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Abbreviations:
FOV = field of view
LITT = laser-induced thermotherapy
TACE = transarterial chemoembolization

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Liver Metastases: Neoadjuvant Downsizing with Transarterial Chemoembolization before Laser-Induced Thermotherapy[1]

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

MATERIALS AND METHODS: One hundred sixty-two patients who had unresectable liver metastases, with the largest lesion as large as 80 mm in diameter, and no more than four lesions were treated with repeated TACE between March 1999 and December 2001. TACE was performed with a maximum of 10 mg/m^2 mitomycin for chemotherapy and a maximum of 15 mL/m^2 of iodized oil and microspheres for vessel occlusion. Tumor volume before and during treatment was measured at magnetic resonance (MR) imaging. If the diameter of the tumor decreased to less than 50 mm, the patients were treated with MR imaging–guided LITT 4–6 weeks following embolization.

RESULTS: Eighty-two patients (62 with metastases from colorectal cancer, 14 with metastases from breast cancer, and six with metastases from other primary tumors) responded to TACE, with a mean reduction in tumor size of 35% ± 14 (SD), and were treated with LITT. Each patient underwent two to seven TACE treatments (mean, 4.3) prior to LITT. In 47 patients, no reduction in tumor size was achieved, which led to further follow-up. In 33 patients, disease progression was found, with either an increasing size of the lesions (n = 18) or newly developing metastases (n = 15), and these results led to further TACE treatments or change to systemic chemotherapy. Median survival of patients who responded to this combined treatment was 26.2 months; in patients treated with only TACE, median survival was 12.8 months (range, 0.3–29.4 months).

CONCLUSION: With repeated TACE, reduction in size of primary unresectable hepatic metastases is achieved in 50.6% of cases and allows local ablative treatments such as MR imaging–guided LITT.

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 that usually is combined with embolization of the vascular supply to the tumor, and this treatment results 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 it

leaves normal liver parenchyma virtually unaffected (5). It has been shown that anoxic damage increases vascular permeability and thereby promotes penetration of chemotherapeutic agents 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 the 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 TACE alone cannot be substituted for it. Sequential ablation of the large liver tumor is therefore advocated as a possible locally curative therapy after effective TACE treatment (10).

Current ablation techniques such as laser-induced thermotherapy (LITT) are effective in lesions that are 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. A safety margin of 1 cm to the tumor is necessary to reduce the risk of residual tumors. This results in a maximum possible tumor size of 4–6 cm in diameter (12,13).

Thus, the purpose of our study was to evaluate a treatment protocol with repeated TACE before LITT in patients with unresectable liver metastases that are too large for LITT alone.

MATERIALS AND METHODS

Patients

A total of 162 patients (75 women, 87 men; age range, 23.2–88.3 years; mean age, 61.8 years) with unresectable liver metastases (metastases of the colon and/or rectum, 116 cases; those of the breast, 25 cases; or those of other primary tumors, 21 cases) were treated between March 1999 and December 2001 with repeated TACE, with respect to 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 was approved by the institutional review board. Informed consent was obtained from all patients.

Inclusion or Exclusion Criteria

The indications for the combined protocol of TACE and LITT were unresectable liver metastases that showed no response to systemic chemotherapy, as seen at contrast material–enhanced magnetic resonance (MR) imaging.

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

Before each treatment, specific laboratory values were monitored. These included white blood cell count, blood platelet count, hemoglobin level, bilirubin level, creatinine level, alanine aminotransferase and aspartate aminotransferase levels, cholinesterase level, and coagulation values.

Contraindications to our combined TACE and LITT protocol were poor performance status (Karnofsky status, ≤70%), nutritional impairment, presence of neoplastic ascites, high serum total bilirubin level (>3 mg/dL [51.3 μmol/L]), poor hepatic synthesis (serum albumin level, <2.0 mg/dL [20 g/L]), and renal failure (serum creatinine level, >2 mg/dL [176.8 μmol/L]). 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 a good mental state and had to be able to provide their own consent.

