Neoadjuvant downsizing of liver metastases by transarterial chemoembolization (TACE) before laser-induced thermotherapy (LITT).

Thomas. J. Vogl, Martin G. Mack, J.O. Balzer, Kerstin Engelmann,
Ralf Straub, Katrin Eichler, Dirk Woitaschek, Stephan Zangos

Department of Diagnostic and Interventional Radiology
University Hospital Frankfurt, Johann Wolfgang Goethe-University
Theodor-Stern-Kai 7
D-60590 Frankfurt/Main

Address for reprints:
Thomas J. Vogl, MD
Institute for Diagnostic and Interventional Radiology
J. W. Goethe University of Frankfurt
Theodor-Stern-Kai 7
63590 Frankfurt
Phone: (+49) 69 6301 7277
Fax: (+49) 69 6301 7258
Email T.Vogl@em.uni.Frankfurt.de

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Abstract

Purpose: To evaluate a treatment protocol with repeated transarterial chemoembolization (TACE) before laser-induced thermotherapy (LITT) in patients with unresectable liver metastases too large for LITT alone.

Materials and Methods: A total of 162 patients with unresectable liver metastases (the largest lesion smaller than 80 mm in diameter, no more than 4 lesions) were treated with repeated TACE between March 1999 and December 2001. TACE was performed with a maximum of 10 mg/m^2 Mitomycin C as the chemotherapeutic agent and a maximum of 15 ml/m^2 of Lipiodol and microspheres for vessel occlusion. The tumor volume before and during the treatment was measured by MRI imaging. If the diameter of the tumor was observed to have decreased to less than 50 mm, the patients were treated with MRI-guided LITT 4 to 6 weeks following embolization.

Results: A total of 82 patients (62 with metastases from colorectal cancer, 14 with metastases from breast cancer and 6 with metastases from other primary tumors) responded to TACE with a reduction in tumor size of a mean value of 29%±14 and were treated with LITT. Each patient underwent 2 to 7 TACE treatments (mean 4.3) prior to LITT. In 47 patients, no reduction in tumor size was achieved, which led to further follow-up, and in 33 patients disease progression was found, with either an increasing size of the lesions (n= 18) or newly developing metastases (n= 15), resulting in further TACE treatments or change to systemic chemotherapy .

Median survival of the patients who responded to this combined treatment was 26.2 months; in the group of the patients treated only with TACE survival was 12.8 months (ranging from 0.3 to 29.4 months).

Conclusion: Repeated TACE is able to reduce the size of primary unresectable hepatic metastases in 50.6% of cases allowing local ablative treatments like MRI-guided LITT.

Key Words: intervention, hepatic tumors, chemoembolization, tumor ablation, LITT

Introduction

In the case of colorectal metastatic disease, the liver is the only metastatic site in 20-30% of patients [1,2]. This hepatic involvement is a life-threatening prognostic indicator, therefore early local or regional treatments, which may improve survival, are viable options [3]. One possible local therapeutic option for unresectable liver metastases is transarterial chemoembolization (TACE), which is the selective administration of chemotherapy usually combined with embolization of the vascular supply to the tumor, resulting in selective ischemic and chemotherapeutic effects on liver metastases. The rationale for TACE is based on the concept that the blood supply to hepatic tumors originates predominantly from the hepatic artery. In contrast, normal liver parenchyma obtains the majority of its blood supply from the portal vein [4]. Therefore, embolization of the hepatic artery can lead to selective necrosis of the liver tumor while leaving normal liver parenchyma virtually unaffected [5]. It has been shown that anoxic damage increases vascular permeability, promoting chemotherapy penetration into the tumor [6].

Early experience with TACE has demonstrated that TACE treatment is therapeutic, and suitable as a size decreasing procedure in patients with large unresectable liver metastases [7-9]. Factors such as the number and size of the tumors, status of tumor capsule, blood supply to the cancer and the interventional skill of the angiographer might influence response to TACE treatment [10,11]. Thus, TACE is not a curative treatment, and tumor necrosis in varying degrees can be found after effective TACE treatment [8,9]. However, tumor cells may remain viable after treatment. As a result, tumor ablation is still a necessary component in the treatment of tumors larger than 5 cm in diameter and cannot be substituted by TACE alone. Sequential ablation of the large liver tumor is therefore advocated as a possible locally curative therapy after effective TACE treatment [10].

Current ablation techniques like LITT are effective in lesions smaller than 5 cm in diameter, so there is a need for neoadjuvant therapy of large liver metastases. With the use of liquid-cooled applicator systems and improved application techniques areas of coagulation with a diameter of 6-8 cm were created. But a safety margin of 1 cm is necessary to reduce the risk of residual tumors resulting in a maximum tumor size of 4-6 cm in diameter [12,13].

Thus the purpose of our study was to evaluate a treatment protocol with repeated transarterial chemoembolization (TACE) before laser-induced thermotherapy (LITT) in patients with unresectable liver metastases too large for LITT alone.

Material And Methods

Patients

A total of 162 patients (75 females and 87 males ranging in age from 23.2 to 88.3 years; mean age 61.8 years) with unresectable liver metastases (metastases of the colon and/or rectum (116 cases), the breast (25 cases) or other primary tumors (21 cases) were treated between March 1999 and December 2001 with repetitive TACE treatments respecting the exclusion criteria for our study protocol.

