Expert Opinion

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Advances in regional chemotherapy of the liver

Oliver Dudeck[†] & Jens Ricke
[†]University of Magdeburg, Department of Radiology and Nuclear Medicine, Magdeburg, Germany

Introduction: Primary and secondary liver tumors resemble some of the most common causes of cancer and represent a major clinical problem owing to the poor prognosis. First-line therapeutic concepts are mainly based on surgical resection and/or systemic chemotherapy (SCT). However, many patients are not suitable for surgery or have failed SCT, although the total tumor load is still limited, which makes a regional therapy approach appealing.
Areas covered: This review focuses on different types of transarterial instillation of chemotherapy, which encompasses conventional and drug-eluting transarterial chemoembolization (TACE), hepatic arterial infusion (HAI) chemotherapy and isolated hepatic perfusion (ILP).
Expert opinion: TACE can be regarded as the treatment of choice in patients with multinodular hepatocellular carcinoma, but it should still be performed as a lipiodol-based regimen, while the value of doxorubicin-eluting beads needs to be exploited in further randomized controlled trials (RCTs). For patients with colorectal liver metastases, HAI chemotherapy has been challenged by the advent of more effective SCT, but encouraging results have been observed for the combination of the most recent, active drugs given by means of HAI with SCT. Nevertheless, data from RCTs comparing SCT with this transarterial regional therapy approach, as well as with TACE and ILP, are urgently needed.

Keywords: colorectal liver metastases, hepatic arterial infusion chemotherapy, hepatocellular carcinoma, isolated hepatic perfusion, regional chemotherapy, transarterial chemoembolization

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1. Introduction

The treatment of patients with primary or secondary hepatic cancer is a challenging issue as the extent of liver disease is the most important factor indicating a dismal prognosis. Unfortunately, only a minority of patients qualify for surgical resection, which resembles the only potentially curative approach. For unresectable (palliative) patients systemic chemotherapy (SCT) is the mainstay of treatment and much hope was associated with the introduction of molecular targeted therapies. Nevertheless, long-term survival can rarely be achieved.

Hepatic transarterial infusion of anticancer drugs either alone or in conjunction with embolic agents is a technique of regional drug delivery designed to improve the effectiveness and selectivity of chemotherapy in patients with liver-confined primary or secondary hepatic cancer. This approach takes advantage of certain aspects of liver tumors. It has been well established that hepatic tumors derive most of their blood supply from the hepatic artery whereas the hepatic parenchyma receives its supply predominantly from the portal vein [1]. This unique feature allows a much higher concentration of chemotherapeutic drugs to reach the tumor by means of the hepatic artery while theoretically sparing normal hepatic parenchyma. Compared with intravenous delivery, higher drug concentrations can be achieved at the desired target site while lower concentrations can be delivered to sites of systemic toxicity, such as bone marrow. Hepatic regional drug delivery is particularly

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Article highlights.

- TACE can be regarded as the gold standard of care for the treatment of patients with multinodular HCC.
- Recent trials in patients with HCC could not prove the superiority of TACE utilizing doxorubicin-eluting beads as compared with lipiodol-based regimens.
- For the treatment of CRC patients with hepatic metastases, TACE utilizing irinotecan-eluting beads has shown promising first results, which need to be confirmed in a larger series of patients.
- At present, HAI monotherapy utilizing a fluoropyrimidine-based protocol should not be offered to patients with CRC liver metastases, but encouraging results were obtained for newer agents given by means of HAI combined with SCT.
- IHP would benefit from technical refinements to allow the procedure to be performed endovascularly.

This box summarizes key points contained in the article.

appealing owing to the ability of the liver to metabolize a variety of drugs, resulting in a high first-pass chemotherapy extraction [2]. Moreover, the conjunction of local infusion of chemotherapeutics together with embolic agents has theoretical benefits beyond those offered by either treatment given alone. In addition to the ischemic damage caused by the embolic agent and the cytotoxicity yielded by the chemotherapy, vascular occlusion results in the prolongation of transit time through the vascular bed of the tumor, with increasing exposure time of tumor tissue to chemotherapy [3]. These principles indicate a potentially valuable role for a hepatic locoregional approach for the treatment of unresectable primary and secondary liver tumors.

In this article, hepatic locoregional treatment modalities available for the treatment of hepatocellular carcinoma (HCC) and colorectal carcinoma (CRC) liver metastases as the most common primary and secondary liver tumors are discussed on the basis of the available literature, and recent advances in these minimally invasive treatments are outlined.

