Eur. Radiol. 9, 675–684 (1999)

Abdominal radiology European Radiology

Review article

Liver metastases: interventional therapeutic techniques and results, state of the art

T.J. Vogl[1], P.K. Müller[1], M.G. Mack[1], R. Straub[1], K. Engelmann[1], P. Neuhaus[2]

[1] Department of Radiology, University of Frankfurt, Theodor Stern Kai 7, D-60590 Frankfurt, Germany
[2] Department of Surgery, Charité, Campus Rudolf Virchow, Humboldt University of Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany

Received: 29 July 1998; Revision received: 30 October 1998; Accepted: 4 November 1998

Abstract. The liver is the most common site of metastatic tumour deposits. Hepatic metastases are the major cause of morbidity and mortality in patients with gastrointestinal carcinomas and other malignant tumours. The rationale and results for interventional therapeutic techniques in the treatment of liver metastases are presented. For the treatment of patients with irresectable liver metastases, alternative local ablative therapeutic modalities have been developed. Technique and results of local interventional therapies are presented such as microwave-, radiofrequency (RF)- and ultrasound ablation, and laser-induced interstitial therapy (LITT), cryotherapy and local drug administration such as alcohol injection, endotumoral chemotherapy and regional chemoembolisation. In addition to cryotherapy, all ablative techniques can be performed percutaneously with low morbidity and mortality. Cryotherapy is an effective and precise technique for inducing tumour necrosis, but it is currently performed via laparotomy. Percutaneous local alcohol injection results in an inhomogeneous distribution in liver metastases with unreliable control rates. Local chemotherapeutic drug instillation and regional chemoembolisation produces relevant but non-reproducible lesions. Laser-induced interstitial thermotherapy (LITT) performed under MRI guidance results in precise and reproducible areas of induced necrosis with a local control of 94%, and with an improved survival rate. Interventional therapeutic techniques of liver metastases do result in a remarkable local tumour control rate with improved survival results.

Key words: Liver metastases – Interventional treatment modalities – Alcohol injection – Drug instillation – Radiofrequency ablation – Cryotherapy – Laser-induced interstitial thermotherapy – Regional chemoembolisation

Correspondence to: T.J. Vogl

Introduction

Hepatic metastases are the major cause of morbidity and mortality in patients with gastrointestinal carcinomas and malignant tumours of different origins. They present a common clinical problem and occur most frequently in patients with colorectal cancer and breast carcinoma. The treatment options for patients with liver metastases are limited. Surgical resection of liver metastases in colorectal cancer offers the only real hope of cure, and can improve 5-year survival from 16 to 40%. Most patients with colorectal liver metastases die within 2–3 years of diagnosis. Only 20% of patients are suitable for surgical resection of metastases [1–3]. This has led to a growing interest in various interstitial treatment methods for destroying liver metastases in situ, which obviate the need for a major surgery and can easily be repeated if new metastases develop [26]. Local ablative therapeutic techniques can be divided into two major groups, either thermotherapy or chemotherapy. Cell death is achieved via the use of RF ablation [4–8], laser-induced interstitial therapy (LITT) [1, 9–11], cryotherapy [12, 13] or local drug instillation such as alcohol injection [14, 15], chemotherapeutic drug instillation [16, 17] and regional arterial chemoembolisation (Fig. 1) [18, 19].

By definition the therapeutic stimulus is delivered directly to a selected site of intended tissue damage, resulting in localised cell damage. The majority of treatment modalities are performed under local anaesthesia involving the active participation by the patient with minimal or no side effects, excluding cryosurgery which is performed during laparotomy. The rationale for the use of interstitial ablative techniques is the reduction or complete destruction of viable tumour volume and improved survival data.

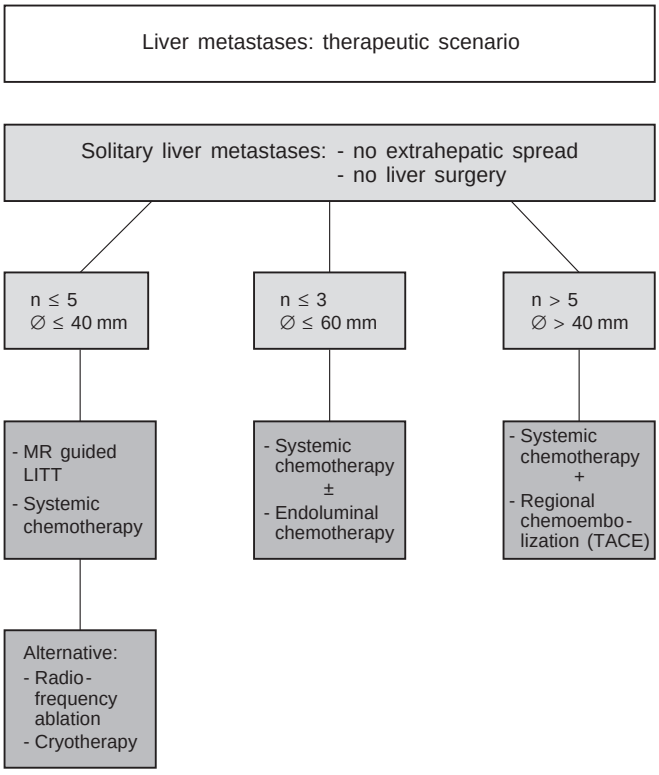


Fig. 1. Liver metastases: therapeutic scenario

Radio-frequency ablation

The use of RF alternating current began in 1891 in Paris. The French physicist D'Arsanval reported that alternating current at frequencies over 250 kHz could be used to generate heat effects in biological tissue without causing motoric stimulation of nerves and muscle. By applying the electrical energy slowly with low-current density to tissue, the cells are heated. The tissue dehydrates and the collagenous structures degenerate [4]. Clinically RF ablation of malignant liver tumours was described by Rossi et al. [20] for the treatment of hepatocellular carcinoma (HCC) and liver metastases. In this study a total of 50 patients were treated (Table 1). Thirty-nine patients suffered from 41 HCC nodules and 11 patients from 13 hepatic metastatic nodules. The mean follow-up was 11 months (range 3–27 months) in 9 patients with 11 metastatic nodules, excluding 2 patients who underwent surgery. On sonographic follow-up, two metastatic nodules of approximately 1.0 cm in diameter were no longer visible, and three metastases that ranged from 2.0 to 3.5 cm in diameter diminished in size and became small hyperechoic or heterogeneous areas less than 1.0 cm in diameter. Three metastases, two approximately 3.5 cm in diameter and the large centrohepatic mass, changed in sonographic pattern but showed only little volume reduction. One metastatic nodule 3.5 cm in diameter showed a local progression.