All patients had previously undergone systemic chemotherapy and had either developed progressive disease or had not responded to systemic chemotherapy. In all cases, the primary cancer had been treated with surgical resection and the synchronous or metachronous liver metastases were unresectable. The study was designed in a prospective manner and approved by the Institutional Review Board. Informed consent was obtained from all patients.

Inclusion or Exclusion Criteria

The indications for the combined protocol of transarterial chemoembolization (TACE) and LITT were unresectable liver metastases showing no response to systemic chemotherapy as seen by contrast-enhanced MRI studies.

The target metastases were between 50 mm and 80 mm in diameter. Treatment was limited to patients with no more than 4 metastases and no extra-hepatic spread. 2 of the 4 metastases were allowed to have a diameter between 50 mm and 80 mm, the other lesions had to be smaller than 50 mm. The TACE treatment was applied to the lesions with a diameter between 50 mm and 80 mm.

Before each treatment specific laboratory values, like white blood cell, elementary bodies, haemoglobin, bilirubin, creatinine, transaminases, choline esterase and coagulation, were monitored.

Contraindications to our combined TACE and LITT protocol were poor performance status (Karnofsky status $\leq$ 70%), nutritional impairment, neoplastic ascites, high serum bilirubin level (> 3 mg%), poor hepatic synthesis (serum albumin < 2.0 mg/dl) and renal failure (serum creatinine > 2 mg%). Partial or complete thrombosis of the main portal vein was a further exclusion criterion for the procedure, as were cardiovascular and respiratory failure. To ensure adequate treatment compliance the patients had to be in good a mental state and had to be able to provide their own consent.

TACE Technique and Imaging

After the introduction of a 4-5 French Pigtail catheter through the femoral artery, an angiographic survey of the abdominal vessels was performed by 3 authors (T.V., J.B., S.Z.). Mesenteric arteriography checked for the presence of a right hepatic artery by selective catheterization. Indirect portography followed, outlining the portal circulation in the venous phase. A 4-5 French Cobra catheter (Terumo, Frankfurt/Main, Germany) was placed in the celiac trunk and advanced beyond the gastroduodenal artery. Depending on the size, location and the arterial supply to the tumor, the tip of the catheter was advanced further into segmental arteries. For superselective embolization, a Tracker catheter (Boston, Frankfurt, Germany) was used in 44 % of all procedures.

The embolization suspension consisted of a maximum of 10 mg/m^2 Mitomycin C (Medac, Hamburg, Germany) as the chemotherapeutic agent and a maximum of 15 ml Lipiodol, an iodized oil (Guerbet, Sulzbach, Germany), followed by injection of 200-450 mg microspheres (Sperex, Pharmacia & Upjohn, Erlangen, Germany) for vascular occlusion.

Mitomycin C was administered according to the body surface area and the physical condition. The embolization suspension was injected slowly under fluoroscopic control until a stasis of the blood flow was observed. After embolization, devascularization was confirmed by additional angiographic study of the hepatic artery. The study was designed to perform three courses of repetitive chemoembolization with treatment intervals 4 weeks apart. If the target lesions showed no response or the lesions were larger than 50 mm in diameter, we continued the TACE. Side effects were evaluated by one author (S.Z.) with a questionnaire [scale ranging from no symptoms (1) to marked symptoms (4)] and physical examination.

Unenhanced and contrast-enhanced (with 0.1 mmol of gadopentate dimeglumine [Magnevist; Schering, Berlin, Germany] per kilogram of body weigth) MRI studies for initial treatment planning were carried out for all patients with a conventional 1.5 T system (Magnetom Symphony; Siemens, Erlangen, Germany).

The MR imaging protocol included T1-weighted nonenhanced and contrast-enhanced gradient-echo sequences (FLASH-2D) with transversal and sagittal slice orientation (TR/TE: 135/6 ms; FA 80°, FOV 350 mm; matrix 134x256; slice thickness 8 mm). Additional were nonenhanced T2-weighted turbo-spin-echo (TSE) sequences (TR/TE: 3800/92 ms; FA 150°, FOV 350 mm; matrix 115x256; slice thickness 8 mm) and dynamic VIBE sequences (TR/TE: 4.5/1.8 ms; FA 15°, FOV 350 mm; matrix 128x256; slice thickness 8 mm) after application of a contrast medium used for the differentiation of the lesions.

Non-enhanced MRI studies were performed after every TACE cycle. Either a conventional 1.5 T (Magnetom Symphony, Siemens) with FLASH-2D sequences in transversal and sagittal slice orientation (TR/TE: 135/6 ms; FA 80°, FOV 350 mm; matrix 134x256; slice thickness 8 mm) and T2-weighted TSE-sequences (TR/TE: 3800/92 ms; FA 150°, FOV 350 mm; matrix 115x256; slice thickness 8 mm) or a 0.5 T (Privileg; Elscint, Haifa, Israel) MRI system with gradient-echo (GRE) sequences (TR/TE: 140/12 ms; FA 80°, FOV 350 mm; matrix 128x200; slice thickness 8 mm) and T1-weighted SE sequences (TR/TE: 450/14 ms; FA 180°, FOV 350 mm; matrix 180x256; slice thickness 8 mm) was used.

Twenty-four hours after embolization, retention of Lipiodol in the tumor and the liver parenchyma was verified with non-contrast-enhanced CT examination protocol by consensus (T.V., S.Z.). All CT studies were performed using spiral technique (slice thickness 8 mm) on fourth-generation scanners (Somatom plus or Somatom plus 4, Siemens, Erlangen, Germany).

