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Colorectal liver metastases: regional chemotherapy via transarterial chemoembolization (TACE) and hepatic chemoperfusion: an update

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Abstract Liver metastasis is one of the main problems encountered in colorectal cancer management as the liver is the most common metastatic site. Several treatment options are available, among which transarterial chemotherapy has proved effective in achieving some local tumour control, improving the quality of life through symptomatic control as well as survival time. The present paper is intended to provide an overview of the techniques, indications and results of regional chemotherapy, which comprises transarterial chemoembolization (TACE) and chemoperfusion. This treatment approach has symptomatic, palliative, adjuvant and potentially curative objectives. We reviewed the studies involving TACE

and chemoperfusion of colorectal liver metastases during the last few years to update the previous reviews published on this subject. The results achieved were so variable, due to the variations in patient selection criteria and regimens used between the different studies. The median survival ranged from 9 to 62 months and the morphological response ranged from 14 to 76%. Technical aspects, results, and complications of this modality will be demonstrated with a detailed analysis and comments.

Keywords Regional chemotherapy · Liver metastases · Hepatic arterial infusion · HAI · Chemoembolization · TACE

Introduction

Metastasis is the most common neoplasm in adult liver, and the liver is the second most common site for metastatic spread, after the lymph nodes. The liver may be the only organ involved in colorectal tumours and neuroendocrine tumours [1]. Liver metastases can be found in up to 80% of colorectal cancer patients; in 25–50% it is encountered at primary presentation [2]. For selected patients with isolated liver metastases (usually up to five, in one lobe of the liver), surgical resection is the standard curative treatment, as it consistently provides long-term disease-free survival in a substantial number of patients. However, less than 20% of patients are candidates for resection. Recent series have described 5-year survival rates of 25–37% and 10-year rates of 20–22%. Sixty-five to 80% of patients have a relapse, with half of the relapses occurring in the liver [3].

For patients with unresectable and/or extrahepatic spread, systemic chemotherapy with fluoropyrimidines has been the basis of treatment for over 40 years. Treatment with 5-fluorouracil (5-FU) roughly produces a 20% response rate and a 2-year survival rate of 20%. Recently it has been shown that the addition of irinotecan or oxaliplatin to 5-FU-based regimens resulted in superior response rates (40–57%) as well as longer median survival times (15–20 months) [3–6], whereas irinotecan and capecitabine yielded a tumour control in 61% of patients [7].

Due to the poor outcome associated with metastatic colorectal cancer, alternative treatment strategies have been investigated. These treatments broadly depend on two approaches. The first is the percutaneous approach for local tumour destruction, which includes radiofrequency ablation (RFA), laser-induced thermotherapy (LITT), cryother-

apy, microwave therapy and percutaneous alcohol injection [8]. In the largest published patient series, magnetic resonance imaging (MRI)-guided LITT was performed in 603 patients with liver metastases. The 1-year survival rate was 94%, 2-year survival 77%, 3-year survival 56% and 5-year survival 37%, while median survival was 3.5 years [9]. In contrast, RFA showed a 3-year survival of 47% in 117 patients with liver metastases [10]. The overall morbidity of such procedures ranges between 0.1 and 2.5%, while mortality is less than 1% [8]. Both LITT and RFA develop rapidly to achieve higher volumes of tumour necrosis and better local response, which was demonstrated, for instance, through successful application of bipolar radiofrequency electrodes [11, 12].

The other approach is the transarterial administration of anticancer drugs, either alone as hepatic chemoperfusion or hepatic arterial infusion (HAI), or combined with vascular occlusive agents [transarterial chemoembolization (TACE)] or bland vascular embolization (TAE).

In this review, we demonstrate the results of HAI and TACE in liver metastases from colorectal carcinoma in order to show their true benefit in local and symptomatic control as well as improved survival. We will try to clarify its potential as an adjuvant, palliative, or symptomatic treatment.

HAI

The transarterial approach depends on the fact that tumour cells in hepatic metastatic foci larger than 3 mm derive up to 95% of their blood supply from the hepatic artery, whereas normal hepatocytes receive predominantly portal venous supply of up to 75% [3, 13]. Therefore, by direct delivery of chemotherapeutic agents through the hepatic artery, rather than systemic administration, a higher concentration of the drug (up to 16 times higher) can be obtained within the neoplasm by first pass effect and with less systemic toxicity [3].

Indications

HAI can be performed as a neoadjuvant therapeutic regimen, aiming at lesion size reduction so that the lesion can later be effectively ablated percutaneously or resected. Thus, non-resectable lesions are converted to resectable ones. On the other hand, it can be used as a palliative measure in cases of extrahepatic spread or post-surgical recurrence. Finally, it can lead to symptomatic relief, for example, in cases of pain due to capsular invasion and in cases of hormone-secreting metastases. The contraindications of this therapy are operability, extensive liver involvement (more than 75%), liver insufficiency, myelodysplasia and brain metastases. Portal vein occlusion is considered a relative contra-indication.

Technique and complications

Intra-arterial infusion is performed via a temporary catheter placed in the hepatic artery as well as via permanent port-catheter systems which are percutaneously implantable for long-term repetitive infusion therapy without arterial puncture [14]. Via subclavian, transfemoral or transaxillary approaches, a standard permanent angiographic catheter is connected to a percutaneous port system, with the catheter tip located in the common or proper hepatic artery for regional intra-arterial chemotherapy of the liver [14, 15]. The configuration of the catheter used depends on the vascular anatomy of the patient [14].

The final position of the catheter tip in the hepatic arterial tree, and thereby the region of perfusion, is chosen according to the anatomy of each patient and the location of the metastatic lesions. The catheter should be placed as distal as possible to avoid extrahepatic drug distribution but not too distal to avoid arterial occlusion [14–17] (Fig. 1).

Angiography is also used by some institutes for planning arterial redistribution to convert multiple hepatic arterial supply using embolizing coils into a single arterial supply. This prevents extrahepatic drug distribution [14–17].

One of the techniques to prevent catheter dislocation is the fixed catheter tip (FCT) method. A side hole is made in a 5-F catheter and its tip is placed in the gastroduodenal artery. Microcoils are introduced via a microcatheter into the gastroduodenal artery through the side hole of the 5-F catheter to close the end hole of the catheter and fix its tip to the gastroduodenal artery, which is also occluded with coils. This technique was modified for easier performance. A tapered microcatheter tip is advanced into the gastroduodenal artery with a side hole located in the orifice of the proper hepatic artery. Through the contralateral femoral artery, a microcatheter is advanced into the gastroduodenal artery beside the distal portion of the tapered catheter. Microcoils, n-butyl cyanoacrylate (NBCA), and iodized oil are deployed to fix the tip of the tapered catheter and occlude the gastroduodenal artery [14, 16].