2. Regional chemotherapy in primary and secondary liver cancer

2.1 Hepatocellular carcinoma

Hepatocellular carcinoma is the sixth most common cause of cancer, and its incidence worldwide is on the rise owing to the dissemination of hepatitis B and C virus infection [4]. Despite widespread implementation of surveillance programs, more than half of the patients with HCC are diagnosed late, when potentially curative treatments such as resection or liver transplantation cannot be applied [5]. As a result, locoregional interventional treatments continue to evolve and to play a major role in the therapeutic management of HCC.

2.1.1 *Conventional transarterial chemoembolization*

Transarterial chemoembolization (TACE) consists of an intra-arterial infusion of an emulsion of chemotherapeutic drugs together with lipiodol as an oily vasoocclusive agent with tumor-targeting properties optionally followed by embolization of the vascular supply to the tumor [6]. Sophisticated angiographic equipment and techniques have made superselective arterial catheterization possible for more focused drug delivery in order to preserve liver function. Nevertheless, important technical questions about TACE remain unanswered at this time. There is increasing evidence that superselective TACE achieves better antitumoral effects and reduces both the dosage of drugs and the number of TACE sessions needed to achieve extensive tumor necrosis as compared with lobar TACE [7,8]. Nevertheless, no randomized controlled data exist to prove whether the degree of selectivity for application of anticancer agents directly translates into a better tumor control rate and ultimately prolongs survival. Repeat treatments are performed with intervals reported ranging from 4 to 8 weeks, but the optimal frequency and timing of repeat treatment sessions remain unknown. Furthermore, there is no consensus regarding the use and type of chemotherapy agents [6,9]. The variety of anticancer drugs utilized for TACE include doxorubicin, cisplatin, epirubicin, mitoxantrone and mitomycin C [9]. For conventional TACE, these agents are vigorously mixed with lipiodol through the use of a pumping method to prepare an emulsion. Lipiodol functions as a microvessel embolic agent, as a carrier of chemotherapeutic agents and as an augmenter of antitumor effects of TACE by efflux into the portal veins [10]. Nevertheless, there have been concerns that such emulsions of hydrophilic chemotherapeutics and oily lipiodol may not be stable and anticancer drugs are released too quickly into the systemic circulation [11,12]. Thus, the current method of chemotherapy delivery to the tumor vascular bed cannot be regarded as optimal. Promising experimental results in the VX2 rabbit liver cancer tumor model have been reported for the use of the lipophilic anticancer drug paclitaxcel, which can be dissolved in lipiodol, but so far no clinical data are available [13]. Similarly to chemotherapeutics, there is no standard for the use and type of embolizing agent. The most frequently utilized material is gelatin sponge, which can be prepared in various forms, such as particles, pellets or fragments. Besides, permanent particles such as polyvinyl alcohol (PVA) and embospheres as well as temporary particles such as degradable starch microspheres (DSM) have also been applied [9]. So far, it is unclear which embolic agent is most appropriate for TACE in HCC, especially as tumors vary greatly in size and vascularity.

These circumstances have most probably contributed to contradictory results of the first randomized controlled trials (RCTs) on TACE in HCC [14-20]. Study details are given in **Table 1**. A cumulative meta-analysis of these studies, however, has clearly shown that the 2-year survival of patients with HCC not suitable for radical therapies who are treated with arterial embolization or chemoembolization is improved

Table 1. Randomized controlled trials comparing TACE or TAE versus SCT or conservative management for the treatment of HCC.

Trial reference and treatment arms	Year of publication	No. of patients	Overall survival (%)	
			1 year	2 years
Lin *et al.* [14]	1988			
TAE (gelfoam)		21	42	25
TAE + SCT (FU)		21	20	20
SCT: FU		21	13	13
Pelletier *et al.* [15]	1990			
TACE (doxorubicin, gelfoam)		21	24	NR
Conservative management		21	33	NR
GETCH [16]	1995			
TACE (cisplatin, gelfoam)		50	62	38
Conservative management		46	43	26
Bruix *et al.* [17]	1998			
TAE (gelfoam + coils)		40	70	49
Conservative management		40	72	50
Pelletier *et al.* [18]	1998			
TACE (cisplatin, gelfoam) + tamoxifen		37	51	24
Tamoxifen		36	55	26
Lo *et al.* [19]	2002			
TACE (cisplatin, gelfoam)		40	57	31*
Conservative management		39	32	11
Llovet *et al.* [20]	2002			
TACE (doxorubicin, gelfoam)		40	82	63*
TAE (gelfoam)		37	75	50
Conservative management		35	63	27

*Statistically significant difference ($p < 0.05$) of TACE versus control.