Laser Technique

If a reduction of the tumor size of the large lesion to a diameter less than 50 mm was observed in the MRI images after TACE, the patient underwent MRI-guided LITT 4 to 6 weeks after the final TACE course. Evaluation was performed by two authors (T.V., S.Z.) and a decision made by consensus.

According to our experience with TACE, a mean recovery time of 2 to 3 weeks after chemoembolization was observed. So after 4 to 6 weeks the patients were normally in a good physical condition when MR-guided laser treatment started. For the interstitial thermal ablation of the tumor, a neodymium yttrium-aluminum-garnet (Nd:YAG) laser (Dornier MedLas 5060 and 5100) was used. From a single, bare 400 µm laser fiber, light of near-infrared (1046 nm) wavelength scatters within tissue and is converted into heat with an ensuing coagulative necrosis, secondary degeneration and atrophy. Tumor destruction occurs with minimal damage to surrounding structures. Laser light is emitted at an effective distance of 20-30 mm. The laser application kit (Somatex, Berlin, Germany) consists of a cannulation needle with a tetragonally-sharpened tip and guide wire; a sheath system with mandrin (length 20 cm, 10 French); and a special protective catheter (length 43 cm, 9 French) which is closed at the distal end. The protective catheter prevents direct contact of the laser applicator with the patient and enables complete removal of the applicator. This increases safety and simplifies the procedure. The catheter is light-transparent and heat-resistant ($\leq$ 400°C). The power laser application system allows permanent cooling with water and prevents carbonization to the tip of the applicator increasing the volume of coagulation necrosis.

The laser energy is delivered through fibers over 10 m in length, with the advantage of being fully compatible with MR imaging. During laser application, temperature changes are monitored by a thermosensitive T1-weighted FLASH-2D sequence (TR/TE: 140/12 ms; FA 80°, FOV 350 mm; matrix 128x200; slice thickness 8 mm, acquisition time 15 sec). Immediately after LITT treatment, 0.1 mmol/kg b.w. Gd-DTPA enhanced FLASH-2D sequences multislice set (TR/TE: 140/12 ms; FA 80°, FOV 350 mm; matrix 128x200 slice thickness 8 mm) provide essential information about the laser-induced necrosis and possible complications. Follow-up examinations are obtained after 24 hours and every 3 months after thermotherapy using contrast-enhanced MRI. The evaluated data included tumor size and number, morphology of the lesions treated with LITT, and complications (T.V., S.Z.).

Quantitative And Statistical Analysis

The follow-up after TACE was based on the MRI volumetric evaluation of the treated versus non-treated liver metastases. Volume measurement was performed using the axial images to evaluate the longest cross-section diameter as the length and the perpendicular diameter as the width. The longest diameter was measured in sagittal images.

Tumor volume was calculated on the basis of the evaluated diameters in axial images with the ellipsoidal volume formula:

$$\text{Volume}=(\text{length} \times \text{width} \times \text{height} \times 0.523).$$

To evaluate treatment success, response was defined in our study as achieving a shrinkage of the target large lesions to a diameter less than 50 mm, so that local ablation was possible. Stable disease was defined as no significant change in size during the TACE treatment courses.

Progressive disease was defined as an increase in size of a target lesion during TACE or newly developing lesions in the liver. The cumulative survival times were calculated beginning with the commencement of the first TACE treatment using the Kaplan-Meier method [14]. We used for statistical analysis the x^2 test. A p value of 0.5 indicated a significant difference.

Results

Preprocedural Findings

The diagnosis of liver metastases was verified by MRI or CT of the liver showing 523 liver metastases in pre-interventional MRI studies with 194 lesions 50 mm or larger in diameter. Thus, an average of 1.2 lesions with a diameter of 50 mm or larger were present in the total patient group. All patients were in good physical condition.

Intraprocedural Findings And Immediate Posttreatment Results After TACE

In all primary neoadjuvantly treated patients (n=162) 891 TACE procedures were performed in the absence of contraindications to the procedure with an average of 5.5 TACE procedures per patient to reduce the tumor size, with a range from 2 to 8. Technically, repeated TACE was successfully performed in all treatments and the first course of TACE was directed to embolize the area of the targeted large metastases. Directly after TACE no major complications (like bleeding, abscess) were observed. After TACE all laboratory values were not affected.

Short-term Results

The MRI scans after the final course of TACE demonstrated in 82 patients (39 females and 43 males) a decrease in the size of the treated lesions (metastases of the colon and/or rectum (62 cases), the breast (14 cases) or other primary tumors (6 cases). A mean decrease in tumor size of 35 % was estimated based on MRI findings in the follow-up as response to treatment, so that MR-guided LITT could follow (Fig. 1 a-d). In this patient group 355 TACE treatments were performed with an average of 4.3 TACE procedures per patient, ranging from 2 to 7.

In the other patients postinterventional imaging after TACE revealed a stable disease in 47 patients and a progressive disease in 33 patients, with an increase in diameter of the targeted lesions in 18 patients and new lesions in 15 patients. The outcome in these patients resulted in further follow-up in 52 patients and/or an additional use of systemic chemotherapy in 35 patients (Fig. 2).