Lencioni et al. [6] reports about the treatment of 29 patients with one to four hepatic metastases 1.1–4.8 cm in diameter (mean 2.9 ± 0.8 cm) from previously resected intra-abdominal primary malignancies. Radiofrequency ablation was performed by using a 100-W generator and 17-gauge, dual lumen, cooled-tip electrode needles with a 2- to 3-cm exposed tip. Findings in spiral CT were used to assess the therapeutic response. Complete tumour response was seen in 41 (71 %) of 53 lesions, including 33 (87 %) of 38 lesions 3 cm or less in diameter. After a mean follow-up of 6.5 ± 2.1 months, recurrence of the treated lesion was seen in 5 (12 %) of the 41 cases. New metastatic lesions appeared in 7 patients. Two patients died after 6 and 8 months. Of the 27 patients still in follow-up, 14 are currently free of disease.

Solbiati et al. [7] described the treatment of 29 patients with a total of 44 hepatic metastases with diameters varying from 1.3 to 5.1 cm in diameter with percutaneous RF ablation with cooled tips under conscious sedation (neuroleptanalgesia) with continuous cardiovascular and respiratory monitoring. The heating of the tissue nearest the RF electrode was reduced, with the cooling system allowing greater energy deposition and an increased coagulation zone.

Technical aspects

Cooled-tip RF electrodes with 2–3 cm of exposed metallic tip are currently used to deliver the RF energy to the tissues. In each treatment session a single electrode is placed within the tumour under sonographic guidance. Grounding is achieved by attaching a large grounding pad. The electrode is then attached to a 500-kHz monopolar RF generator capable of producing 100-W power. During lesion ablation, a thermocouple continuously measures the local temperature. Tissue impedance is monitored continuously by means of circuitry incorporated within the generator. Cooling is achieved infusing 0 °C normal saline solution into the cooling lumen of the RF electrode at a rate sufficient to maintain a tip temperature of 20–25 °C. To prevent tissue boiling, initially generator output is slowly increased to 950–1.100 mA. If an increase in impedance ≥ 10 Ohm above baseline is observed, the current is reduced in 50-mA intervals until stable impedance is observed. Standard RF application lasted 12–25 min.

The results of this study by Solbiati et al. [7] for the cooled-tip RF ablation technique are encouraging, but they must be interpreted in view of several important limitations. The control rate of 18 months is too short to show meaningful differences in survival rates with other treatment strategies. Full evaluation and larger studies with a longer follow-up of this technique will be necessary. An RF-induced coagulation necrosis with a mean diameter of 2.8 ± 0.3 cm (mean ± standard deviation) in diameter (range 2.5–3.1 cm) and 3.4 ± 0.3 cm was achieved in the study documented by CT and MR imaging. This limits the practical efficacy for smaller metastases (Table 1).

Table 1. Characteristics and outcomes of interventional therapeutic treatments of liver metastases. *PEI* percutaneous ethanol injection; *ILP* interstitial laser photocoagulation

Reference	Technique	Primary tumour of liver metastases	Follow-up			
			< 1 year	< 2 years	< 3 years	< 4 years
[20]	RF	Colorectal cancer, gastrinoma, breast cancer, ovarian carcinoma, thymoma, gastric cancer	Mean 11 months (range 2–27 months)			
[6]	RF, cooled tip	Colorectal cancer, gastric cancer, glucagonoma	Mean 6.5 ± 2.1 months (range 3–9 months)			
[7]	RF, cooled tip	Colorectal cancer, gastric cancer, pancreatic cancer, breast cancer	All patients in 6 months; 94 % of patients in 12 months	89 % in 18 months		
[24]	Cryosurgery	Colorectal		Range 5 months to 5 years		
[25]	Cryosurgery	No statement				
[10]	Laser-induced thermotherapy	Colorectal cancer, breast cancer, gastric cancer, pancreatic cancer, lung cancer, melanoma, thyroid cancer				40, 8 months cumulative survival rate
[35]	Chemoembolisation		10 months			
[18]	Chemoembolisation	Neuroendocrine cancer			33 months	
[19]	Chemoembolisation	Colorectal cancer	Median survival 10 months			
[40]	PEI	Colorectal cancer, breast cancer, gallbladder cancer				
[42]	PEI, ILP	Colorectal cancer	Median survival: 7 months for 15 patients; 6.5 months for 6 patients (PEI or ILP)	Median survival:	Median survival: 27 months for 8 patients (ILP)	

Cryotherapy

Cryosurgery is defined as local tumour destruction in situ by freezing. Cryosurgery is currently used in patients with prostatic malignancy and in some institutions for patients with liver malignancies. Currently studies are performed in a wide range of other benign and malignant disease.

The mechanism of tumour cell destruction by freezing depends on the location of the tissue in relation to the cryoprobe. In areas close to the cryoprobe, temperatures rapidly achieve –190 °C, causing ice crystals to form within and around cells. Subsequent rupture of the cell membrane during thaw and rehydration results in tissue death. In a certain distance from the probe, where temperatures drop more slowly, ice forms within venules and arterioles, because cell walls impede intracellular ice crystal formation. Unfrozen parenchymal cells dehydrate to equilibrate the resultant chemical gradient, which causes expansion of blood vessels which rupture during thawing. The resultant short term hypoxia contributes to the death of surviving cells. Cell death within the freezing zone is due to a combination of intra- and extracellular ice crystal formation, cellular dehydration and rupture and hypoxia from small vessel destruction [10, 21–23].

Technical aspects

Ravikumar et al. [24] have analysed cryosurgery in 24 patients (15 men and 9 women; median age 67 years, range 36–81 years) with liver metastases from colorectal cancer during a 5-year period from 1985 to 1990). Cryosurgery is done by an operative standard exploration and the entire liver is scanned with an intraoperative ultrasound unit. The probe is placed into the lesion under ultrasound guidance. The probes have insulated shafts with cold tips of varying sizes. Cryogen liquid nitrogen at –196 °C circulates by a cryosurgical system. Under ultrasound guidance the freeze–thaw is controlled. The freezing therapy takes approximately 10–20 min. The therapeutic response to cryosurgery is monitored by CT scan and ultrasound of the liver at 1 week, 6 weeks and every 3 months after therapy. At median follow-up of 2 years (range 5 months to 5 years), 7 patients

(29%) are disease free, 8 patients (33.5%) were alive with recurrent tumours and 9 patients (37.5%) have died (Table 1) [24].

Lee et al. [25] conclude that the benefits of hepatic cryosurgery are potentially maximised through collaboration between surgeons with experience in hepatic surgery and radiologists, who are well versed in US. In combination with intraoperative US monitoring, cryosurgery allows specific targeting of the diseased tissue with minimal damage to uninvolved liver parenchyma. Continued technological advantages related to laparoscopic surgery, cryoprobe design and imaging guidance with modalities such as CT and MR imaging should make this technique even more effective and less invasive in future.

Laser-induced interstitial therapy

Interstitial hyperthermia via laser technology with the insertion of the light-conducting quartz fibre into tumour was described first by Bown [26]. Although this method of energy delivery is invasive it has the advantages that there is little back-scattering and impact loss as light strikes tissue, and in order to reach a specific point within an organ, the surface is not heated by a thermal conduit.

