homogeneous impact on overall survival across studies.[86,87] One retrospective study on the outcome of more than 900 patients who had undergone a complete resection of liver metastases showed that receiving post-surgical adjuvant HAI of chemotherapy was among the strongest predictive factors for a favourable outcome.[88] Only FP was used in previous randomised adjuvant studies (as for unresectable metastases), while recent non-comparative studies showed a good tolerance and suggest promising efficacy of newer HAI and/or IV adjuvant chemotherapy regimens.[89,90]

6. Conclusion

Despite uncertainties, there is a growing consensus on the following points: (1) complete resection of metastases from CRC is the only chance for cure/prolonged survival and should be attempted in fit patients in case of disease confined (or predominantly located) to the liver, even in initially non-resectable disease. (2) Preoperative chemotherapy is indicated in both non-resectable and resectable mCRC. (3) Modern standard IV doublet regimens are more effective than IV FP alone in terms of response rate, PFS and/or overall survival, and (4) HAI of FP is more effective than IV FP, at least in terms of response rate and secondary resectability of initially non-resectable disease. Thus, it is anticipated that the integration of HAI in the strategy against mCRC should improve outcome of the patients. The benefit of HAI should be, therefore, fully re-assessed, using modern cytotoxic and targeted agents, modern surgical and catheter placement techniques, as well as appropriate study designs. The ideal studies should be conducted in centres highly experimented in hepatic surgery, imaging and drug delivery techniques and surgical and/or radiological techniques of catheter placement. Patients randomised in the control arm should be given an IV regimen corresponding to modern standards and should not be suspected of being suboptimally treated. In order to properly address the question of HAI benefit, patients in the experimental arm should ideally receive the same IV regimen, plus single agent or multidrug HAI regimens. Innovative combined IV and HAI schedules should be tested. The primary study end-point should be overall survival. Randomisation should be stratified according to possible predictive and prognostic factors, including liver tumour burden and extra-hepatic deposits. It is not ethically possible to avoid crossover of patients failing on IV therapy alone. Hence the study should prospectively plan a subgroup analysis of patients not undergoing crossover, in order to minimise the bias of inconclusive statistical subgroup analysis due to small sample and insufficient power. Alternatively specific analyses aimed at correcting the crossover effect, should be planned, such as rank-preserving structural failure time (RPSFT) models.[91,92] Separate studies are to be conducted in the different clinical settings[93]: patients with non-resectable metastases (with R0–R1 resection rate as a major study end-point), neoadjuvant treatment in initially resectable disease and adjuvant treatment in both settings. All studies should carefully examine clinical and histological hepato-biliary toxicity and perioperative complications to fully determine the benefit/risk ratio of the HAI strategy.

Conflict of interest statement

None declared.

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