GETCH: Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; HCC: Hepatocellular carcinoma; NR: Not reported; SCT: Systemic chemotherapy; TACE: Transarterial chemoembolization; TAE: Transarterial embolization.

compared with conservative management [21]. Sensitivity analysis assessing 323 patients in 4 studies [16,18-20] showed a significant benefit of chemoembolization with cisplatin or doxorubicin, but no benefit with embolization alone when 215 patients in 3 studies were assessed [14,17,20]. The outcome of the treatment appears to be dependent on careful patient selection. In a RCT that recruited patients with compensated cirrhosis (70% in Child-Pugh A), absence of cancer-related symptoms, and large or multinodular HCC with neither vascular invasion nor extrahepatic spread, 2-year survival after conventional TACE reached 63%, compared with 27% of the untreated control arm ($p = 0.009$) [20]. By contrast, in another RCT, the use of broader enrollment criteria with inclusion of patients with symptoms of limited portal vein invasion resulted in a 2-year survival of only 31% [19]. As a result of these investigations, TACE has been established as the standard of care for patients who meet the criteria for the intermediate stage of the Barcelona Clinic Liver Cancer (BCLC) staging system, that is, those with multinodular HCC, relatively preserved liver function, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread [6,22]. Furthermore, TACE can be applied as an important bridging therapy before liver transplantation in an attempt to delay tumor growth or to achieve downstaging [23].

2.1.2 *Drug-eluting beads*

Recently, embolic microspheres have been introduced that have the ability actively to sequester doxorubicin from solution and release it in a controlled and sustained fashion. It has been shown that the amount of chemotherapy that reaches the systemic circulation compared with lipiodol-based regimens can be substantially diminished, thus significantly increasing the local concentration of the drug and the antitumoral efficacy [24]. These beads consist of polyvinyl alcohol microspheres modified with sulfonic acid groups, which are available at different size ranges varying from 100 to 900 µm in diameter. In a multicenter Phase II RCT that included 201 European patients ('PRECISION V'), use of doxorubicin-eluting beads (DC Bead; Biocompatibles, Surrey, UK) resulted in a marked and statistically significant reduction in liver toxicity as expressed in significantly smaller elevation of aspartate and alanine aminotransferase and drug-related adverse events as compared with conventional TACE with doxorubicin [25]. As a result of the improved safety and tolerability profile, high-dose doxorubicin treatment could be applied according to the planned schedule in the whole drug-eluting bead group, regardless of patient baseline characteristics, resulting in consistently high rates of objective response and disease control in all subgroup analyses. Nevertheless, only data of the tumor response assessed

6 months after TACE are available so far, which failed to demonstrate a statistically significant superiority of TACE with doxorubicin-eluting beads over conventional TACE (p = 0.11). Comparative data on time to progression and overall survival are awaited. A recent investigation assessing the degree of necrosis in explanted livers after chemoembolization with epirubicin-loaded beads versus bland embolization in patients on a transplant waiting list found that TACE with drug-eluting beads achieved higher rates of complete histologic response than bland embolization [26]. In a prospective randomized comparison of chemoembolization with doxorubicin-eluting beads (n = 41) and bland embolization (n = 43), a better local response, fewer recurrences and a longer time to progression of 42.4 ± 9.5 weeks were found for TACE with doxorubicin-eluting beads as compared with bland embolization with 36.2 ± 9.0 weeks (p = 0.0008) [27]. Conversely, a recent efficacy analysis from a large mono-institutional observation with a total of 150 patients found conventional TACE with lipiodol to be superior as compared with TACE with doxorubicin-eluting beads in terms of time to progression (30 versus 16 months; p = 0.003) and overall survival (OS; 46 versus 14 months; p = 0.0002), while no differences in toxicity profile or response rate were found [28]. Hence, the value of TACE utilizing doxorubicin-eluting beads as compared with lipiodol-based regimens urgently needs to be determined in a large prospectively controlled multi-center trial.