Laser light is produced using a neodymium yttrium aluminium garnet (Nd:YAG; wavelength 1064 nm) delivered through a quartz fibre optic with a diameter of 400 μm with diffuse light emission. Laser light is converted into heat in the target area with an ensuing coagulative necrosis, secondary degeneration and atrophy, and tumour shrinkage with minimal damage to surrounding structures [27–29]. The size of heated volume depends on laser power, laser irradiation time, the way it reaches the target area and optical and thermal characteristics of the treated tissue. Pilot clinical studies have demonstrated that this technique is practical for the palliation of hepatic tumours. The clinical success of the thermotherapy depends on the optimal positioning of the laser applicator in the centre of the lesion, an optimal "on-line monitoring" of thermal changes in the treated tissue and an exact documentation of the therapy effect and the local tumour control rate. The optimisation of a specially developed thermosensitive magnetic resonance sequence allows exact monitoring of the progress of LITT to the treated lesion and surrounding structures; thus, MR imaging and MR thermometry (MRTH) have become essential tools for the monitoring of thermotherapies in the liver [30–32].

Technical aspects

Patients chosen for the local LITT destruction should have less than five lesions with none measuring more than 50 mm, be unfit for surgical resection or suffer from irresectable tumours or lesions in both hepatic lobes or refuse surgical resection [10, 11].

All patients are evaluated with MR imaging 2–5 days prior to LITT, which includes precontrast T2- and T1-weighted sequences, the dynamic contrast-enhanced turbo-FLASH sequence and postcontrast T1-weighted sequences (0.1 mmol/kg b.w. Gd-DTPA). Informed written consent is obtained at least 24 h before therapy. Immediately prior to the procedure, diazepam (10–15 mg) and pethidine (50–100 mg) are administered intravenously. After localisation of the metastases on plain CT scans, the distances from the abdominal wall to the lesion and the puncture channel are defined. The abdominal wall and the liver capsule are anaesthetised (20 ml lidocaine 1%) at the intended puncture side and afterwards a Chiba needle is positioned percutaneously using a lateral or a ventral approach. A guidewire is introduced and the puncture channel is dilated to 7-F, to introduce a thermostable plastic catheter [3, 10, 11].

After inserting the laser catheter into the thermostable plastic catheter sheath, the optimal position of the magnetite marker and the laser applicator is established with MR imaging. A thermosensitive T1-weighted FLASH 2D sequence (TR/TE: 102/8 ms, flip angle 70°, FOV 350 mm, matrix 128 × 256, slice thickness 8 mm) is used to monitor the progress of LITT. The thermosequence is more sensitive for the detection of the laser-induced thermal changes in signal and morphology. Magnetic resonance imaging "on-line thermometry" allows an exact documentation of signal changes around the laser applicator and the border of the lesion (Fig. 2) [33, 34].

Immediately after LITT, an 0.1 mmol/kg b.w. Gd-DTPA enhanced FLASH-2D sequence provides essential information about the laser-induced necrosis and possible complications. Follow-up examinations are obtained 2 days and every 3 months after thermotherapy (Fig. 2).

Clinical results

A total of 251 patients 28–84 years of age (mean age 5.5 years, 144 males and 107 females) with a total of 733 liver tumours were treated with LITT. A total of 1822 laser applications and 1429 cannulations were performed in 680 treatment sessions. The patient group consisted of hepatic metastases of colorectal cancer, breast cancer, HCC and miscellaneous tumours.

One hundred fifty-nine patients suffered from metastases of colorectal cancer, 42 patients from metastases of breast cancer (16.7%), and in 36 patients there were miscellaneous tumours of the liver. A primary HCC was observed in 14 patients.

The complication rate is based on the number of therapy sessions, not on the number of laser applications. All patients tolerated the procedure under local anaesthesia well. One patient died 4 weeks after treatment; the patient had developed a leakage in the jejunum after LITT of a liver metastases in the liver segment 4a. The patient underwent surgery and died due to peritonitis and acute respiratory distress syndrome.