The catheter system is regularly flushed with saline solution at the end of each chemotherapeutic cycle, before final withdrawal of the port needle [14]. Continuous heparin infusion can be used [17]. Correct catheter position can be checked by plain radiograms. Correct position and functioning of the system is verified by digital subtraction angiography and/or helical CT arteriography prior to each chemotherapeutic treatment cycle [14–17].

Complications can be classified on the basis of their cause. Local complications due to the arterial puncture include mild hematoma, hemorrhage, mild pain or discomfort and disconnection between the catheter and port. Technical or mechanical complications include dislodgement, thrombosis and occlusion, infection, peripheral arterial embolization, mesenteric ischemia and inadvertent infusion embolization of the hepatic artery during catheter fixation [14–17]. Pharmacological complications

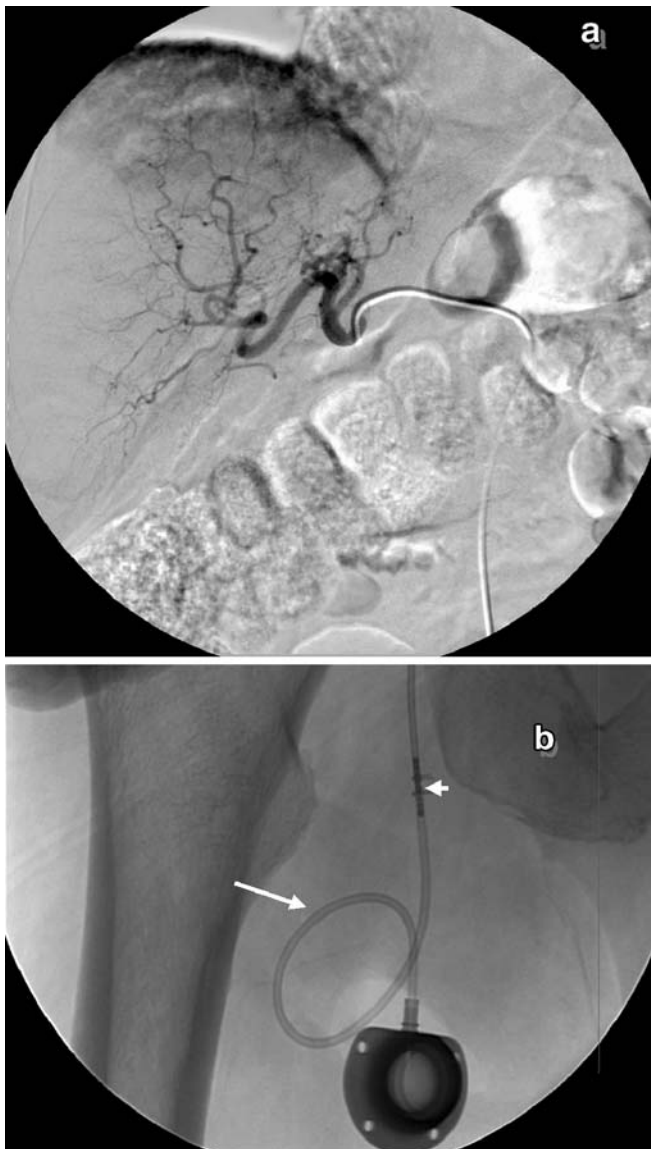


Fig. 1 **a** Control arteriogram after placing a Cobra catheter in the hepatic artery proper distal to the gastroduodenal artery yet allowing perfusion of both hepatic lobes. **b** Plain radiograph of the port placed in the upper thigh. The connecting catheter (*long arrow*) links the port to the Cobra catheter. The point of connection is secured by metal clips (*short arrow*)

due to the prolonged chemotherapeutic drug infusion such as gastroduodenitis, gastroduodenal ulcer, cholecystitis, hepatobiliary toxicity, and arteriobiliary fistula have been reported [17].

The subclavian/transaxillary approach has specific complications not seen in the transfemoral approach such as pneumothorax [15, 17] and cerebral infarction due to the catheter crossing the vertebral artery origin or vertebral artery embolization during catheter removal [15]. This approach also shows a higher possibility of dislocation [14]. Percentages of the other major complications are

shown in Table 1, without a significant difference between the transaxillary and transfemoral approaches.

Results

Regional intra-arterial chemotherapy has demonstrated better response rates than has systemic chemotherapy, in cases of liver metastases of colorectal cancer [8, 16]. In several clinical trials the value of HAI was assessed in this condition. The results of these trials are shown in Table 2 (Figs. 2, 3). Several meta-analyses were performed to evaluate the results of randomized controlled trials studying the efficiency of HAI in the treatment of colorectal liver metastases. One metaanalysis was published in 1999, in which the results of seven randomised trials were reviewed. Five of the studies included a comparison of HAI with systemic chemotherapy and two a comparison of HAI with either systemic chemotherapy or symptomatic treatment. It showed that HAI had the advantage of better tumour response (41 vs 14%, P value less than 0.001) and significantly longer median survival (15 months for HAI vs 11 months, P value less than 0.009) [18]. Another study was published in 2004 and reviewed the results of seven trials in which patients were randomised to the HAI arm and to the control arm which received either systemic chemotherapy or only symptomatic treatment. HAI was associated with a 5-year survival of 45%, while in the control arm it was 40%. The rate of hepatic recurrence was 14.8% in the HAI arm and 32.1% in the control arm. However, differences in these results did not reach statistical significance [19]. The most recent analysis was published in 2005, where seven prospective clinical trials compared hepatic arterial chemotherapy after curative hepatic resection of colorectal cancer metastases with a control arm and measured survival difference at 1 and 2 years after surgery. The survival difference in months was 1.8 at 1 year and 9.6 at 2 years. Neither was statistically significant [20].

These three reviews used different studies with different criteria of treatment evaluation, which were response and median survival [18], 5-year survival and hepatic recurrence [19], and 1- and 2-year survival [20]. Thus, their results are not contradictory because they are not comparable. They show that HAI has a significant local control effect and a long-term advantage in median survival, although it showed no significant advantage in the 1-, 2- and 5-year survival rates.