2.1.3 *Locoregional and molecular anticancer combination strategies*

Increased understanding of the molecular signaling pathways involved in HCC has led to the development of molecular targeted therapies aimed at inhibiting tumor cell proliferation and angiogenesis. Sorafenib, a multikinase inhibitor with antiangiogenic and antiproliferative properties, has been shown to prolong median OS and median time to radiological progression compared with placebo in RCTs and has become the current standard of care for patients with advanced stage tumors not suitable for surgical or locoregional therapies [29,30]. Studies of sorafenib have demonstrated its efficacy in advanced HCC; however, there may also be a role for this agent in earlier stage disease, either as adjuvant treatment after curative therapy or in combination with TACE. Tumor recurrence following TACE, in particular, is characterized by increased expression of vascular endothelial growth factor and other proangiogenic factors, such as hypoxia-inducible factor 1 alpha, which trigger subsequent angiogenesis [31,32]. Based on these findings, combination of TACE with agents with antiangiogenic properties would appear to be a rational approach. The availability of drug-eluting beads, which ensure minimal systemic exposure to the chemotherapeutic agent at the time of the TACE, is very appealing for combination regimens including transcatheter treatment in association with a systemically active drug. The first large studies in which an interventional locoregional treatment is being evaluated in combination with a systemically active molecular targeted drug are already continuing, which have the potential to revolutionize the treatment of HCC.

2.2 Colorectal carcinoma

Colorectal carcinoma is the fourth most commonly diagnosed cancer and the second leading cause of cancer death in western countries [33]. Liver metastases have a fundamental impact on patient prognosis and can be found in up to 80% of CRC patients; in 25 – 50% it is encountered at primary presentation [34]. It is well recognized, that the liver resembles a very effective filter for tumor cells, so that in many patients there is no further tumor dissemination. For selected patients with isolated liver metastases – usually up to five, in one lobe of the liver – surgical resection is the standard curative treatment, resulting in 5-year OS rates of 20 – 40% [35-37]. However, < 20% of patients are candidates for resection and 65 – 80% of patients have a relapse, with half of the relapses occurring in the liver [37,38].

The therapeutic management of unresectable metastases is more controversial and is generally associated with a dismal prognosis. Nevertheless, many patients would benefit from an effective treatment of isolated or predominant liver metastases, which represents a difficult but common clinical problem. For many years, the standard SCT for metastatic CRC was 5-fluoropyrimidines. Response rates were ~ 20%, with median survival times of 12 months [39]. New chemotherapy combinations with the addition of irinotecan or oxaliplatin to 5-fluorouracil (5-FU)-based regimens report superior response rates of 40 – 57% as well as longer median survival times of 15 – 20 months [40,41]. Still, there are virtually no long-term survivors with 5-year OS rates close to 0% [42,43]. The addition of biological agents such as bevacizumab and cetuximab indicates a benefit, at least in patients with the wild-type KRAS gene [44-46]. However, these data were not confirmed for cetuximab by the COIN trial, which represents the largest randomized Phase III study available so far, so that at present options in patients with chemoresistant CRC are limited [47].

2.2.1 *Conventional transarterial chemoembolization*

Similar to the treatment in HCC patients, TACE for the treatment of CRC liver metastases consists of an intra-arterial infusion of a mixture of chemotherapeutic drugs together with embolizing agents in order to prolong chemotherapy-to-tumor contact time. Contraindications for this regional therapy are portal vein occlusion, marginal liver function indicated by bilirubin level > 2 mg/dl, a poor performance status as well as the presence of dominant extrahepatic disease. Technically, a catheter is placed in the celiac trunk and advanced beyond the gastroduodenal artery. Depending on size, location and arterial supply to the tumor, the tip of the catheter is advanced further into the segmental arteries. Then, the embolization suspension is injected slowly under fluoroscopic control until stasis of the blood flow is observed. Chemotherapeutic regimens described vary considerably with 5-FU, floxuridine (FUDR), mitomycin C,