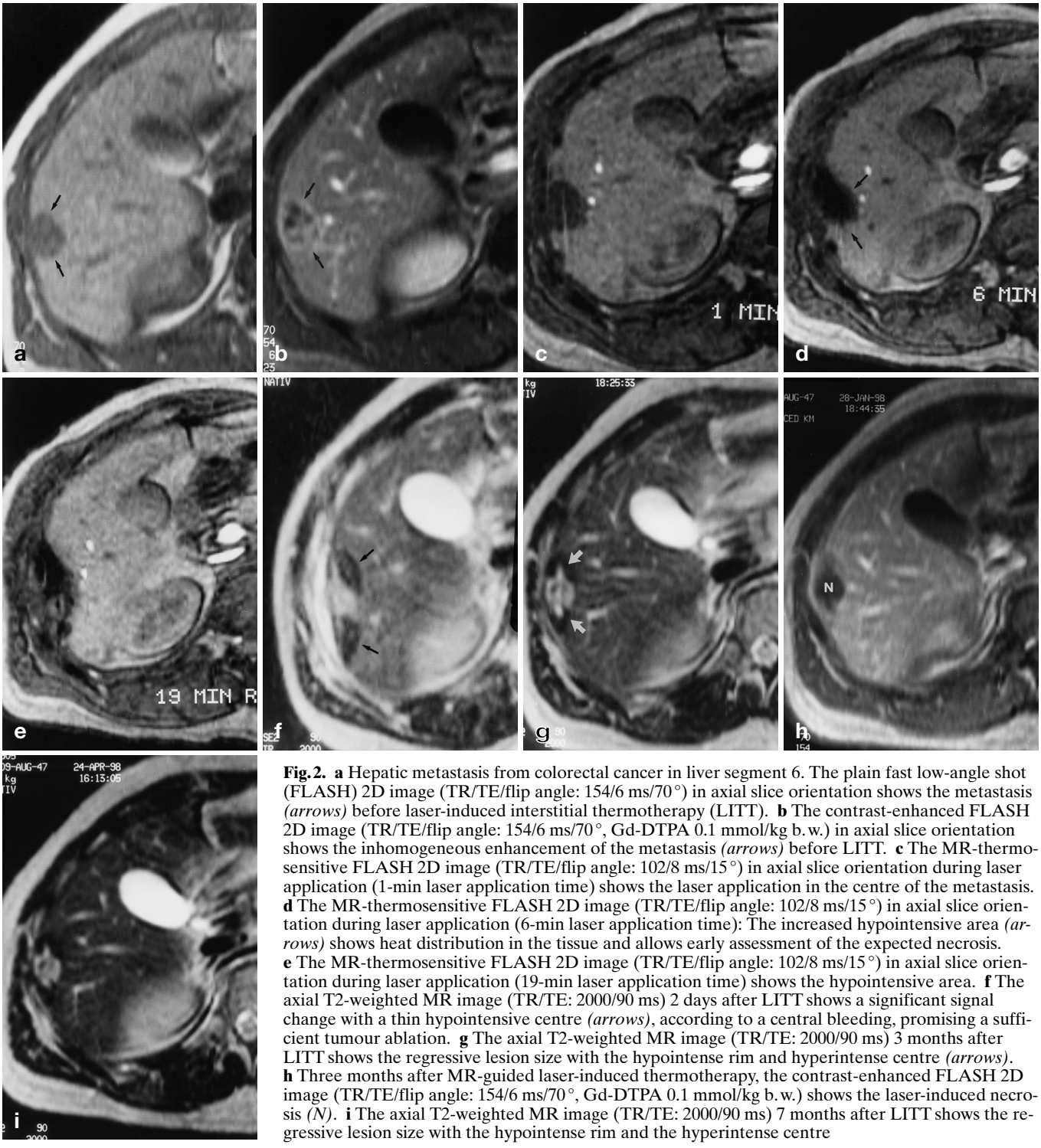


Fig. 2. **a** Hepatic metastasis from colorectal cancer in liver segment 6. The plain fast low-angle shot (FLASH) 2D image (TR/TE/flip angle: 154/6 ms/70°) in axial slice orientation shows the metastasis *(arrows)* before laser-induced interstitial thermotherapy (LITT). **b** The contrast-enhanced FLASH 2D image (TR/TE/flip angle: 154/6 ms/70°, Gd-DTPA 0.1 mmol/kg b.w.) in axial slice orientation shows the inhomogeneous enhancement of the metastasis *(arrows)* before LITT. **c** The MR-thermosensitive FLASH 2D image (TR/TE/flip angle: 102/8 ms/15°) in axial slice orientation during laser application (1-min laser application time) shows the laser application in the centre of the metastasis. **d** The MR-thermosensitive FLASH 2D image (TR/TE/flip angle: 102/8 ms/15°) in axial slice orientation during laser application (6-min laser application time): The increased hypointensive area *(arrows)* shows heat distribution in the tissue and allows early assessment of the expected necrosis. **e** The MR-thermosensitive FLASH 2D image (TR/TE/flip angle: 102/8 ms/15°) in axial slice orientation during laser application (19-min laser application time) shows the hypointensive area. **f** The axial T2-weighted MR image (TR/TE: 2000/90 ms) 2 days after LITT shows a significant signal change with a thin hypointensive centre *(arrows)*, according to a central bleeding, promising a sufficient tumour ablation. **g** The axial T2-weighted MR image (TR/TE: 2000/90 ms) 3 months after LITT shows the regressive lesion size with the hypointense rim and hyperintense centre *(arrows)*. **h** Three months after MR-guided laser-induced thermotherapy, the contrast-enhanced FLASH 2D image (TR/TE/flip angle: 154/6 ms/70°, Gd-DTPA 0.1 mmol/kg b.w.) shows the laser-induced necrosis *(N)*. **i** The axial T2-weighted MR image (TR/TE: 2000/90 ms) 7 months after LITT shows the regressive lesion size with the hypointense rim and the hyperintense centre

The death was considered possibly LITT related, most likely due to a stress ulceration of the jejunum. In one case (0.15%) a liver abscess was observed. After two LITT treatments, patients (0.29%) suffered from pain for more than 24 h and less than 1 week; the pain was treated with an oral analgesic drug. In eight cases (1.2%) subcapsular haematomas without clinical symptoms and in 39 treatments pleural effusion (5.7%) on the right side were documented.

The cumulative survival times were calculated using the Kaplan-Maier method. The overall cumulative survival rate of patients with liver metastases was 40.8 months (median 40.97 months, 95% confidence interval 36.37–45.24%) (Fig. 3). The cumulative survival rate of the patients group with hepatic metastases of colorectal carcinoma was 38.11 months (median 36.43 months, 95% confidence interval 33.05–43.16%). No significant difference was documented between the

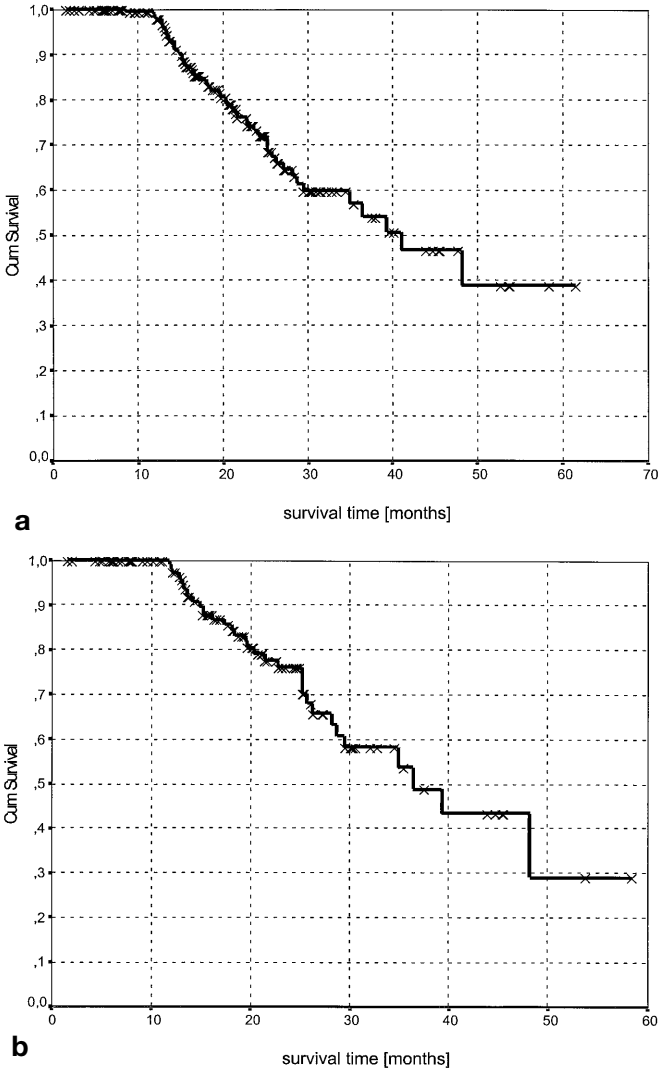


Fig. 3. **a** Cumulative survival curve of all patients with hepatic metastases after MR-guided LITT. *X* censored cases. **b** Cumulative survival curve of all patients with hepatic metastases of colorectal carcinomas after MR-guided LITT. *X* censored cases

survival data in patients with liver metastases of colorectal cancer and other primary tumours.

Magnetic-resonance-guided laser-induced thermotherapy is a safe and sufficient therapeutic modality for local tumour destruction in patients with liver metastases and improves the clinical outcome [3, 10, 11].

Regional chemoembolisation

Transcatheter arterial chemoembolisation (TACE) is currently performed mainly for the curative or palliative treatment of HCC and liver metastases [18, 19, 35]. Combined with percutaneous ethanol injection (PEI), TACE has proven to offer an alternative curative approach for patients with local involvement of HCC. In patients with liver metastases the therapeutic strategy, including transarterial embolisation (TAE) or transarterial chemoembolisation (TACE), is a strictly palliative one. In liver metastases of malignant neuroendocrine tumours TAE with Lipiodol and TACE with Lipiodol and chemotherapeutic drugs do allow the induction of a partial remission of liver metastases in a small number of patients [35].