Compared with surgical implantation, radiological implantation of port-catheter systems is a fast and simple procedure that does not require general anesthesia and can be performed on an outpatient basis. Patency rates are equal to those of surgically implanted systems. Radiological placement is also possible in patients with anatomic vascular variations, such as a hepatomesenteric trunk. In contrast to the surgical method, port-catheter systems

Table 1 Review of percentage of technical complications in percutaneously implanted port-catheter systems for intraarterial hepatic chemotherapy (used with some additions with permission;

courtesy of Prof. Venturini, Scientific Institute S. Raffaele, Vita-Salute University, Milan, Italy)

Study	Patient no.	Approach	Local complications	Catheter dislocation	Catheter occlusion	Hepatic artery thrombosis	Sepsis
Yoshikawa [52]	48	Transaxillary	4.1	8.2	0	4.1	8.3
Oi [53]	31	Transaxillary	3.2	12.9	0	12.9	0
Wacker [54]	33	Transaxillary	15.1	6	15.1	15.1	0
Zanon [55]	95	Transaxillary	4.2	10.5	0	4.2	1
Tanaka [15]	425	Subclavian	0.5%	2.8%	0.7%	0.2%	0.2%
Venturini [17]	204	Transaxillary	1.5	8.8	0	6.8	1.9
Irie [16]	20	Transfemoral	0	5%	0	5%	0
Jung [56]	21	Transfemoral	4.7	14.3	9.5	4.7	0
Hermann [14]	32	Transfemoral	0	6.3	6.3	0	0
Kuroiwa [57]	90	Transfemoral	0	10	11.1	1.1	3.4

placed radiologically cause less morbidity in case of dysfunction, because these systems can be removed or repositioned more easily. Difficult surgical revisions or corrections requiring laparotomy can be avoided [14]. However, complications such as catheter dislodgement or hepatic arterial occlusion are more frequently associated with radiological procedures than with surgical ones [15, 16]. These problems may be related to the absence of fixation of the in-dwelling catheter tip to the vessel when simple radiological catheter placement in the hepatic artery is employed, in contrast to the surgical procedure in which the catheter tip is fixed to the gastroduodenal artery by ligation [15]. Fixation methods overcome this problem in the percutaneous radiological approach.

TACE

By definition, TACE is the use of vascular embolizing material combined with cytotoxic drugs to induce tumour ischemic necrosis and prolonged drug transit time.

Indications

TACE is used, like HAI, as a neoadjuvant means to surgery or thermal ablation. It has the ability to reduce size,

vascularity, and metastatic spread induced by surgical manipulation to improve the outcome of surgery. Besides, it shares the same palliative and symptomatic indications to HAI. The contra-indications are those of HAI, in addition to other relative contraindications related to the vascular occlusion effect, which are extensive liver involvement (more than 75%), and portal vein occlusion.

Technique and complications

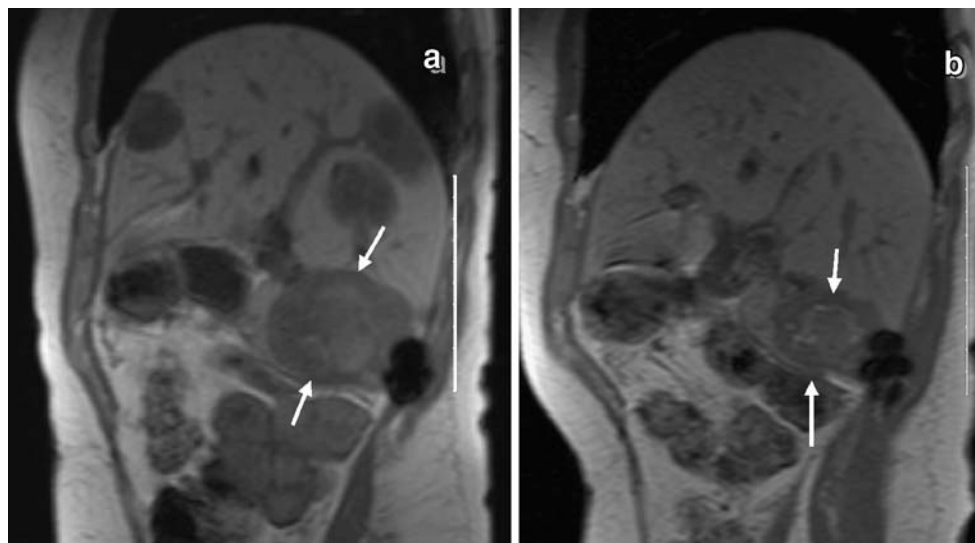
Vascular occlusive agents can be either temporary [usually microspheres, degradable starch microspheres (DSM), collagen and gelatine sponge (Gelfoam)] or permanent [polyvinyl alcohol (Ivalon)]. Lipiodol, in addition to its microvascular occlusive effect, has a special affinity to be uptaken and retained by hepatic tumour cells. Thus, when it is emulsified with cytotoxic drugs it significantly enhances their effect [21].

The most common associated complication to TACE is the “post-embolization syndrome” or the “tumour lysis syndrome”, which consists of pain in the right upper quadrant, nausea, vomiting, and mild transient or persistent fever as well as elevation of liver enzymes. This occurs in 3.8–100% of all interventions [22–24]. Compared with TACE with long or permanent arterial occlusion, the post-embolization syndrome seems to be less pronounced using

Table 2 Treatment regimens and results of HAI in colorectal liver metastases during the last 5 years (NA not available)

Study	Patient no.	Drug	CR(%)	PR(%)	Median survival(months)
Lorenz [58]	50	5-FU	–	56	22.3
Okamoto [59]	27	5-FU	3.7	26	17.9
Tono [60]	30	5-FU	–	–	62.6
Fiorentini [61]	12	Irinotecan	–	33	NA
Fazio [62]	44	5-FU Cisplatin Mitomycin C	–	35	NA
Oberfield [63]	42	5-FU Floxuridine	–	48	10.6
Kemeny [64]	63	Mitomycin C and Floxuridine	73	–	23

Fig. 2 a, b Remarkable morphological response in regression of colorectal liver metastases after a 5-month course of chemoperfusion. **a** Non-contrast sagittal T1-weighted MRI after the first session showing multiple right lobe lesions, the largest of them in segment 5 (*arrows*). **b** Post-treatment MRI after 5 months using the same imaging technique showing notable size reduction of the segment 5 mass (*arrows*) and complete regression of the other lesions. No newly developed lesions were detected



temporary embolizing material like DSM. Hence, in TACE performed as a palliative measure, temporary embolizing material is generally considered to be more suitable [24]. Moreover, in extensive metastases involving both lobes it is not feasible to permanently occlude all the feeding arteries on the expense of liver blood supply. More serious but relatively less common complications are liver abscess, infarction, tumour rupture, and acute liver failure. Pulmonary complications include lipiodol embolism, which is symptomatic only in 2–4% of cases [22].