cisplatin, doxorubicin, oxaliplatin, irinotecan, dexamethasone and IFN-α_{2b}, representing commonly used agents [48,49]. No data are available that have proved the superiority of one agent over another. In addition, vascular occlusion has also been accomplished with various agents, including steel coils, lipiodol, PVA, gelatin sponge, DSM and collagen particles [48,50-52]. The occlusion efficacy afforded by these agents, which all display unique properties, has not been directly compared. Agents such as lipiodol or DSM occlude small tumor vessels and cause obstruction in the vascular tumor bed. These effects are used in an attempt to concentrate and prolong the retention of the chemotherapeutic agents in the tumor to increase anticancer effects while systemic toxicity is reduced [12,52,53]. The greatest amount of data exists on the use of lipiodol as an embolic agent. It appears that retention of lipiodol occurs in lesions with high vascularity, similar to TACE in HCC. However, metastatic CRC tends to display various degrees of vascularity [54]. Therefore, accumulation of lipiodol cannot be expected to the same extent as for HCC, in which it has been suggested as a positive predictive marker following TACE [55-57]. This is supported by the finding of a direct relationship between tumor vascularity and improved response to treatment [50]. Another substance frequently used is DSM, which has a half-life of only 20 min, thus representing the embolic agent with the shortest duration of vessel occlusion [58-60]. In general, temporary embolic agents have the advantage over permanent embolics that TACE can be applied repetitively. Repeat treatments are performed with intervals reported ranging from 4 to 8 weeks, but as for TACE in HCC, no standards exist [48,49]. In addition, there is at least a theoretical advantage that the use of DSM does not evoke neoangiogenesis, which occurs when vessel occlusion exceeds 1 – 2 h [61]. Nevertheless, there are no randomized data available comparing tumor response and survival of patients with CRC liver metastases treated with or without the use of DSM or in comparison with permanent embolics such as PVA.

Several single-center investigations have evaluated the efficacy and safety of TACE for the treatment of patients with metastatic CRC to the liver [48,49,58,62-65]. These studies utilized multiple chemotherapy regimens together with different embolic agents. In general, the treatment was tolerated well with only transient mild-to-moderate toxicities observed. Response rates reported ranged between 25 and 87% when radiologic with and without biologic (CEA) criteria were applied and median OS was between 7 and 23 months [48,49,58,62-65]. Interestingly, in the trial reporting the highest response rates and also the longest survival, a total of 46 patients were included who received a TACE regimen that involved the selective administration of doxorubicin and lipiodol to different liver subsegments while sparing non-tumorous liver parenchyma [65]. However, eventually all patients experienced progression of disease. Thus, data of RCTs in patients with unresectable CRC liver metastases of TACE using a reproducible technique for local delivery of chemotherapeutic agents compared with modern SCT would help to determine the value of this locoregional treatment.

2.2.2 Drug-eluting beads

Drug-eluting beads that release irinotecan (DEBIRI) in a controlled manner may be useful in patients who failed systemic therapy of unresectable CRC metastases to the liver. Current first- and second-line regimens containing irinotecan have become standard therapy in the treatment of metastatic CRC. However, the most common and severe side effect of irinotecan treatment is diarrhoea, which can be dose limiting and sometimes necessitates termination of chemotherapy. Local delivery to the site of the tumor in the liver may reduce the likelihood of such side effects by limiting intestinal exposure. Recent reports have shown that this drug-eluting therapy is generally well tolerated by patients, with the most common adverse events being postembolic symptoms [66-68]. Potential risks include liver failure and gastric irritation caused by seepage into the gastrointestinal tract, but modern angiographic techniques can deliver DEBIRI safely directly to the tumor [69].

A recently published open-label, multi-center, single-arm study of a total of 55 patients with unresectable CRC hepatic metastases who had failed standard therapy showed a high response rate of 75% at 12 months. Overall survival in these patients was 19 months, with progression-free survival of 11 months [70]. These promising results need to be confirmed in larger populations of patients in conjunction with SCT to demonstrate optimally the timing and use of this new liver-directed regional treatment.

2.2.3 Hepatic arterial infusion chemotherapy

Organ-specific delivery of chemotherapy for the treatment of liver tumors, known as hepatic artery infusion (HAI), has been used for nearly half a century [71,72]. Agents with high hepatic extraction rates are particularly attractive for HAI. FUDR, a fluoropyrimidine that is transformed to FU in the liver, has a 95% hepatic extraction rate when given in the hepatic arteries, which results in a 100 – 400-fold advantage when compared with venous administration [73]. As a result, most data are available for HAI with fluoropyrimidine-based protocols. Other drugs studied include doxorubicin, cisplatin, mitomycin C, oxaliplatin and irinotecan, but all have significantly lower extraction rate [73-75].