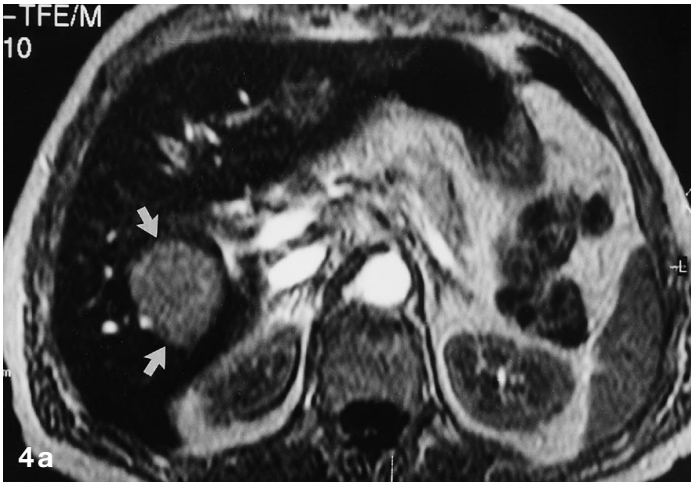
Technical aspects

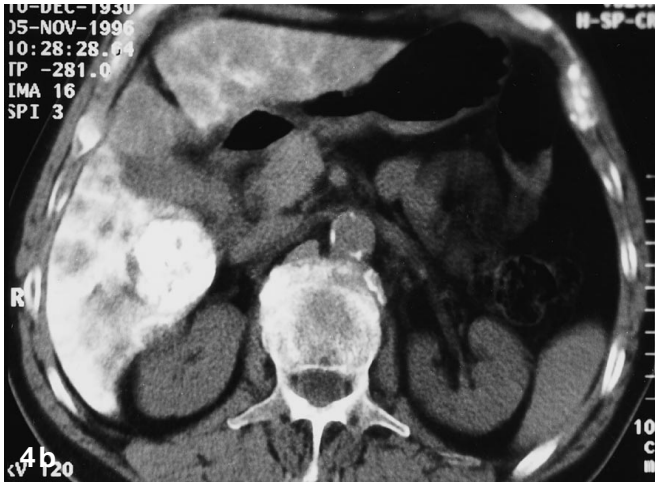
After introduction of the catheter in the femoral artery, an angiographic survey of the abdominal vessels is performed. An indirect portography is consecutively obtained by selective application in the superior mesenteric artery or the splenic artery. A selective catheterisation of the coeliac trunk is performed, and a catheter is advanced beyond the gastroduodenal artery. Dependent on size, localisation and arterialisation of the tumour and its satellites, the tip of the catheter is advanced further into segmental arteries for selective embolisation using a special tracker catheter. The TACE technique is performed by injecting an emulsion of iodised oil (Lipiodol, Ultra Fluid, Laboratories Guerbet, Aulnay-sous-Bois, France) and adriblastin, cisplatin and other chemotherapeutic drugs, followed by microspheres (Spherex, Pharmacia, Erlangen, Germany) into the segmental or subsegmental arteries, feeding the tumour. The anticancer-in-oil emulsion is injected until Lipiodol has densely accumulated in the tumour. The actual Lipiodol volume injected varies between 5 and 20 ml. Embolic material is regularly injected until feeding arteries are completely obliterated.

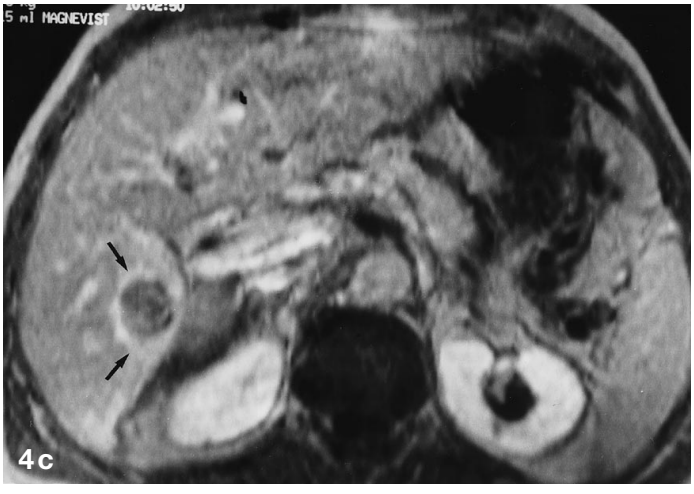
Pretherapeutically unenhanced, arterial-phase (volume 100 ml, flow 4 ml/s, delay 15 s) and venous phase (volume 70 ml, flow 1 ml/s, delay 80 s) spiral CT is performed. Twenty-four hours after embolisation, the retention of Lipiodol in the tumour and the liver parenchyma is verified via unenhanced CT examination protocol. Plain and contrast-enhanced CT studies are performed at an interval of 3 months in the first year and twice a year thereafter. Alternatively, unenhanced and enhanced MRI is used for the initial evaluation of patients and follow-up studies. Currently limited data on the clinical value of TACE are available as a palliative treatment protocol for patients with liver metastases (Table 1) [36].

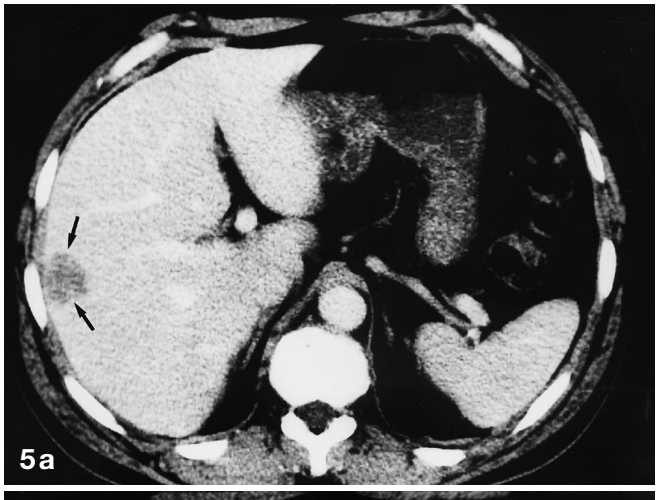
Lopez et al. [35] describes 23 TACE treatments in 15 patients. Ten of 15 patients had HCC, and 5 patients had metastatic tumours. Seven patients had a single treatment, whereas 8 patients had two sequential treatments for bilobar disease. At a median for 10 months (range 2–15 months), 14 of 15 (93 %) patients are alive. At the follow-up, 2 patients were found to have metastases within 2 months.