TACE Technique and Imaging

After the introduction of a 4–5-F pigtail catheter (Pigtail; Terumo, Frankfurt/Main, Germany) through the femoral artery, an angiographic survey of the abdominal vessels was performed by three authors (T.J.V., J.O.B., S.Z.). With mesenteric arteriography, we checked for the presence of a right hepatic artery by using selective catheterization. Indirect portography was performed afterward, with outlining of the portal circulation in the venous phase. A 4–5-F cobra-shaped catheter (Cobra; Terumo) was placed in the celiac trunk and advanced beyond the gastroduodenal artery. Depending on the size, location, and arterial supply to the tumor, the tip of the catheter was advanced farther into segmental arteries. For superselective embolization, an infusion catheter (Tracker; Boston Scientific, Frankfurt, Germany) was used in 44% of all procedures.

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

Mitomycin was administered according to the body surface area and the physical condition. The embolization suspension was injected slowly with fluoroscopic control until stasis of the blood flow was observed. After embolization, devascularization was confirmed with additional angiography of the hepatic artery. The study was designed to include the performance of three courses of repeated 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 to perform TACE. Side effects were evaluated by one author (S.Z.) with a physical examination and a questionnaire. The scores on the questionnaire ranged from 1 to 4, with a score of 1 indicating no symptoms and a score of 4 indicating marked symptoms.

For initial treatment planning, unenhanced and contrast-enhanced MR imaging with 0.1 mmol of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) per kilogram of body weight was performed in all patients. A conventional 1.5-T system (Magnetom Symphony; Siemens, Erlangen, Germany) was used.

The MR imaging protocol included T1-weighted unenhanced and contrast-enhanced two-dimensional fast low-angle shot gradient-echo sequences with transverse and sagittal section orientation (repetition time msec/echo time msec, 135/6; flip angle, 80°; field of view (FOV), 350 mm; matrix, 134 × 256; section thickness, 8 mm). In addition, unen-

hanced T2-weighted turbo spin-echo sequences (3,800/92; flip angle, 150°; FOV, 350 mm; matrix, 115 × 256; section thickness, 8 mm) and dynamic volume-interpolated breath-hold examination sequences (4.5/1.8; flip angle, 15°; FOV, 350 mm; matrix, 128 × 256; section thickness, 8 mm) after administration of a contrast medium used for the differentiation of the lesions.

Unenhanced MR imaging was performed with one of two systems after every TACE cycle. A conventional 1.5-T system as described previously was used to perform two-dimensional fast low-angle shot sequences in transverse and sagittal section orientation (135/6; flip angle, 80°; FOV, 350 mm; matrix, 134 × 256; section thickness, 8 mm) and T2-weighted turbo spin-echo sequences (3,800/92; flip angle, 150°; FOV, 350 mm; matrix, 115 × 256; section thickness, 8 mm). A 0.5-T system (Privileg; Elscint, Haifa, Israel) was used to perform gradient-echo sequences (140/12; flip angle, 80°; FOV, 350 mm; matrix, 128 × 200; section thickness, 8 mm) and T1-weighted spin-echo sequences (450/14; flip angle, 180°; FOV, 350 mm; matrix, 180 × 256; section thickness, 8 mm).

Twenty-four hours after embolization, retention of iodized oil in the tumor and the liver parenchyma was verified with findings at unenhanced computed tomography (CT) by two authors (T.J.V., S.Z.) in consensus. CT was performed with the spiral technique (section thickness, 8 mm) by using fourth-generation scanners (Somatom plus or Somatom plus 4; Siemens).

Laser Technique

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

According to our experience with TACE, a recovery time of 2–3 weeks after chemoembolization was observed. After 4–6 weeks, the patients were normally in good physical condition when MR imaging–guided laser treatment was started. For the interstitial thermal ablation of the tumor, an Nd:YAG laser (MedLas 5060 and 5100; Dornier MedTech, Kennesaw, Ga) was used. From a single, bare 400-μm laser fiber, light of near infrared (1,046 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 F), and a special protective catheter (length, 43 cm; 9 F) that 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 (≤400°C). The power laser application system allows permanent cooling with water and prevents carbonization to the tip of the applicator, which permits an increase in the volume of coagulation necrosis.