Extrahepatic metastases are a known limitation to the use of TACE. The extent of liver involvement by metastatic lesions can be another limitation. Patients with a tumour burden of more than 75% of the liver may not benefit from TACE due to the development of major complications, whereas patients with lower (less than 50%) tumour burden and higher (more than 50%) lipiodol uptake show a trend towards longer survival [23, 25]. Hence significant liver toxicity can be a limiting factor that compromises the safety of such a procedure [26].

Results

Colorectal cancer metastases treatment was evaluated in several studies. In a relatively large patient series, continuous intra-arterial chemotherapy with 5-FU plus granulocyte-macrophage colony-stimulating factor (GM-CSF) was combined with chemoembolization of Melphalan, lipiodol and gelfoam via an angiographically positioned hepatic artery catheter. Responses to this treatment combination were complete response (CR) in 10%, partial response (PR) in 42.4%, stable disease (SD) in 18.2%, and no response (NR) in 12.1%. Two-year survival was 66%. There was no statistically significant difference between chemo-naïve patients and patients pretreated by any kind of systemic

therapy [27]. The results of TACE in several studies are shown in Table 3 (see Figs. 3, 4).

An interesting observation is the equally satisfactory results achieved using transarterial embolization alone without cytotoxic drugs [28, 29]. Three randomized controlled trials elaborated on this point by comparing TACE and transarterial embolization in colorectal liver metastases. Hunt et al. [30] randomised their patients to either TACE using 5-FU and degradable starch microspheres (DSM) or to embolization using Gelfoam and lyophilised dura mater. There was a slightly higher median survival in the TACE arm not yet reaching statistical significance. No statistically significant difference between both arms was noted in survival or tumour response in similar studies conducted by Martinelli et al. [31] and Salman et al. [32]. Thus, the main limiting factor to the use of embolization is the extent of liver involvement which defines the possible degree of vascular compromise. In bilobar extensive lesions chemoperfusion can be more feasible. In more localised lesions, adding embolization to chemoperfusion would be useful to achieve a better outcome, especially in cases of hypervascular metastases as renal cell carcinoma secondaries. Also, embolization is useful in the presence of an associated vascular lesion as an AV malformation, fistula, or a hemangioma. HAI, TAE and TACE have shown promising symptomatic, morphological and survival results in liver metastases from other primary tumours, like malignant melanoma, neuroendocrine and carcinoid tumours, breast and gastric cancer [22, 23, 28, 29, 33–41].

Discussion

A few observations can be made from the available data. The median survival rate observed in colorectal metastases

in most studies using regional chemotherapy is lower than that achieved by surgical resection, which ranges between 28 and 46 months [42]. However, this can be due to the more favourable liver and general patient condition, as well as the earlier tumour stage in surgical patients. As we have mentioned earlier, a small percentage of patients are surgical candidates and a high rate of recurrence is expected [3, 42]. Besides, the operative morbidity and mortality can reach up to 39% and 5%, respectively [42]. However, there is not much benefit in comparing surgery and TACE because both play a complementary and supplementary role to each other. TACE increases the possibility of surgery, improves its outcome and can be used when surgery is not possible or not successful.

There is a similar relationship between transarterial chemoembolization and percutaneous ablation, where TACE achieves downsizing of metastases so that they can be treated by thermal ablation. If the metastasis progresses out of the inclusion domain of ablation, TACE or HAI can be the alternative. In our institute this was applied to a group of 162 patients with metastatic lesions larger than 5 cm. After the final course of TACE, a significant decrease in lesion size was estimated using MRI as a response to treatment so that imaging-guided LITT could follow [43, 44] (Fig. 5). Similarly, hepatic arterial infusion chemotherapy via a port-catheter system performed for six patients with unresectable colorectal liver metastases led to a decrease in lesion number and size paving the way for subsequent radiofrequency (RF) ablation, which resulted in stable disease as well as complete or partial remission in all six patients documented by computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) [45].

Systemic and transarterial chemotherapy have a different relationship because they share more common grounds. Both can be combined or can replace one another. Systemic treatment is required in the presence of extrahepatic metastases. In any case, the results achieved by TACE and HAI in terms of response rate and median survival times, as seen in the tables, can surpass those of systemic chemotherapy mentioned earlier, avoiding at the same time the systemic side effects of the latter [3, 46]. Improved survival was also shown when HAI was combined with systemic chemotherapy in the post-resection setting [46]. Oxaliplatin by HAI and intravenous (iv) FU plus leuco-

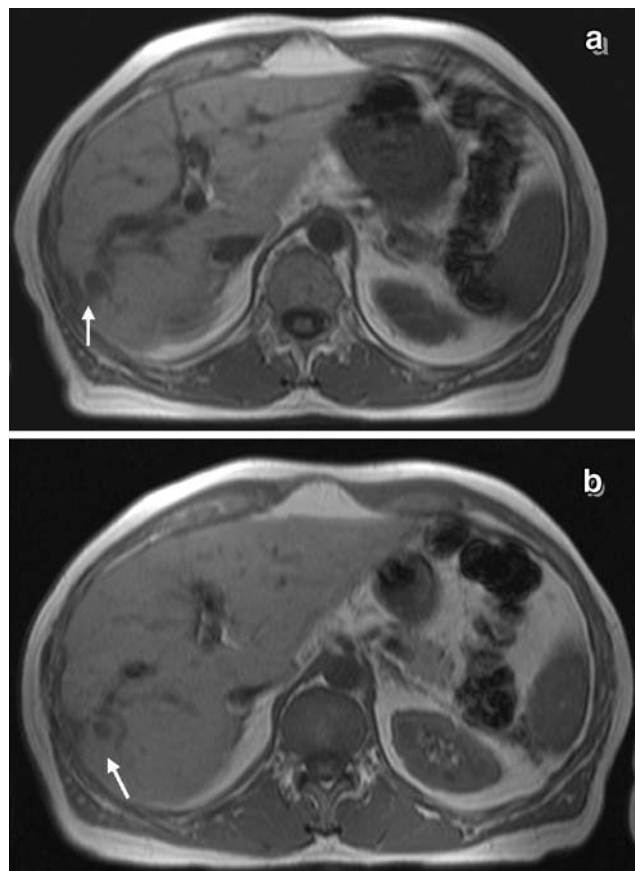


Fig. 3 a, b A situation of stable disease achieved after 20 months of regional chemotherapy in a 50-year-old patient (CRC: T2, N1, M1) including three sessions of TACE, followed by three sessions of chemoperfusion. **a** Pre-treatment non-contrast axial T1-weighted MRI showing a small right lobe lesion (*arrow*). **b** Follow-up MRI after 20 months using the same imaging technique showing notable size reduction of the tumour (*arrow*). No newly developed lesions were detected

vorin resulted in an objective response rate of 64%. The median overall survival time was 27 months [47], while concurrent HAI and systemic Oxaliplatin plus irinotecan achieved a total response rate of 90% and median survival time of 36 months [48].