Early experience with HAI involved the use of external infusion pumps. This was associated with a significant incidence of complications such as catheter dislodgement, catheter sepsis, external pump failures and variability in flow rates that occur with prolonged infusions [76]. In addition, patient acceptance of an external catheter system that restricted lifestyle and activity was limited. These problems were overcome with the development of totally implantable subcutaneous pumps with reservoirs that can be filled percutaneously with a large volume, thereby minimizing the need for frequent refilling [77].

Hepatic arterial infusion may be used in palliative, neoadjuvant and adjuvant settings, with most data available for patients with unresectable liver metastases. However,

despite objective response rates of > 40% obtained with fluoropyrimidine-based HAI chemotherapy, the superiority of HAI over SCT in the frontline treatment of liver-confined metastatic CRC in terms of OS has not been not clearly demonstrated in most randomized studies or in a recent meta-analysis [78-91]. This may be due to a high cross-over rate in most studies, to the occurrence of numerous technical problems preventing optimal regional administration of chemotherapeutic agents, and to extrahepatic metastatic progression in patients treated with HAI-only chemotherapy [86,91,92]. Further study details are given in **Table 2**. In addition, traditional implantation of HAI catheter systems requires laparotomy and extensive dissection to expose the gastroduodenal artery, which is associated with a certain morbidity [93]. In addition, device failure, which would be a consequence of repeat operation, often results in a crossover to SCT. Hence, a statistically significant treatment benefit of HAI could be lost as a result of such technical issues with surgically implanted catheter systems. Alternatively, arterial port systems can be implanted radiologically with standard angiography catheters via the subclavian or femoral artery [94,95]. Compared with surgical implantation, radiologic port implantation is a quick and simple procedure that does not require general anesthesia and can be performed in outpatients. Patency rates are equal to those for surgically implanted systems [92,96]. Radiologic placement is also possible in patients with anatomic vascular variations, which are frequently encountered as the arterial blood supply of the liver is very variable [97]. In contrast to the surgical method, catheter-port systems placed radiologically cause less morbidity and allow for a more protocol-conforming drug delivery. In case of dysfunction the system can be corrected more easily, allowing for a higher assisted port patency rate as compared with surgically implanted ports [92,96]. Thus, the results of a RCT comparing HAI treatment administered via percutaneously placed catheter-port systems versus SCT would be of high interest to determine the merits of advances in interventional radiology.

Nevertheless, HAI chemotherapy has been challenged by the advent of more effective SCT combinations [98,99]. Therefore, new strategies for regional chemotherapy regimens have to be developed. Combining HAI with SCT has the theoretical benefit of suppressing systemic micro-metastases and demonstrating higher hepatic response rates. The combination of HAI FUDR and dexamethasone plus systemic oxaliplatin, 5-FU and leucovorin (LV) has been reported to be both feasible and effective in the adjuvant as well as the palliative setting [100-102]. Encouraging results were observed for the combination of the most recent, active drugs given by means of HAI with SCT in heavily pretreated patients with unresectable CRC liver metastases refractory to modern oxaliplatin- or irinotecan-based systemic regimens [75,103-106]. For the combination of intra-arterial administration of oxaliplatin combined with intravenous 5-FU and LV, tumor control rate of up to 87% and a median OS of up to 36 months were reported, which were markedly superior to the results obtained with classical fluoropyrimidine-based HAI [75,104,106]. Such high response rates seen with newer chemotherapies given by means of HAI can lead to increased resectability of liver metastases, with R_0 resection rates of up to 18% described [75]. This approach seems to offer a second chance in a considerable fraction of patients so that long-term survival can be obtained. In a recently reported study of CRC patients with initially unresectable liver metastases who received HAI of oxaliplatin, 23 of a total of 87 patients (26%) became operable, with an OS at 3 and 5 years of 73 and 56% as compared with 16 and 0%, respectively, in the non-surgical group [107]. This promising modality approach should be confirmed in a larger population of chemoresistant patients, including those who failed the most modern systemic regimens combining FOLFOX or FOLFIRI with angiogenesis inhibitors.

Neoadjuvant SCT for unresectable colorectal liver metastases can downsize tumors for curative resection. Resectability rates after the irinotecan- or oxaliplatin-based regimens were reported as being 13 – 32%, and the 5-year survival rate of these patients similar to what could be obtained with patients who were initially resectable [108-110]. Neoadjuvant locoregional chemotherapy appears attractive as HAI has consistently demonstrated higher response rates than SCT. In Phase I/II studies of patients with unresectable liver metastases treated with fluoropyrimidine-based HAI plus oxaliplatin and irinotecan-based SCT, a high rate of conversion to resection of 45 – 47% was found [101,111,112]. Certainly, future randomized trials to compare HAI plus SCT with systemic therapy alone are needed to assess the extra value of HAI chemotherapy in converting patients with hepatic metastases to resectability.