Outcome After LITT And Long-term Follow-up

After the TACE courses 169 LITT treatment sessions were performed, with a mean of 2.0 LITT procedures, resulting in an ablation of 147 lesions with 574 laser applications. Based on size and topographical relationship of the metastases, a minimum number of 2 applicator systems and a maximum number of 5 applicator systems were positioned with a mean of 3.2 applicator systems per MR-guided LITT. The initial size of all treated lesions before LITT treatment presented with a mean of 37 cm^3 in the downsized lesions, with the resulting necrosis after LITT showing a diameter of 62 cm^3 with an adequate safety margin so that a safe ablation of the treated lesions could be achieved. Post-interventional evaluation revealed a tumor recurrence rate of 4.9% (4 patients) in the 6-month control after LITT at large lesions. Any additionally treated lesions presented with a local tumor recurrence rate of 2.4% (2 patients).

The overall cumulative survival rate of patients with liver metastases was 17.0 months after the first course of TACE (median 12.8 months, 95% confidence interval 10.4-15.3). The cumulative survival rate of the patients treated with the combined protocol was 24.9 months (median 26.2 months, 95% confidence interval 20.3-32.9) after the first treatment (Fig. 3).

Lower response rate was observed for patients with higher tumor load and a higher number of lesions. Patients with a less number (median survival: 27.8 vs. 23.3 months), high vascularisation (median survival: 29.6 vs. 24.7 months), or small diameter of the liver lesions (median survival: 28.8 vs. 25.8 months), presented with a better response.

Side Effects And Complications

Generally, the patients tolerated the TACE procedure well. No fatal or major complications related to this step of treatment were observed.

In 89.3 % of the patients monitored with the questionnaire, the side effects observed after TACE were mild (no or less symptoms), and included fever, abdominal pain, nausea, and vomiting for 2–7 days (Tab 1). These symptoms responded to treatment with oral medication. All patients were discharged on the same day after TACE treatment. There was no procedure-related mortality. Only three incidents of embolization of non-targeted areas (2 stomach and 1 kidney) occurred and were also treated accordingly with oral medication. Follow-up did not show any long-term sequelae in these patients. In one additional case, a hepatic abscess was recognized and treated with a percutaneous implanted drainage catheter.

During and immediately after laser treatments, no major complications occurred (Figure 3a-d). In 7 patients (8.5%) minor complications such as pain, pleural effusion or subcapsular hematoma were noted.

One major complication (1.2% of all with LITT-treated patients) was observed in the first 30 days after the LITT session. A 73-year-old patient died, most likely due to sepsis. In this case, a hemi-hepatectomy of the liver segments II, III and VIII had been performed 3 years previously, and a recurrent metastasis was treated with percutaneous ethanol injection (PEI).

Discussion

The majority of patients diagnosed with liver metastases present with unresectable hepatic disease. Only 20% of these patients currently benefit from radical therapeutic options such as surgical resection [15].

In patients with colorectal liver metastases, surgical resection results in a median survival of 28-46 months and a five-year survival rate ranging from 24 - 38% [16]. The mean survival of untreated patients with liver metastases is 7 to 8 months [17,18].

Thus, new forms of treatment aimed at improving survival are needed like several minimally invasive treatment techniques available for treatment of secondary malignant hepatic tumors which may replace or augment surgical resection. Promising minimally invasive ablative treatment techniques include laser-induced thermotherapy (LITT), radiofrequency ablation (RF), microwave ablation or cryoablation [19-26]. Up to now, all procedures are limited by the size of the metastases (diameter $\leq$ 5 cm), and in case of hypervascular lesions, the risk of bleeding. Currently all methods of thermal ablation are limited in their ability to achieve large volume tumor coagulation in a reproducible and predictable fashion. So several groups study techniques on thermal ablation combined with intravenous chemotherapy or chemoembolic materials applied via an arterial access.

As previously demonstrated in an animal model, the combination of a single intravenous dose of one particular liposomal doxorubicin preparation can increase the extent of RF ablation-induced coagulation necrosis in an animal breast tumor model compared with the therapy alone [27].

Transarterial chemoembolization (TACE) has been developed as a palliative treatment modality for unresectable liver tumors, made possible by the fact that liver metastases are almost exclusively supplied by the hepatic artery [4,28], whereas the portal vein supplies up to 75% of the liver parenchyma. In the chemoembolization, embolization of the hepatic artery reduces the blood flow, creates ischemia, and increases the contact time between the chemotherapeutic agent and tumor cells [29]. Subsegmental chemoembolization enhances the local effect on the neoplasm while minimizing further damages to the surrounding liver tissue [29].

The same results were observed in patients with primary hepatocellular carcinoma (HCC). TACE combined with other local therapeutic options (percutaneous ethanol injection (PEI) or radiofrequency (RF) ablation) increases the effectiveness of the treatment, and better results were reported than with either of these therapies alone [30-35].

In our study, the combination of TACE and LITT (with blood inflow occlusion of the hepatic tumors by TACE) was used for total ablation of the treated liver metastases (Fig 4a-e). With a major complication rate up to 1 %, this is a less invasive and less traumatic treatment than the laparotomy-guided treatment, which has a major complication rate of 2.4 % [13,36].

Laser ablation (LITT) destroys tumors within solid organs by directing laser light energy into a tissue through one or more implanted optic fibers [37]. The final size of the thermal lesion depends on the total heat deposition in the tissue, the thermal conductivity of the tissue, and the heat loss by convection through blood flow, which acts as a drop in heat. High vascularity of the tumor tissue and/or the presence of large vessels within or near the tumor can result in small or irregular thermal lesions, leading to treatment failure or early recurrence.

To increase the effectiveness of LITT, Wacker et al. injected degradable starch microspheres into the proper hepatic artery through an MR-visible catheter directly before the laser treatment. They observed that LITT of liver metastases in an open MRI system in combination with arterial inflow reduction is both technically feasible and safe [38].