However, the precise difference in the effectiveness of the various embolizing materials and cytotoxic drugs is yet

Table 3 Means and results of TACE in patients with liver metastases during the last 3 years

Study	Patient no.	Sessions	Anticancer drug	Embolizing material	Morph. response	Median survival
Wasser [24]	21	3.4	Mitomycin	Starch (DSM)	14%	13.8 months
Muller [27]	66	4.5	Melphalan (5-FU & GM-CSF)	LipiodolGelfoam	76.6%	Not reached ^a
Popov [26]	11	1	Mitomycin	Gelfoam	NA	9 months
Voigt [65]	10	4.3	Mitomycin Interferon (Oxaliplatin & 5-FU)	Starch (DSM)	50%	Not reached ^b

^aMedian survival was not reached after an observation period of 28 months

^bFour patients were still undergoing treatment by the time of publication

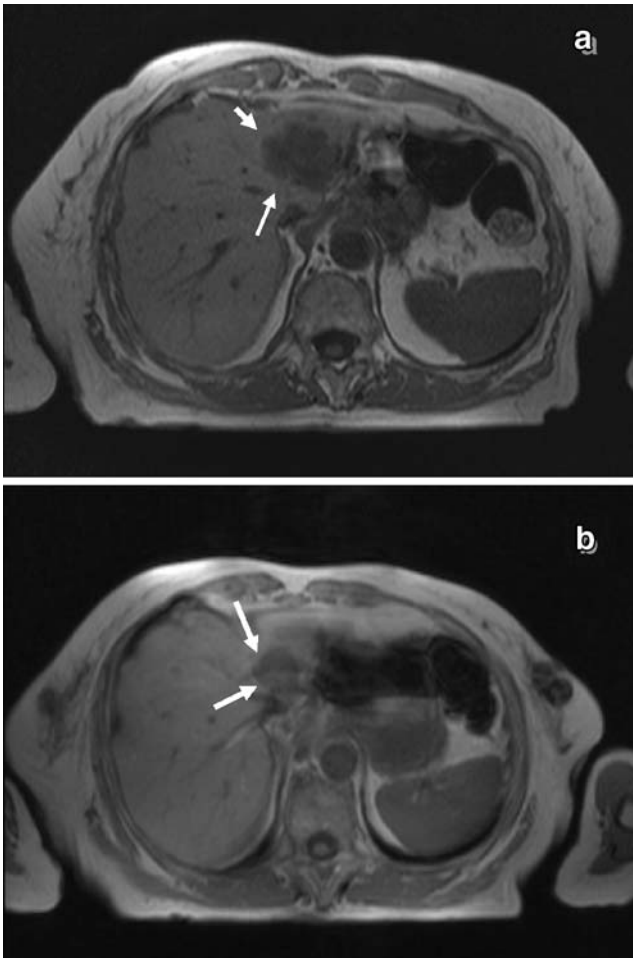


Fig. 4 a, b A 51-year-old patient (CRC: T3, N1, M1) demonstrating colorectal liver metastases regression after a three-session TACE treatment course. **a** Pre-treatment non-contrast axial T1-weighted MRI showing a left lobe lesion (*arrow*). **b** Post-embolization MRI using the same imaging technique after the third session, showing notable size reduction of the tumour (*arrow*). No newly developed lesions were detected

unclear in the studies available due to the difference in primary tumours, treatment regimens, doses, and intra- or extrahepatic extent of the metastases. They have to be evaluated and compared in a series of dedicated randomised trials, in which two or more agents can be used in randomised patient groups to avoid selection bias and limit the influence of any confounding factors. This will provide a non-biased accurate view of the better treatment combinations in each metastatic primary tumour.

The cost-effectiveness of both HAI and TACE is another point worth discussing. The costs (both in terms of healthcare and to society) and benefits (treatment-added survival and normal quality of life survival) of HAI patients with implanted pump and systemic chemotherapy were compared with those in symptomatic treatment. HAI chemotherapy was the most costly and symptomatic

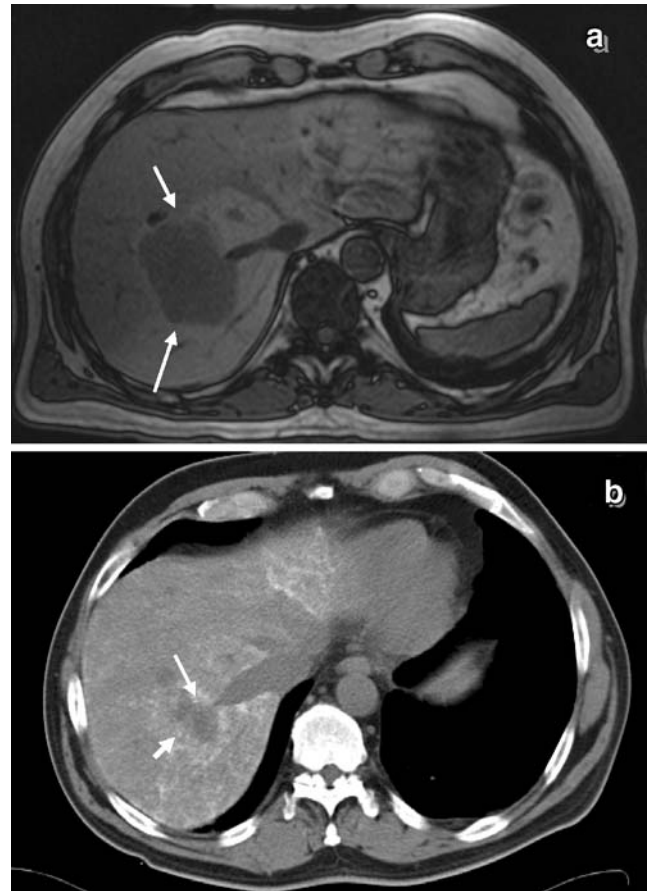


Fig. 5 a, b Downsizing of colorectal liver metastases using TACE followed by LITT. **a** Post-contrast T1-weighted MRI showing a large right hepatic lobe metastatic mass (*arrows*) in a patient with colorectal carcinoma which was not treatable by LITT. **b** Non-contrast CT showing the same lesion after three TACE sessions with lipiodol retention and size reduction (*arrows*) paving the way for thermal ablation with LITT