Regional chemotherapy can also be used as an adjuvant treatment after resection of liver metastases to reduce the rate of hepatic recurrence, which may develop in hepatic or extrahepatic sites in nearly 70% of surgical patients [113]. Although definitive randomized data are missing, adjuvant SCT is now increasingly accepted as the standard of care [114]. As the highest risk for recurrence after liver resection is in the liver, several randomized trials comparing resection alone with resection followed by adjuvant regional therapy have been performed, most of which could demonstrate a benefit of adjuvant HAI [85,115-119]. A recent review of 1000 patients who underwent liver resection demonstrated in a multivariate analysis that one of the significant factors to improve survival after liver resection was HAI therapy, with a median OS of 68 months with HAI therapy as compared with 50 months without [120]. Nevertheless, there is a need for adequately powered randomized studies in the adjuvant setting.

2.2.4 *Isolated hepatic perfusion*

Isolated hepatic perfusion (IHP) is a regional therapy in which the vascular supply of the liver is isolated, all collateral

Table 2. Randomized controlled trials comparing HAI with SCT for unresectable colorectal liver metastases.

Trial reference and treatment arms	Year of publication	No. of patients	Crossover	Tumor response rate (%)	Median overall survival time (months)
Kemeny *et al.* [78]	1987		Yes		
HAI: FUDR		48		53*	17
SCT: FUDR		51		21	12
Chang *et al.* [79]	1987		No		
HAI: FUDR		32		62*	17
SCT: FUDR		32		17	12
Hohn *et al.* [80]	1989		Yes		
HAI: FUDR		67		42*	16.5
SCT: FUDR		76		9	15.8
Martin *et al.* [81]	1990		No		
HAI: FUDR		39		48*	12.6
SCT: FU-LV		35		21	10.5
Wagman *et al.* [82]	1990		Yes		
HAI: FUDR		31		55	13.8
SCT: FU		10		20	11.6
Rougier *et al.* [83]	1992		No		
HAI: FUDR		81		41*	15*
SCT: FU or BSC		82		9	11
Allen-Mersh *et al.* [84]	1994		No		
HAI: FUDR		51		NR	13.5*
SCT: FU or BSC		49			7.5
Lorenz and Muller [85]	2000		Yes		
HAI: FUDR		54		43	12.7
HAI: FU-LV		57		45	18.7
SCT: FU-LV		57		27	17.6
Kerr *et al.* [86]	2003		No		
HAI: FU-LV		145		22	14.7
SCT: FU-LV		145		19	14.8
Kemeny *et al.* [87]	2006		No		
HAI: FUDR		68		47*	24.4*
SCT: FU-LV		67		24	20
Fiorentini *et al.* [88]	2006		No		
HAI + SCT: FU-LV		38		48	20*
SCT: FU-LV		38		42	14

*Statistically significant difference ($p < 0.05$).

BSC: Best supportive care; FU: Fluorouracil; FUDR: Floxuridine; HAI: Hepatic arterial infusion; LV: Leucovorin; NR: Not reported; SCT: Systemic chemotherapy.

circulation is controlled, and the organ is perfused using hyperthermia with chemotherapy or biological agents (i.e., tumor necrosis factor) via a recirculating oxygenated perfusion circuit [121]. This allows the use of high drug doses that would otherwise cause fatal complications if delivered systemically. Another potential advantage of IHP is the ability to achieve hyperthermia within the tissue by heating the perfusate solution, which is known to enhance the cytotoxic effects of antineoplastic drugs [122].

Several centers have reported high response rates of up to 74% in patients with unresectable CRC metastases confined to the liver [121-127]. Interestingly, response rates after IHP were not different in patients who had or had not been previously treated with chemotherapy, suggesting that IHP may have utility as a second-line treatment option after failure of SCT [122]. Nevertheless, owing to its technical complexity, its non-repeatability as a surgical procedure and the attendant potential morbidity, it has not gained widespread application [123]. As a result, no randomized comparative data to assess the unique value of IHP over SCT or other regional treatments in patients with unresectable CRC liver metastases are available.