The thermal effect can be significantly increased by interrupting blood flow before or during the thermal ablation. Heisterkamp et al. [39] showed in pigs that the hepatic blood flow had an influence on the coagulated volumes produced by laser coagulation. In these experiments, the authors showed that the size of the thermal lesion under flow condition was only 20% of the size produced under partial flow or no flow condition. Likewise Heisterkamp et al. [39,40] showed that the hepatic blood flow substantially reduces the size of the lesion produced by laser coagulation. The portal flow should therefore be reduced during the laser treatment to produce lesions of clinically relevant dimensions. No difference could be found between clamping of both portal vein and hepatic artery or of portal vein alone [41]. Some investigators performed the laser treatments during total occlusion of the arterial and/ or portal inflow under general anesthesia and laparotomy [39,42,43]. Other groups showed that the temporary occlusion of tumor arteries by injection of particles would be a suitable approach [44,45].

Likewise microwave coagulation therapy (MCT) was performed under laparotomic ischemia induced by partial obstruction of the hepatic artery and portal vein, and was conducted on patients with multiple liver metastases from colorectal cancer. A comparison of the survival rate of patients receiving MCT under ischemic and non-ischemic conditions revealed that the ischemic MCT group had a higher one-year survival rate (50%) than the non-ischemic MCT group (14%) [31,34,46].

Temporary hepatic vein or portal branch occlusion during radiofrequency ablation facilitated the treatment of large tumors or tumors in contact with the walls of large vessel. This resulted in an increase in energy deposition [47], improving heat conductivity and decreasing of the tumor tolerance to heat.

Aschoff et al showed in a rabbit model that the major factor influencing the size of the coagulation area is the portal venous flow. Occlusion of the hepatic artery alone did not seem to increase the lesions size significantly [48].

The efficacy of our TACE protocol for metastases is possibly based on the decrease of tumor tolerance to heat, due to cellular hypoxia, and an increase in the tumor sensitivity to heat. Thus, this technique would also be suitable for a combined protocol using RF after TACE.

Complications and mortality rates for our outpatient treatment protocol with TACE followed by LITT should be judged in comparison with the results of surgical treatment. The overall mortality for surgical treatment of liver metastases is approximately 4 to 7.6% [49-51].

Accordingly, the 30-day mortality rate for all sessions of LITT after TACE was only 0.8% (1 case). A death from multiple organ failure after treatment was observed by Tranberg et al. 10 days after laser treatment of an 8-cm lesion [43]. In comparison, after the combined protocol patients showed a longer recovery phase than patients treated with LITT alone. This situation may be due to the large size of the treated lesions and the increasing amount of tumor necroses. The advantages of our presented treatment protocol are threefold: First, TACE decreases the hypervascularity of the liver metastases with a diameter of more than 50 mm, reducing the bleeding risk during the following ablative procedure. Second, TACE increases laser effectiveness by reducing the cooling effect of blood flow via intratumoral vessels. Third, it proved advantageous to get a more detailed insight about the biological data of the tumor during the three-month courses of therapy. The disadvantages of our protocol were a slight increase in risks associated with the ablation procedure itself due to possible infection [52] as well as a higher incidence of liver infarction. Prophylactic antibiotics pre and post laser treatment may reduce this infection risk.

The treated patients were an inhomogeneous population with different primary cancers and different treatments before our treatment protocol was applied. The problems with the interpretation of the collected data showed that further studies are needed for more controlled data to evaluate criteria, like tumor vascularization , pre-treatments or number of lesions, for a better response to the neoadjuvant treatment. This especially refers to the exact selection of those patients who might be possible candidates for a neoadjuvant protocol.

Further studies are needed to establish the exact correlation between the size of created thermal lesion and the vascularization of the tumors after TACE. However, the full effectiveness and the exact role of the combined treatment protocol in the management of primary unresectable liver tumors must be investigated.

In the present study it was shown that repeated TACE is able to reduce the size of liver metastases with a diameter larger than 50 mm, so that a safe ablation of the lesions is possible. In the current study, there was no lasting impairment of liver function or liver failure caused by the combination of these procedures. Our experience with the LITT protocol revealed the high volume of induced necrosis, thus resulting in a complete tumor ablation and a sufficient safety margin (Figure 4a-e). While an increase in survival was well documented in the patients who responded to chemoembolization and underwent LITT in this study, this experimental design does not distinguish between the effects of chemoembolization and the effects of LITT. However, we believe that this technique should be used to treat only liver metastases larger than 5 cm in diameter, because the need for angiography adds to the complexity and costs of the procedure. Hepatic TACE combined with MR-guided thermal ablation of liver metastases appears to be a safe and useful therapeutic approach in patients with previously untreatable large liver metastases thus enabling to destroy focal tumors using of imaging guidance in a minimally invasive way.

With increasing experience in embolization and LITT, the rate of complications and mortality is significantly reduced. Recruitment of further patients is necessary to better assess the indication for the combination of TACE and LITT and to determine the optimal intervals between several courses of TACE and LITT.

Further studies are aimed at the development of new cytostatic drugs with higher local efficacy if applied via an intravascular approach.

CONCLUSION

TACE can stabilize the liver disease and reduce the size and perfusion of treated metastases in the half of the patients, and thus, it can influence patient survival. Combined with an ablative procedure such as LITT local tumor control and survival are possible.