Martin et al. [18] report about preoperative hepatic arterial chemoembolisation (CET) followed by liver transplantation (OLT). Twenty-three of 41 patients (56 %) referred with primary ($n = 16$) or metastatic neuroendocrine ($n = 7$) liver tumours met eligibility requirements. Four of 5 patients ultimately received OLT. Three patients are alive and free of disease at mean follow-up of 17 months, one died of recurrent









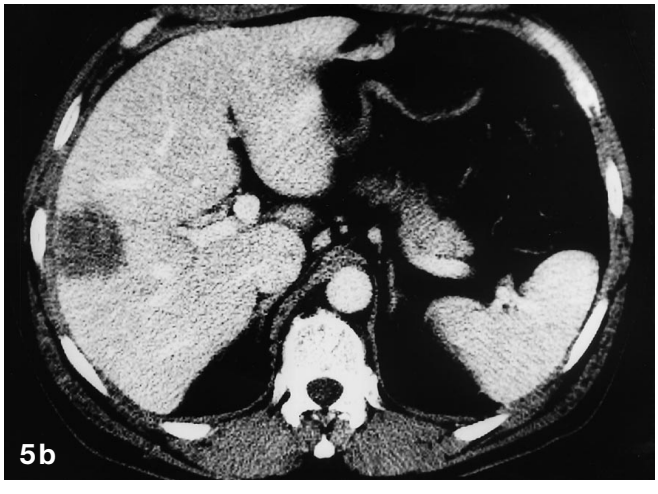


Fig. 4. **a** Hepatic metastasis from colorectal cancer in liver segment 6. The contrast-enhanced FLASH 2D image (TR/TE/flip angle: 154/6 ms/70°, iron oxide mmol/kg b. w., slice thickness 8 mm) in axial slice orientation shows the metastasis with hyperintense signal *(arrows)* before chemoembolisation. **b** The plain unenhanced CT image 2 days after chemoembolisation shows the injected Lipiodol with hyperdense signal intensity in both liver lobes and primarily in the liver metastasis. **c** The contrast-enhanced FLASH 2D image (TR/TE/flip angle: 154/6 ms/70°, Gd-DTPA 0.1 mmol/kg b. w.) in axial slice orientation 6 months after chemoembolisation shows a lower contrast enhancement of the metastasis *(arrows)* compared with the normal liver parenchyma

Fig. 5. **a** The enhanced CT image (150 ml Ultravist 370, intravenously administered) before injection of the matrix gel and cisplatin shows the liver metastasis *(arrows)* with a maximum diameter of 2 cm. **b** The enhanced CT image (150 ml Ultravist 370, intravenously administered) 3 months after injection of the matrix gel and cisplatin shows the nearly unenhanced liver lesion with an increased diameter

hepatocellular carcinoma and one (NET) remains well at 33 months with elevated glucagon levels but no measurable disease. All NET patients are alive with resolution of hormonal symptoms. Four of five non-cirrhotic patients died of disease, and one has progressive tumour growth. Although OLT following CET achieves superior survival, its application is limited to a minority of patients with such tumours.

Sanz-Altamira et al. [19] describes the treatment of 40 patients suffering from colorectal liver metastases with chemoembolisation. Selective angiography of the hepatic artery was performed. The injected chemoemulsion consisted of 1000 mg of 5-fluorouracil, 10 mg mitomycin C and 10 ml of ethiodised oil in a total volume of 30 ml. Gelfoam embolisation then followed, until stagnation of blood flow was achieved. Patients were evaluated for response, overall survival and toxicities. Overall median survival from date of first chemoembolisation was 10 months. Factors that predicted a longer median survival included favourable performance status

(24 months), serum alkaline phosphatase and lactate dehydrogenase levels less than three times normal (24 and 12 months, respectively), and metastatic disease confined to the liver (14 months). Three patients died within 1 month of the procedure. The data of this study suggest that TACE of hepatic metastases in colorectal cancer should be evaluated further.

Locoregional drug application

Percutaneous ethanol injection

Percutaneous ethanol injection has been indicated as an effective alternative to surgery for small hepatocellular nodules, since complete necrosis of lesions less than 3 cm in diameter has been achieved. However, several studies have proven that in liver metastases the local tumour control is low, most probably due to an inhomogeneous distribution of the ethanol within the lesion [37–39].

Results of PEI in the treatment of liver metastases were far less encouraging than those obtained with HCC. Histopathological examinations of metastatic lesions resected after PEI showed only partial necrosis of the tumour [37, 40, 41].

Livraghi [15] treated 30 patients, 29 of them carriers of 51 focal lesions and one with approximately 40% of the liver involved by metastases. Primary cancer was colorectal in 19, stomach in 4, breast in 2, abdominal leiomyosarcoma in 1, endocrine in 3 cases. Size of the lesion ranged from 1.1 to 10 cm. Complete response was obtained in 13 of 17 lesions < 2 cm, 4 of 16 lesions 2–3 cm, 1 of 10 lesions 3–4 cm and 0 of 8 lesions > 4 cm. All endocrine metastases were associated with complete response, because of their small size (max. 2.1 cm), slow growth and hypervascularity. The longer follow-up of complete response is 4 years in a patient with three metastases from gastrinoma of unknown origin.

Amin et al. [42[performed a comparative study of interstitial laser photocoagulation (ILP) and PEI for local treatment of colorectal metastases: in their series, complete necrosis was obtained in 28 of 54 (52%) tumours treated by ILP and in 0 of 22 lesions underwent PEI. Therefore, at present, the role of PEI in the treatment of liver metastases seems to be extremely limited. Surgical resection is advisable whenever possible. In non-operable patients, other interventional treatments, such as RF electrocautery or ILP, seem to provide a superior local control rate.

Endotumoural chemotherapy

A different approach was developed on the local image-guided percutaneous application of chemotherapeutic drug agents in malignant liver tumours, especially liver metastases. Newly developed concepts are directed towards endotumoral chemotherapeutic strategies for the palliative treatment of liver tumours. Direct intratumoral injection of the chemotherapeutic agents leads to higher local drug concentration and reduces the systemic toxicity [17, 43].

Curley et al. [16] studied a novel drug delivery compound to treat induced liver cancer in an animal model. Hepatic VX-2 tumours, a highly vascular epithelioid tumour cell line, underwent direct intratumoral injection of a collagen matrix gel mixed with cisplatin (CDDP) and epinephrine. Control tumours were injected with CDDP and epinephrine or CDDP alone. Intratumoral levels of platinum were significantly higher ($p < 0.01$) at all time points in the tumours treated with CDDP in the collagen matrix. Tumours treated with the collagen matrix gel, CDDP and epinephrine showed complete tumour necrosis 7, 14 and 21 days after intratumoral injection, whereas control animals treated with CDDP and epinephrine, CDDP alone or collagen matrix gel alone showed marked hepatic tumour progression at all time points. This novel drug delivery method significantly increased intratumoral platinum levels and enhanced CDDP-related tumoricidal activity [17, 43].

The newly designed collagen matrix gel and cisplatin offers some advantages vs standard regional systemic chemotherapeutic strategies. The collagen matrix gel and cisplatin contains 4 mg cisplatin, 0.1 mg epinephrine, 20 mg purified bovine collage and substances for stability and pH adjustment (Matrix Pharmaceutical, Fremont, Calif.), and was used for intratumoral injection.