treatment the least costly. When survival was included, HAI was the most cost-effective treatment in terms of healthcare costs per year of life gained, but there was no difference as far as healthcare cost with respect to normal quality of life gained is concerned. Costs to society incurred by lost work-time and welfare payments during illness were higher for HAI, simply because HAI-treated patients lived longer and, although working longer and contributing more productivity to society, lost more work days than other patients [49]. The cost-effectiveness of regional chemotherapy for colorectal liver metastases was proved to be within the range of accepted treatments for serious medical conditions in terms of cost-effectiveness [50]. The marginal cost-effectiveness of TACE compared with palliative care, given survival benefits of 3, 6, and 12 months, was significantly higher at 12-month survival [51].

Summary statement

Regional chemoperfusion and chemoembolization of liver metastases in colorectal cancer is of clinical use in

symptomatic and palliative indication. Further studies have to be directed towards the prospective analysis of possible neoadjuvant and curative indication.

References

1. Pickren JW, Tsukada Y, Lane WW (1982) Liver metastasis. In: Weiss L, Gilbert HA (eds) *Analysis of autopsy data*. GK Hall, Boston, pp 2–18
2. Vogl TJ, Zangos S, Balzer JO, Thalhammer A, Mack MG (2002) Transarterial chemoembolization of liver metastases: indication, technique, results. *Röfo* 174(6):675–683
3. Cohen AD, Kemeny NE (2003) An update on hepatic arterial infusion chemotherapy for colorectal cancer. *Oncologist* 8(6):553–566
4. Ji SH, Park YS, Lee J, Lim do H, Park BB, Park KW, Kang JH, Lee SH, Park JO, Kim K, Kim WS, Jung CW, Im YH, Kang WK, Park K (2005) Phase II study of irinotecan, 5-fluorouracil and leucovorin as first-line therapy for advanced colorectal cancer. *Jpn J Clin Oncol* 35(4):214–217
5. Kuehr T, Ruff P, Rapoport BL, Falk S, Daniel F, Jacobs C, Davidson N, Thaler J, Boussard B, Carmichael J (2004) Phase I/II study of first-line irinotecan combined with 5-fluorouracil and folinic acid Mayo Clinic schedule in patients with advanced colorectal cancer. *BMC Cancer* 4:36
6. Kemeny N, Garay CA, Gurtler J, Hochster H, Kennedy P, Benson A, Brandt DS, Polikoff J, Wertheim M, Shumaker G, Hallman D, Burger B, Gupta S (2005) Randomized multicenter phase II trial of bolus plus infusional fluorouracil/leucovorin compared with fluorouracil/leucovorin plus oxaliplatin as third-line treatment of patients with advanced colorectal cancer. *J Clin Oncol* 22(23):4753–4761; erratum: *J Clin Oncol* 23(1):248
7. Hofheinz RD, Gnad-Vogt U, Wein A, Saussele S, Kreil S, Pilz L, Hehlmann R, Hochhaus A (2005) Irinotecan and capecitabine as second-line treatment after failure for first-line infusional 24-h 5-fluorouracil/folinic acid in advanced colorectal cancer: a phase II study. *Anticancer Drugs* 16(1):39–45
8. Germer CT, Buhr HJ, Isbert C (2005) Nonoperative ablation for liver metastases. Possibilities and limitations as a curative treatment. *Chirurg* 76(6):552–563
9. Vogl TJ, Straub R, Eichler K, Söllner O, Mack MG (2004) Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy—local tumor control rate and survival data. *Radiology* 230(2):450–458
10. Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, Cova L, Halpern EF, Gazelle GS (2001) Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology* 221(1):159–166
11. Burdio F, Navarro A, Sousa R, Burdio JM, Guemes A, Gonzalez A, Cruz I, Castiella T, Lozano R, Berjano E, Figueras J, de Gregorio MA (2006) Evolving technology in bipolar perfused radiofrequency ablation: assessment of efficacy, predictability and safety in a pig liver model. *Eur Radiol* [epub ahead of print]
12. Lee JM, Han JK, Kim SH, Lee JY, Park HS, Eo H, Choi BI (2005) Radiofrequency ablation in the liver using two cooled-wet electrodes in the bipolar mode. *Eur Radiol* 15(10):2163–2170
13. Sullivan RD, Norcross JW, Watkins E (1964) Chemotherapy for metastatic liver cancer by prolonged hepatic-artery infusion. *N Engl J Med* 270:321–327
14. Herrmann KA, Waggenshauser T, Sittek H, Reiser MF (2000) Liver intraarterial chemotherapy: use of the femoral artery for percutaneous implantation of catheter-port systems. *Radiology* 215(1):294–299
15. Tanaka T, Arai Y, Inaba Y, Matsueda K, Aramaki T, Takeuchi Y, Kichikawa K (2003) Radiologic placement of side-hole catheter with tip fixation for hepatic arterial infusion chemotherapy. *J Vasc Interv Radiol* 14(1):63–68
16. Irie T (2001) Intraarterial chemotherapy of liver metastases: implantation of a microcatheter-port system with use of modified fixed catheter tip technique. *J Vasc Interv Radiol* 12(10):1215–1218
17. Venturini M, Angeli E, Salvioni M, De Cobelli F, Ronzoni M, Aldrighetti L, Stella M, Carlucci M, Staudacher C, Di Carlo V, Ferla G, Villa E, Del Maschio A (2004) Complications after percutaneous transaxillary implantation of a catheter for intraarterial chemotherapy of liver tumors: clinical relevance and management in 204 patients. *AJR Am J Roentgenol* 182(6):1417–1426
18. Link KH, Kornmann M, Formentini A, Leder G, Sunelaitis E, Schatz M, Pressmar J, Beger HG (1999) Regional chemotherapy of nonresectable liver metastases from colorectal cancer - literature and institutional review. *Langenbecks Arch Surg* 384(4):344–353
19. Nelson RL, Freels S (2004) A systematic review of hepatic artery chemotherapy after hepatic resection of colorectal cancer metastatic to the liver. *Dis Colon Rectum* 47(5):739–745
20. Clancy TE, Dixon E, Perlis R, Sutherland FR, Zinner MJ (2005) Hepatic arterial infusion after curative resection of colorectal cancer metastases: a metaanalysis of prospective clinical trials. *J Gastrointest Surg* 9(2):198–206
21. Ohtsuka Y, Matsunaga T, Yoshida H, Kouchi K, Okada T, Ohnuma N (2004) Optimal strategy of preoperative transcatheter arterial chemoembolization for hepatoblastoma. *Surg Today* 34(2):127–133
22. Fiorentini G, Rossi S, Bonechi F, Vaira M, De Simone M, Dentico P, Bernardeschi P, Cantore M, Guadagni S (2004) Intraarterial hepatic chemoembolization in liver metastases from neuroendocrine tumors: a phase II study. *J Chemother* 16(3):293–297
23. Kress O, Wagner HJ, Wied M, Klose KJ, Arnold R, Alfke H (2003) Transarterial chemoembolization of advanced liver metastases of neuroendocrine tumors - a retrospective single-center analysis. *Digestion* 68(2–3):94–101