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Table 1:

Complications and side effects evaluated with a questionnaire (scale ranging from no symptoms (1) to marked symptoms (4)) after TACE treatment in patients (n=82) with combined treatment TACE and LITT.

Figure 1

52-year-old patient with bilobar colorectal liver metastases

Figure 1a

Unenhanced transverse GRE T1-weighted MR images (TE/TR=140/12, flip angle 80°) demonstrate a 65x 45 mm target lesion (arrows) in segment 6 with irregular borders before treatment.

Figure 1b

Unenhanced transverse CT scan obtained after the third TACE course during the application of the laser catheters (arrow heads). Note: residual tumor lesions with attenuation areas due to lipiodol retention (arrow).

Figure 1c

Unenhanced transverse T1-weighted GRE MR scan (TE/TR=140/12, flip angle 80°) with the residual lesion (arrow). Laterally placed laser catheter (arrow head) during application procedure for achieving a complete ablation. During the procedure 4 catheters were applied.

Figure 1d

Gd-DTPA enhanced transverse T1-weighted GRE MR images (TE/TR=140/12, flip angle 80°) MR scan following 24 hours after LITT with demarcation of the volume of the induced necrosis (arrow heads). Note the sharp delineation of the border of the induced lesion.

Figure 2

Flow chart of neoadjuvant study.

Figure 3

Survival data of patients (n= 287) with liver metastases of various primary tumors treated with (——) TACE and of patients (n=82) treated with (**----**) combined treatment protocol (TACE followed by LITT).

The mean survival of the patients with TACE treatment was 17.0 months and with the combined protocol it was 24.9 months.

Figure 4

62-year-old patient with newly developed liver metastases of colorectal carcinoma.

Figure 4a

Transverse GRE T1-weighted (TR/TE= 135/6; flip angle 80°) MR image shows a large liver metastasis (arrows) in segment 6. In the coronal orientation the lesion presented with a diameter of 55 mm.

Figure 4b

Frontal angiogram during the first course of chemoembolization reveals the hypervascularity of the target metastasis (arrow heads) and the additional target lesions (not shown in (a) arrows).

Figure 4c

Unenhanced transverse GRE MR image (TR/TE= 140/12; flip angle 80°) obtained after the third course of TACE with a 50% decrease in tumor volume (arrows).

Figure 4d

Unenhanced transverse CT scan obtained after the third TACE course during the application of the laser catheters (arrow heads). Documentation of the residual tumor lesions with attenuation due to lipiodol retention (arrow).

Figure 4e

Contrast-enhanced transverse MR scan (TR/TE= 135/6; flip angle 80°) following 24 hours after LITT demonstrates the ablated volume (arrow heads), characterized by a low signal intensity surrounded by a hyperintense rim. The area of necrosis is larger than the original lesions.

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Complications and side effects evaluated with a questionnaire (scale ranging from no symptoms (1) to marked symptoms (4)) after TACE treatment in patients (n=82) with combined treatment TACE and LITT.

Side effect	Incidence (%)	
	no (1) to less symptoms (2)	moderate(3) to marked symptoms (4)
Pain	57.1	42.9
Nausea	82.2	17.8
Emesis	89.3	10.7
Fever (> 38.5°C)	86.4	13.6
Lethargy	38.4	61.6

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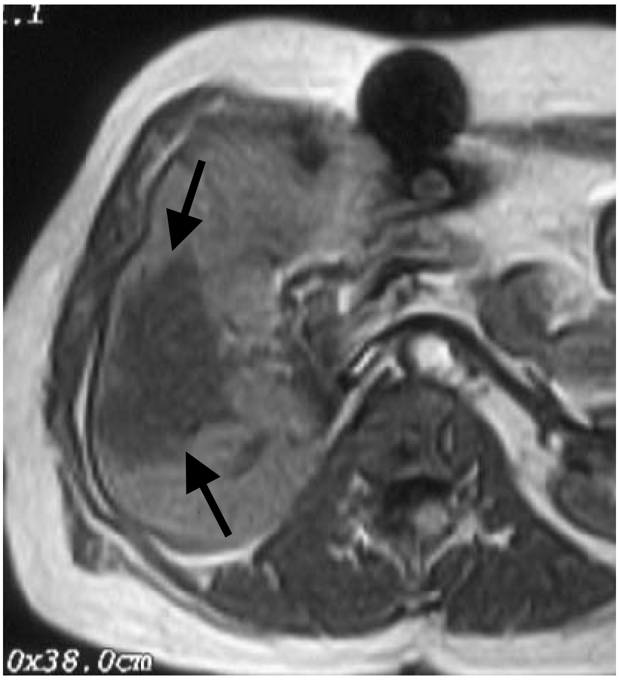