Materials and methods

In a phase-two study we treated 6 patients with 14 liver metastases of colorectal cancer and 7 patients with 9 HCC nodules with endotumoral chemotherapy. The included patients could have up to three tumours with no tumour diameter > 7 cm. The patients suffering from liver metastases of colorectal cancer had previous chemotherapy with 5-FU and Leucovorin.

Before starting the treatment cycles, the patients were screened for the inclusion and exclusion criteria. For the pretherapeutic evaluation plain and contrast-enhanced spiral CT was performed. The treatment phase consisted of 4 weekly treatments within 6 weeks followed by an evaluation at 2 weeks after the last treatment.

Technique

Prior to treatment, a plain CT-generated scan was obtained. Under local anaesthesia the intratumoral treatment was performed using a needle and a computer-generated guidance system. This technique allows the collagen matrix gel and cisplatin to be applied to the total tumour volume. (An optional second cycle of treatment followed by a 2-week evaluation can be added individually. Then the patient enters follow-up. Control CT scans and magnetic resonance tomography are done at regular intervals.)

Results

The volumes of tumour and necrosis before and after therapy were measured by computer-generated volumetric analysis. The volumetric CT and MRI evaluations show a significant development of induced necrosis. The tissue around the necrosis is changed in accordance with peritumoral reaction within the observation period. The area of peritumoral reaction is larger than the initial pretherapeutic tumour volume, but the surrounding liver tissue appears unchanged after treatment. Especially volumetric CT imaging revealed a mean tumour volume of 44.2 ml (range 2–114 ml) in liver metastases. Contrast-enhanced studies verified pretherapeutic tumour necrosis as non-enhancing areas with a value of 7.6 % for liver metastases. Intratumoral drug application resulted in a necrotic volume of 126 % in metastases. Volumetric CT imaging after direct intratumoral injection of the novel collagen matrix and cisplatin documents a therapeutically relevant necrosis for liver metastases.

Conclusion

The liver is the most common site of metastatic tumour deposits. Colorectal cancer is the third leading cause of death in Western communities, outnumbered only by lung and breast cancer [1, 3]. At the time of death, approximately two thirds of patients with colorectal cancer have liver metastases. If feasible, surgical tumour resection is still considered one of the best options for radical treatment for malignant liver tumours, but only 20 % of patients are suitable for surgical resection [26, 31]. Clinical conditions such as the presence of lesions in both hepatic lobes or the reduced clinical condition of a patient do exclude a surgical treatment. Moreover, liver surgery is a method that carries a mortality rate of approximately 5 % [1, 3].

These facts have led to the development of therapeutic alternatives in the treatment of liver metastases. Unfortunately, the results of already published ongoing clinical trials are inconclusive in terms of providing data for the therapeutic scenarios in non-surgical candidates with solitary liver metastases (Fig. 1). Local ablative therapies are indicated in patients with a low number of liver lesions and a maximum diameter ≤ 40 mm in diameter. Magnetic-resonance-guided LITT has demonstrated a high local tumour control rate and a possible positive influence on survival in a larger series of patients [10, 11]. Alternatively, RF ablation [7, 20] or cryotherapy [24, 25] might be applied in centres with expertise. Compared with percutaneous ethanol injection, RF treatment produces a more predictable volume of necrosis at every insertion and is not impaired by the consistency of metastatic tissue, which makes ethanol injection ineffective in secondary tumours. With respect to laser photocoagulation, RF treatment is less expensive. Cryosurgery, on the other hand, can be effective in the treatment of metastatic tumours of the liver, but has disadvantages in requires laparotomy to place the probe directly into the lesion and the larger probe size significantly increases the morbidity of the procedure [6]. In patients with larger solitary liver metastases, endotumoral chemotherapy might be an alternative strategy, although this technique needs clinical validation. Systemic chemotherapy should be the therapeutic means in all patients with liver metastases; in patients with insufficient results TACE could mean a therapeutic adjunct especially in hypervascularised metastases such as the group of neuroendocrine tumours [18, 35]. The therapeutic scenario becomes even more difficult if there is a local recurrence of liver metastases after surgery or chemotherapy. Here the local ablative therapies, such as LITT, have proven their therapeutic strength via a reliable local tumour control rate and a low degree of side effects [10, 11]. Future intentions are directed towards multidisciplinary studies, analysing in a randomised technique the effect of the different therapeutic strategies, solitary or combined, on the clinical outcome and survival of the patients. Ongoing clinical studies are comparing liver surgery vs local ablative technique and a combined protocol. In light of the enormous threat of liver metastases for the survival and quality of life of cancer patients, the development of further strategies to improve the outcome seems necessary. Endotumoral gene therapy, on the basis of sophisticated image-guided access to liver tumours, might promise a better future for these patients suffering from liver metastases.

References

1. Nolsoe CP, Torp-Pedersen S, Burcharth F, Horn T, Pedersen S, Christensen NH, Olldag ES, Andersen PH, Karstrup S, Lorentzen T, Holm H (1993) Interstitial hyperthermia of colorectal liver metastases with a US-guided Nd-YAG laser with a diffuser tip: a pilot clinical study. Radiology 187: 333–337
2. Stangl R, Altendorf Hofmann A, Charnley RM, Scheele J (1994) Factors influencing the natural history of colorectal liver metastases. Lancet 343: 1405–1410
3. Vogl T, Müller PK, Hammerstingl R, Weinhold N, Felix R (1995) Malignant liver tumors treated with imaging guided laser induced thermotherapy, technique and prospective results. Radiology 196: 257–265
4. Desinger K, Stein T, Tschepe J, Müller G (1996) Investigation on radio-frequency current application in bipolar technique for interstitial thermotherapy (RF-ITT). Minim Invasive Med 7: 92–97
5. Goldberg SN, Gazelle GS, Solbiati L, Rittman WJ, Mueller PR (1996) Radio-frequency tissue ablation: increased lesion diameter with a perfusion elelctrode. Acad Radiol 3: 636–644
6. Lencioni R, Goletti O, Armilotta N, Paolicchi A, Moretti M, Cioni D, Donati F, Cicorelli A, Ricci S, Carrai M, Conte PF, Cavina E, Bartolozzi C (1998) Radio-frequency thermal ablation of liver metastases with cooled tip electrode needle: results of a pilot clinical trial. Eur Radiol 8: 1205–1211
7. Solbiati L, Goldberg SH, Ierace T, Livraghi T, Meloni F, Dellanoce M, Sironi, Gazelle GS (1997) Hepatic metastases: percutaneous radio-frequency ablation with cooled-tip electrodes. Radiology 205: 367–373
8. Solbiati L, Ierace T, Goldberg SN, Sironi S, Livraghi T, Fiocca R, Servadio G, Rizzatto G, Mueller PR, DelMaschio A, Gazelle GS (1997) Percutaneous US-guided radio-frequency tissue ablation of liver metastases: treatment and follow-up in 16 patients. Radiology 202: 195–203