24. Wasser K, Giebel F, Fischbach R, Tesch H, Landwehr P (2005) Transcatheter arterial chemoembolization of colorectal liver metastases using degradable starch microspheres (Spherex (R)). Own investigations and review to the literature. [German] *Radiologe* 45 (7):633–643
25. Ruzsniwski P, O'Toole D (2004) Ablative therapies for liver metastases of gastroenteropathic endocrine tumors. *Neuroendocrinology* 80 (suppl 1):74–78
26. Popov I, Lavrnic S, Jelic S, Jezdic S, Jasovic A (2002) Chemoembolization for liver metastases from colorectal carcinoma: risk or a benefit. *Neoplasma* 49(1):43–48
27. Muller H, Nakchbandi V, Chatzisavvidis I, von Voigt C (2003) Repetitive chemoembolization with melphalan plus intraarterial immunochemotherapy within 5-fluorouracil and granulocyte-macrophage colony-stimulating factor (GM-CSF) as effective first- and second-line treatment of disseminated colorectal liver metastases. *Hepatogastroenterology* 50(54):1919–1926
28. Schell SR, Camp ER, Caridi JG, Hawkins IF (2002) Hepatic artery embolization for control of symptoms, octreotide requirements, and tumor progression in metastatic carcinoid tumors. *J Gastrointest Surg* 6(5):664–670
29. Loewe C, Schindl M, Cejna M, Niederle B, Lammer J, Thurnher S (2003) Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and lipiodol: assessment of mid- and long-term results. *AJR Am J Roentgenol* 180 (5):1379–1384
30. Hunt TM, Flowerdew AD, Birch SJ, Williams JD, Mullee MA, Taylor I (1990) Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases. *Br J Surg* 77(7):779–782
31. Martinelli DJ, Wadler S, Bakal CW, Cynamon J, Rozenblit A, Haynes H, Kaley R, Wiernik PH (1994) Utility of embolization or chemoembolization as second-line treatment in patients with advances or recurrent colorectal carcinoma. *Cancer* 74(6):1706–1712
32. Salman HS, Cynamon J, Jagust M, Bakal C, Rozenblit A, Kaley R, Negassa A, Wadler S (2002) Randomized phase II trial of embolization therapy versus chemoembolization therapy in previously treated patients with colorectal carcinoma metastatic to the liver. *Clin Colorectal Cancer* 2 (3):173–179
33. Agarwala SS, Panikkar R, Kirkwood JM (2004) Phase I/II randomized trial of intrahepatic arterial infusion chemotherapy with cisplatin and chemoembolization with cisplatin and polyvinyl sponge in patients with ocular melanoma metastatic to the liver. *Melanoma Res* 14(3):217–222
34. Bedikian AY, Legha SS, Mavligit G, Carrasco CH, Khorana S, Plager C, Papadopoulos N, Benjamin RS (1995) Treatment of uveal melanoma metastatic to the liver: a review of the M.D. Anderson Cancer Center experience and prognostic factors. *Cancer* 76 (9):1665–1670
35. Gupta S, Yao JC, Ahrar K, Wallace MJ, Morello FA, Madoff DC, Murthy R, Hicks ME, Ajani JA (2003) Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. *Cancer J* 9 (4):261–267
36. Roche A, Girish BV, de Baere T, Baudin E, Boige V, Elias D, Lasser P, Schlumberger M, Ducreux M (2003) Transcatheter arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumors. *Eur Radiol* 13(1):136–140
37. Tarazov PG (2000) Transcatheter therapy of gastric cancer metastatic to the liver: preliminary results. *J Gastroenterol* 35(12):949–950
38. Taniguchi H, Takahashi T, Sawai K, Yamaguchi T, Hagiwara A, Kitamura K et al (1997) Comparison in survival between hepatic metastases of gastric and colorectal cancers. *Hepatogastroenterology* 44(15):897–900
39. Ikeda T, Adachi I, Takashima S, Ogita M, Aoyama H, Sano M, Ando J, Tabei T, Tominaga T, Enomoto K, Kanda K, Fukutomi T, Shimoyama M (1999) A phase I/II study of continuous intraarterial chemotherapy using an implantable reservoir for the treatment of liver metastases from breast cancer: a Japan Clinical Oncology Group (JCOG) study 9113. *JCOG Breast Cancer Study Group. Jpn J Clin Oncol* 29(1):23–27
40. Egerer G, Lehnert T, Max R, Naeher H, Keilholz U, Ho AD (2001) Pilot study of hepatic intraarterial fotemustine chemotherapy for liver metastases from uveal melanoma: a single-center experience with seven patients. *Int J Clin Oncol* 6(1):25–28
41. Arai Y, Endo T, Sone Y, Tohyama N, Inaba Y, Kohno S et al (1992) Management of patients with unresectable liver metastases from colorectal and gastric cancer employing an implantable port system. *Cancer Chemother Pharmacol* 31 [Suppl 1]:99–102
42. Yoon SS, Tanabe KK (1999) Surgical treatment and other regional treatments for colorectal cancer liver metastases. *Oncologist* 4(3):197–208
43. Vogl TJ, Mack MG, Balzer JO, Engelmann K, Straub R, Eichler K, Woitaschek D, Zangod S (2003) Liver metastases: neoadjuvant downsizing with transarterial chemoembolization before laser-induced thermotherapy. *Radiology* 229(2):457–464
44. Vogl TJ, Mack MG, Müller PK, Straub R, Engelmann K, Eichler K (1999) Interventional MR: interstitial therapy. *Eur Radiol* 9(8):1479–1487
45. Yamagami T, Kato T, Tanaka O, Hirota T, Nishimura T (2005) Radiofrequency ablation therapy of remnant colorectal liver metastases after a course of hepatic arterial infusion chemotherapy. *J Vasc Interv Radiol* 16(4):549–554
46. Barber FD, Mavligit G, Kurzrock R (2004) Hepatic arterial infusion chemotherapy for metastatic colorectal cancer: a concise overview. *Cancer Treat Rev* 30(5):425–436
47. Ducreux M, Ychou M, Laplanche A, Gamelin E, Lasser P, Husseini F, Quenet F, Viret F, Jacob JH, Boige V, Elias D, Delpero JR, Luboinski M (2005) Gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol* 23 (22):4881–4887