Figure 1b

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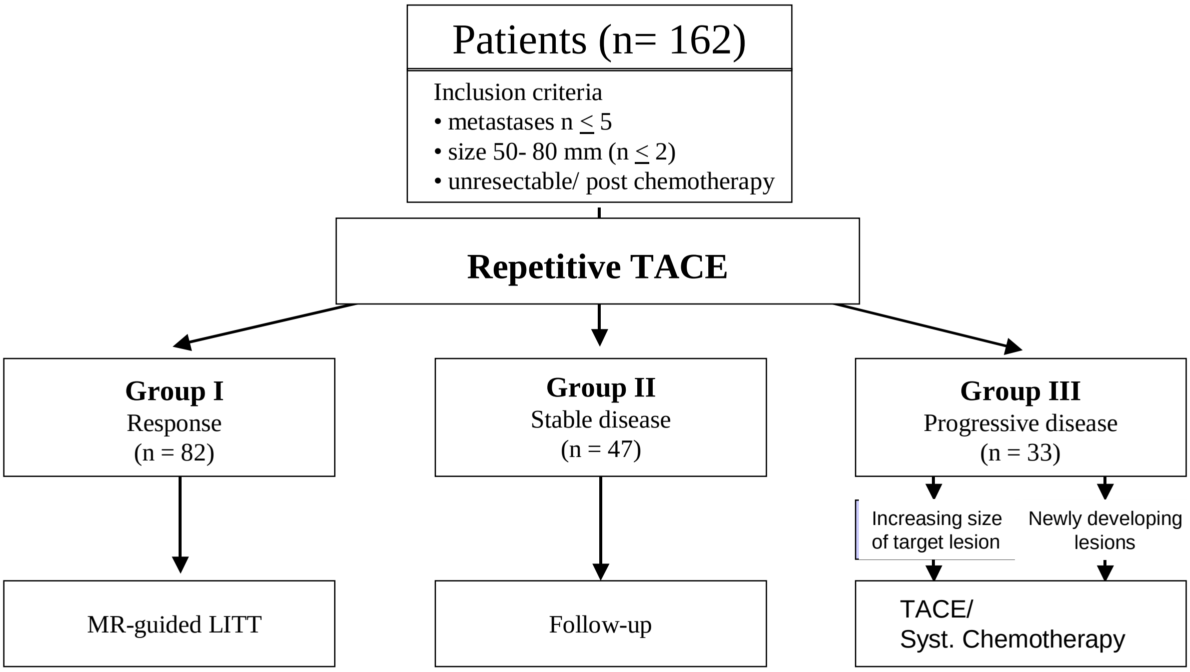

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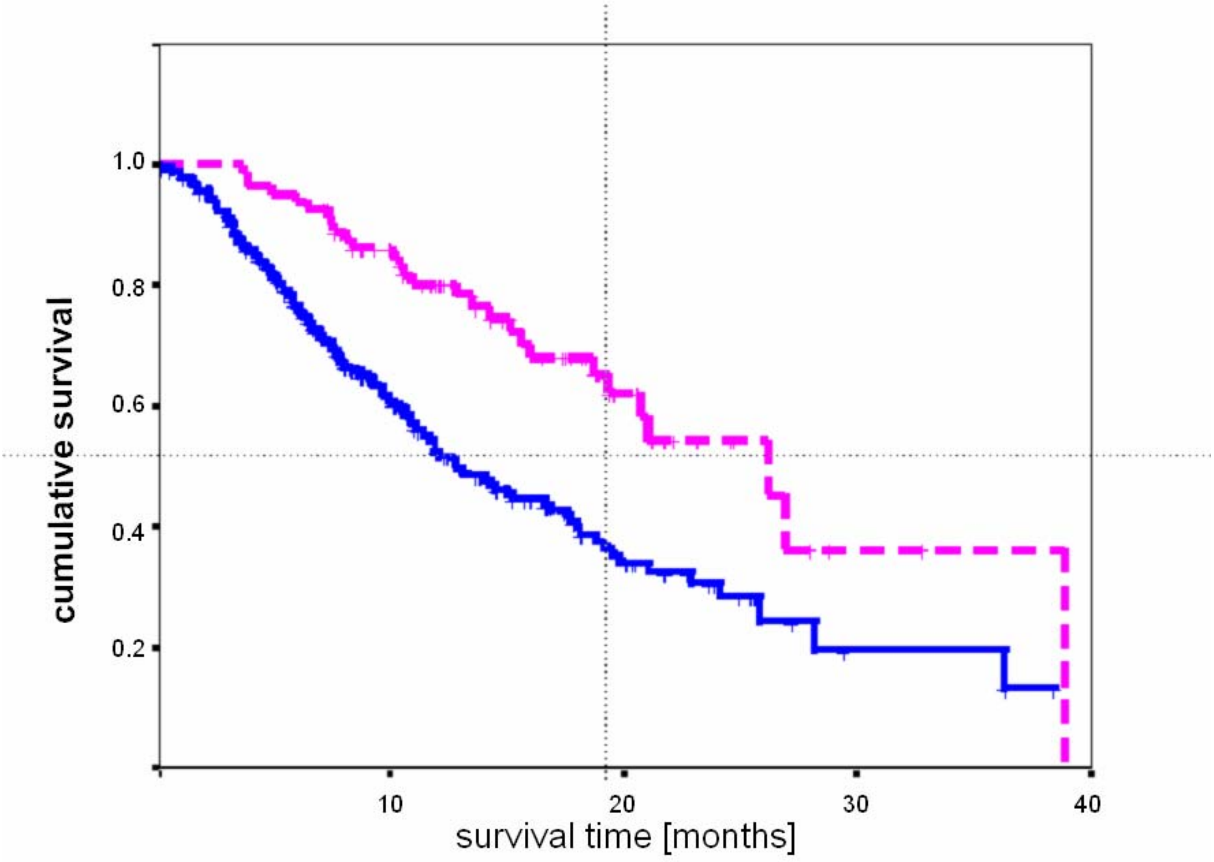