9. Amin Z, Donald J, Masters A, Kant R, Steger A, Bown C, Lees R (1993) Hepatic metastases: interstitial laser photocoagulation with real-time US monitoring and dynamic CT evaluation of treatment. Radiology 187: 339–347
10. Vogl TJ, Mack MG, Straub R, Roggan A, Felix R (1997) Percutaneous MRI-guided laser-induced thermotherapy for hepatic metastases for colorectal cancer. Lancet 350: 29
11. Vogl TJ, Mack MG, Straub R, Roggan A, Felix R (1997) Magnetic resonance imaging-guided abdominal interventional radiology: laser-induced thermotherapy of liver metastases. Endoscopy 29: 577–583
12 Rubinsky B, Lee CY, Bastacky J, Onik GM (1990) The process of freezing and the mechanism of damage during hepatic cryosurgery. Cryobiology 27: 85–97
13. Whittaker DK (1984) Mechanisms of tissue destruction following cryosurgery. Ann R Coll Surg Engl 66: 939–949
14. Nagel HS, Bernardino ME (1993) Contrast-enhanced MR imaging of hepatic lesions treated with percutaneous ethanol ablation therapy. Radiology 189: 265–270
15. Livraghi T (1993) Ultrasound guided percutaneous ethanol injetion therapy of hepatic tumors and metastases. Z Gastroenterol 31: 260–264
16. Curley SA, Fuhrmann GM, Siddik ZH, Davidson BS, Cleary KR, Cromeens DM (1995) Direct intratumoral injection of a novel collagen matrix gel and cisplatin effectively controls experimental liver tumors. Cancer Res Ther Control 4: 247–254
17. Davidson BS (1994) Matrix therapeutic implant increases intratumoral liver cisplatin levels and enhances tumoricidal activity. Surg Forum 45: 466–468
18. Martin M, Tarara D, Wu YM, Ukah F, Fabrega A, Corwin C, Lang E, Mitros F (1996) Intrahepatic arterial chemoembolization for hepatocellular carcinoma and metastatic neuroendocrine tumors in the era of liver transplantation. Am Surg 62: 724–732
19. Sanz-Altamira PM, Spence LD, Huberman MS, Posner MR, Steele G Jr, Perry LJ, Stuart KE (1997) Selective chemoembolization in the management of hepatic metastases in refractory colorectal carcinoma: a phase-II trial. Dis Colon Rectum 40: 770–775
20. Rossi S, Stasi M, Carini E, Quaretti P, Garbagnati F, Squassante L, Paties CT, Silverman DE, Buscarini L (1996) Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. AJR 167: 759–768
21. Steele G Jr (1994) Cryoablation in hepatic surgery. Semin Liver Dis 14: 120–125
22. Lee F, Bahn DK, McHugh TA, Onik GM, Lee FT Jr (1994) US-guided percutaneous cryoablation of prostate cancer. Radiology 192: 132–142
23. Kane RA (1993) Ultrasound-guided hepatic cryosurgery for tumor ablation. Semin Intervent Radiol 10: 132–142
24. Ravikumar TS, Steele G, Kane R, King V (1992) Experimental and clinical observations on hepatic cryosurgery for colorectal metastases. Cancer Res 51: 6323–6327
25. Lee FL, Mahvi DM, Chosy SG, Onik GM, Wong WS, Littrup PJ, Scanlan KA (1997) Hepatic cryosurgery with intraoperative US guidance. Radiology 202: 624–632
26. Bown SG (1983) Phototherapy of tumors. World J Surg 7: 700–709
27. Beuthan J, Müller G, Schaldach B, Zur CH (1991) Fiber design for interstitial laser treatment. SPIE 1420: 234–241
28. Roggan A, Müller G (1992) Computer simulations for the irradiation planning of LITT. Minim Invasive Med Tech 4: 18–24
29. Beuthan J, Müller G, Schaldach B, Zur Ch (1991) Fiber design for interstitial laser treatment. SPIE 1420: 234–241
30. Delannoy J, Le Bihan D, Hoult DI, Levin RL (1990) Hyperthermia system combined with a magnetic resonance imaging unit. Med Phys 17: 855–860
31. Dickinson RJ, Hall AS, Hind AJ, Young IR (1986) Measurement of changes in tissue temperature using MR imaging. J Comput Assist Tomogr 10: 468–472
32. Le Bihan D, Delannoy J, Levin R (1989) Non-invasive mapping with MR imaging of molecular diffusion: application to hyperthermia. Radiology 117: 853–857
33. Vogl TJ, Mack MG, Scholz WR, Müller P, Weinhold N, Philipp C, Böttcher H, Roggan A, Felix R (1996) MR imaging guided laser-induced thermotherapy. Minim Invas Ther Allied Technol 5: 243–248
34. Vogl TJ, Mack MG, Hirsch HH, Müller P, Weinhold N, Wust P, Philipp C, Roggan R, Felix R (1997) In-vitro-Evaluierung der MR-Thermometrie zum Einsatz der laserinduzierten Thermotherapie. Fortschr Röntgenstr 167: 638–644
35. Lopez RL, Pan SH, Lois JF, McMonigle ME, Hoffmann AL, Sher LS, Lugo D, Makowka L (1997) Transarterial chemoembolization is a safe treatment for unresectable hepatic malignancies. Am Surg 63: 923–926
36. Vogl TJ, Trapp M, Pegios W, Mack M, Bechstein WO, Keck W, Scholz A, Schröder H, Neuhaus P, Felix R (1997) Volumetrische und morphologische CT-Parameter zur Prognoseabschätzung und Therapiekontrolle des hepatozellulären Karzinoms unter arterieller Chemoembolisation. Fortschr Röntgenstr 167: 219–226
37. Bartolozzi C, Lencioni R (1996) Ethanol injection for the treatment of hepatic tumours. Eur Radiol 6: 682–696
38. Lencioni R, Paolicci A, Moretti M, Pinto F, Armilotta N, Giulio M di, Cicorelli A, Donati F, Cioni D, Bartolozzi C (1998) Combined transcatheter arterial chemoembolization and percutaneous ethanol injection for the treatment of large hepatocellular carcinoma: local therapeutic effect and long-term survival rate. Eur Radiol 8: 439–444
39. Livraghi T, Bolandi L, Lazzaroni S, Marin G, Morabito A, Rappaccini GL, Salmi A, Torzilli G (1992) Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis:a study of 207 patients. Cancer 69: 925–929
40. Livraghi T, Lazzaroni S, Pellicano S, Ravasi S, Torzilli G, Vettori C (1993) Percutaneous ethanol injection of hepatic tumors: single-session therapy with general anesthesia. AJR 161: 1065–1069
41. Livraghi T (1991) Liver metastases: results of percutaneous ethanol injection in 14 patients. Radiology 179: 709–712
42. Amin Z, Bown SG, Lees WR (1993) Local treatment of colorectal metastases: a comparison of interstitial laser photocoagulation and percutaneous alcohol injection (PAI). Clin Radiol 48: 166–171
43. Kuang L, Yang DJ, Inoue T, Liu WC, Wallace S, Wright KC (1996) Percutaneous intratumoral injection of cisplatin microspheres in tumor-bearing rats to diminish acute nephrotoxicity. Anti-Cancer Drugs 7: 220–227