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48. Kemeny N, Jarnagin W, Paty P, Gonen M, Schwartz L, Morse M, Leonard G, D'Angelica M, DeMatteo R, Blumgart L, Fong Y (2005) Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. *J Clin Oncol* 23(22):4888–4896
 49. Durand-Zaleski I, Earlam S, Fordy C, Davies M, Allen-Merish TG (1998) Cost-effectiveness of systemic and regional chemotherapy for the treatment of patients with unresectable colorectal liver metastases. *Cancer* 83(5):882–888
 50. Durand-Zaleski I, Roche B, Buyse M, Carlson R, O'Connell MJ, Rougier P, Chang AE, Sondak VK, Kemeny MM, Allen-Merish TG, Fagniez PL, Le Bourgeois JP, Piedbois P (1997) Economic implications of hepatic arterial infusion chemotherapy in treatment of nonresectable colorectal liver metastases. *Meta-Analysis Group in Cancer. J Natl Cancer Inst* 89(11):790–795
 51. Abramson RG, Rosen MP, Perry LJ, Brophy DP, Raeburn SL, Stuart KE (2000) Cost-effectiveness of hepatic arterial chemoembolization for colorectal liver metastases refractory to systemic chemotherapy. *Radiology* 216(2):485–491
 52. Yoshikawa M, Ebara M, Nakano T, Minoyama A, Sugiura N, Ohto M (1992) Percutaneous transaxillary catheter insertion for hepatic artery infusion chemotherapy. *AJR Am J Roentgenol* 158(4):885–886
 53. Oi H, Kishimoto H, Matsushita M, Hori M, Nakamura H (1996) Percutaneous implantation of hepatic artery infusion reservoir by sonographically guided left subclavian artery puncture. *AJR Am J Roentgenol* 166(4):821–822
 54. Wacker FK, Boese-Landgraf J, Wagner A, Albrecht D, Wolf KJ, Fobbe F (1997) Minimally invasive catheter implantation for regional chemotherapy of the liver: a new percutaneous transsubclavian approach. *Cardiovasc Interv Radiol* 20(2):128–132
 55. Zanon C, Grosso M, Clara R et al (2001) Combined regional and systemic chemotherapy by a mini-invasive approach for the treatment of colorectal liver metastases. *Am J Clin Oncol* 24(4):354–359
 56. Jung HY, Shim HJ, Kwak BK et al (1999) Percutaneously implantable catheter-port system for chemotherapeutic infusion through the hepatic artery. *AJR Am J Roentgenol* 172(3):641–644
 57. Kuroiwa T, Honda H, Yoshimitsu K et al (2001) Complications encountered with a transfemorally placed port-catheter system for hepatic artery chemotherapy infusion. *Cardiovasc Intervent Radiol* 24(2):90–93
 58. Lorenz M, Mueller HH, Mattes E, Gassel HJ, Junginger T, Saeger HD, Schramm H, Staib-Sebler E, Vetter G, Heinrich S, Kohne CH (2001) German Cooperative Group on Liver Metastases (Arbeitsgruppe Lebermetastasen und -tumoren (ALM) in der Chirurgischen Arbeitsgemeinschaft Onkologie) Phase II study of weekly 24-hour intra-arterial high-dose infusion of 5-fluorouracil and folinic acid for liver metastases from colorectal carcinomas. *Ann Oncol* 12(3):321–325
 59. Okamoto N, Maruta M, Maeda K, Sato H, Takizawa K, Masumori K, Aoyama H, Kato R (2003) Clinical outcome of intra-hepatic arterial infusion therapy for multiple liver metastases from colorectal cancer *Gan To Kagaku Ryoho* 30(4):501–504
 60. Tono T, Hasuike Y, Ohzato H, Takasuka Y, Kikkawa N (2000) Limited but definite efficacy of prophylactic hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases. *Cancer* 88:1549–1556
 61. Fiorentini G, Rossi S, Dentico P, Bernardeschi P, Calcinai A, Bonechi F, Cantore M, Gaudagni S, De Simone M (2003) Irinotecan hepatic arterial infusion chemotherapy for hepatic metastases from colorectal cancer: a phase II clinical study. *Tumori* J 89(4):382–384
 62. Fazio N, Orsi F, Grasso RF, Ferretti G, Medici M, Rocca A, Zampino G, Curigliano G, De Pas T, Colleoni M, Bonomo G, Marrocco E, Lunghi L, De Braud F (2003) Hepatic intraarterial chemotherapy using a percutaneous catheter in pretreated patients with metastatic colorectal carcinoma. *Anti-cancer Res* 23(6D):5023–5030
 63. Oberfield RA, Sampson E, Heatley GJ (2004) Hepatic artery infusion chemotherapy for metastatic colorectal cancer to the liver at the lahey clinic: comparison between two methods of treatment, surgical versus percutaneous catheter placement. *Am J Clin Oncol* 27(4):376–383
 64. Kemeny N, Eid A, Stockman J, Gonen M, Schwartz L, Tetzlaff E, Paty P (2005) Hepatic arterial infusion of floxuridine and dexamethasone plus high-dose Mitomycin C for patients with unresectable hepatic metastases from colorectal carcinoma. *J Surg Oncol* 91(2):97–101
 65. Voigt W, Behrmann C, Schlueter A, Kegel T, Grothey A, Schmoll HJ (2002) A new chemoembolization protocol in refractory liver metastasis of colorectal cancer: a feasibility study. *Onkologie* 25(2):158–164