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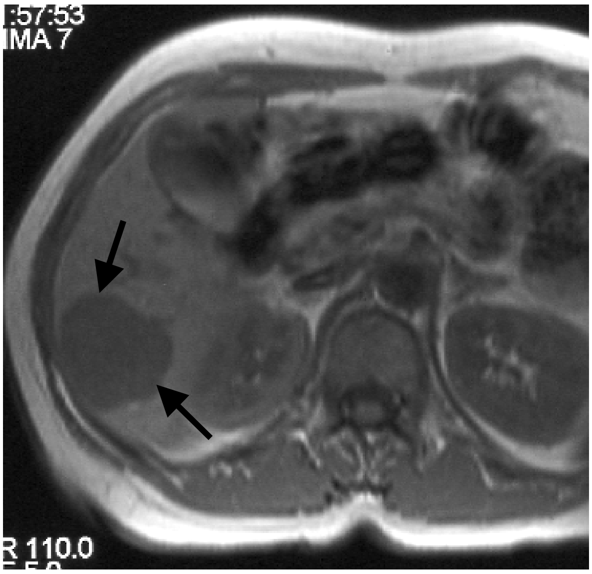

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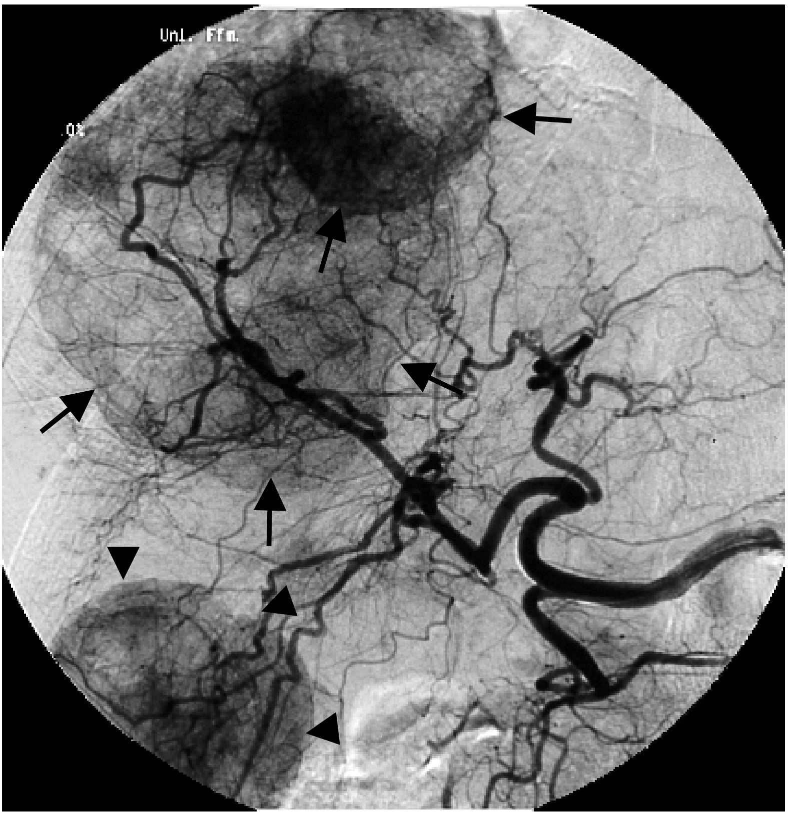

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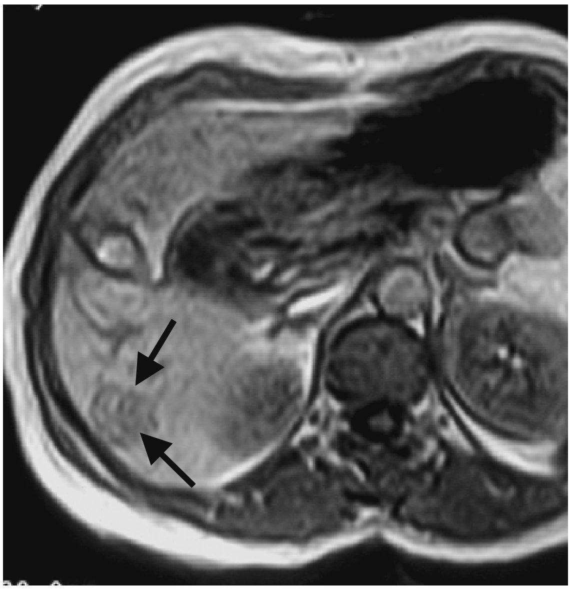

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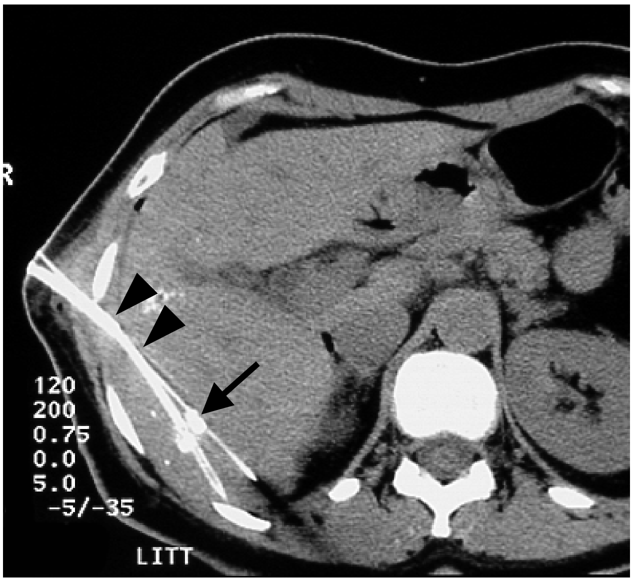

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