In an attempt to make IHP less invasive, less complex, less expensive and less time-consuming, endovascular alternatives allowing the percutaneous placement of balloon catheters referred to as isolated hypoxic hepatic perfusion are being exploited [128,129]. The first clinical trials have been performed, but a major drawback of the technique is a high rate of systemic leakage [130]. Hopefully, technical refinements will result in a more liberal use of this promising method [131].

3. Conclusions

The prognosis for patients with unresectable primary or secondary liver malignancy is – despite improvements in surgical techniques and SCT regimens – poor. Therefore, several regional treatment modalities have been exploited

in order to achieve a higher rate of local tumor control. For the treatment of patients with multinodular HCC, TACE can be regarded as the gold standard of care. Nevertheless, important technical questions such as degree of selectivity, use and type of chemotherapeutic and embolizing agents, as well as treatment frequency remain a matter of debate. Moreover, the value of TACE utilizing doxorubicin-eluting beads as compared with lipiodol-based regimens remains indistinguishable and needs to be determined in a large population in a prospectively controlled multi-center trial. For the treatment of CRC patients with hepatic metastases, many regional therapies, including conventional TACE, TACE with DEBIRI, HAI, as well as IHP, can be offered. For conventional TACE, the results reported display a high degree of variation, with OS varying between 7 and 23 months. Research should focus on the identification of predictive factors such as the degree of tumor vascularization in order to recognize those patients who will most probably profit from this kind of therapy. TACE utilizing irinotecan-eluting beads has shown promising preliminary results, which need to be confirmed in a larger series of patients. At present, HAI monotherapy utilizing a fluoropyrimidine-based protocol should not be offered to patients with CRC liver metastases for palliative treatment as the greater tumor response rate obtained with regional chemotherapy has not been shown to translate into a survival advantage over modern SCT. However, encouraging results were obtained for newer chemotherapies, that is, oxaliplatin, given via HAI combined with SCT, which urges further investigation. In addition, promising results have been reported for HAI utilized in a neoadjuvant as well as adjuvant setting. Surgical IHP has not gained widespread application because of its technical complexity and potential morbidity. Nevertheless, technical refinements to allow this procedure to be performed endovascularly would result in more widespread use of this interesting treatment modality.

4. Expert opinion

In this section, important points are summarized.

TACE should be considered as the first-line treatment in patients with multinodular HCC. Superselective arterial catheterization should be attempted in order to achieve a more focused drug delivery and to preserve liver function, which is crucial for HCC patients because of the underlying cirrhosis. On the basis of the current evidence available, TACE should still be performed as a lipiodol-based regimen while the value of doxorubicin-eluting beads should be exploited in clinical trials. Current clinical data suggest TACE to be superior to bland embolization, although no clear recommendation can be given for the use of the most potent chemotherapeutic drug or drug combination. The need for embolizing agents is limited owing to the vasoocclusive effect of lipiodol. In clinical need, temporary agents such as gelatin sponge or DSM should be preferred in an attempt to prevent induction of neoangiogenesis. The authors recommend performing TACE repetitively every 6 – 8 weeks with cross-sectional imaging for staging after every third cycle. The combination of TACE with targeted molecular drugs appears appealing because induction of neoangiogenesis may be suppressed, but the results of continuing trials assessing the value of this strategy are awaited.

Therapeutic management of CRC liver metastases is controversial, although a variety of different treatment modalities such as TACE, HAI and IHP can potentially be offered. Until now, RCTs comparing such therapies with SCT are available only for HAI, making recommendations for TACE and IHP difficult. Although HAI has been challenged by advances in SCT, promising results for the combination of the most recent, active drugs given via HAI with SCT justify considering such a multimodal approach, but preferentially in the setting of clinical trials. This would allow assessment of its value versus best-supportive care, SCT regimens including biologic agents or other liver-directed regional therapies such as radioembolization.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Oliver Dudeck[†1] & Jens Ricke[2]
[†]Author for correspondence
[1]Priv.-Doz., University of Magdeburg, Department of Radiology and Nuclear Medicine, Leipziger Strasse 44, 39120 Magdeburg, Germany
Tel: +49 391 67 13030; Fax: +49 391 67 13029; E-mail: oliver.dudeck@med.ovgu.de
[2]University of Magdeburg, Department of Radiology and Nuclear Medicine, Leipziger Strasse 44, 39120 Magdeburg, Germany