The laser energy is delivered through fibers longer than 10 m, with the advantage of being fully compatible with MR imaging. During laser application, temperature changes are monitored by using a thermosensitive T1-weighted two-dimensional fast low-angle shot sequence (140/12; flip angle, 80°; FOV, 350 mm; matrix, 128 × 200; section thickness, 8 mm; acquisition time, 15 seconds). Immediately after LITT, a multisection set of images were obtained with contrast-enhanced (0.1 mmol/kg of gadopentetate dimeglumine) two-dimensional fast low-angle shot sequences (140/12 msec; flip angle, 80°; FOV, 350 mm; matrix, 128 × 200; section thickness, 8 mm) that were performed to provide essential information about the laser-induced necrosis and possible complications. Follow-up examinations were performed 24 hours after LITT and every 3 months thereafter by using contrast-enhanced MR imaging. Data were evaluated by two authors (T.J.V., S.Z.) and included tumor size and number, morphology of the lesions treated with LITT, and complications.

Quantitative and Statistical Analyses

The follow-up after TACE was based on the MR imaging volumetric evaluation of the treated versus the nontreated liver metastases. Volume measurement was performed by using the transverse images to evaluate the longest cross-sectional diameter as the length and the perpendicular diameter as the width. The longest diameter was measured on sagittal images.

Tumor volume was calculated on the basis of the evaluated diameters on transverse images with the following ellipsoidal volume equation: volume = length × width × height × 0.523.

To evaluate treatment success, response was defined in our study as achievement of 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 substantial 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 by using the Kaplan-Meier method (14). For statistical analysis, we used the χ^2 and log-rank tests. A P value of .5 indicated a significant difference.

RESULTS

Preprocedural Findings

The diagnosis of liver metastases was verified with MR imaging or CT of the liver. Results indicated 523 liver metastases at preinterventional MR imaging, with 194 lesions that were 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. An average of 5.5 (range, 2–8) TACE procedures per patient were performed to reduce the tumor size. Technically, repeated TACE was successfully performed in all treatments, and the first course of TACE was directed toward embolization of the area of the targeted large metastases. Immediately after TACE, no major complications such as bleeding or abscess were observed. After TACE, all laboratory values were not affected.

Short-term Results

After the final course of TACE, the MR images obtained in 82 patients (39

women, 43 men) showed a decrease in the size of the treated lesions (ie, metastases of the colon and/or rectum, 62 cases; those of the breast, 14 cases; or those of other primary tumors, six cases). A mean decrease in tumor size of 35% ± 14 (SD) was estimated on the basis of MR imaging findings at follow-up as a response to treatment so that MR imaging–guided LITT could follow (Fig 1). In this patient group, 355 TACE treatments were performed with an average of 4.3 (range, 2–7) TACE procedures per patient.

In the other 80 patients, findings at 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 courses of TACE, 169 LITT treatment sessions were performed, with a mean of 2.0 LITT procedures. As a result, ablation of 147 lesions with 574 laser applications was accomplished. On the basis of size and topographic relationship of the metastases, a minimum of two and a maximum of five applicator systems were positioned with a mean of 3.2 applicator systems per MR imaging–guided LITT session. Before LITT treatment, the initial size of all treated lesions was a mean of 37 cm^3 in the downsized lesions. After LITT, the resulting necrosis was 62 cm^3, with an adequate safety margin so that safe ablation of the treated lesions could be achieved. Postinterventional evaluation revealed a tumor recurrence rate of 4.9% (four patients) in the 6-month control group after LITT for large lesions. With any additionally treated lesions, the local tumor recurrence rate was 2.4% (two patients).

The overall cumulative survival of patients with liver metastases was 17.0 months after the first course of TACE (median, 12.8 months; 95% CI: 10.4, 15.3). The cumulative survival of the patients treated with the combined protocol was 24.9 months (median, 26.2 months; 95% CI: 20.3, 32.9) after the first treatment (Fig 3). The log-rank test indicated a significant difference in the survival between the patients treated with only TACE and the patients treated with the combined protocol.

A lower response rate was observed for patients with a higher tumor load and a greater number of lesions. Patients with fewer lesions (median survival, 27.8 vs 23.3 months), high vascularization (median survival, 29.6 vs 24.7 months), or small diameter of the liver lesions (median survival, 28.8 vs 25.8 months) had a better response. A log-rank test indicated no significant difference for these analyzed factors in these patient groups.

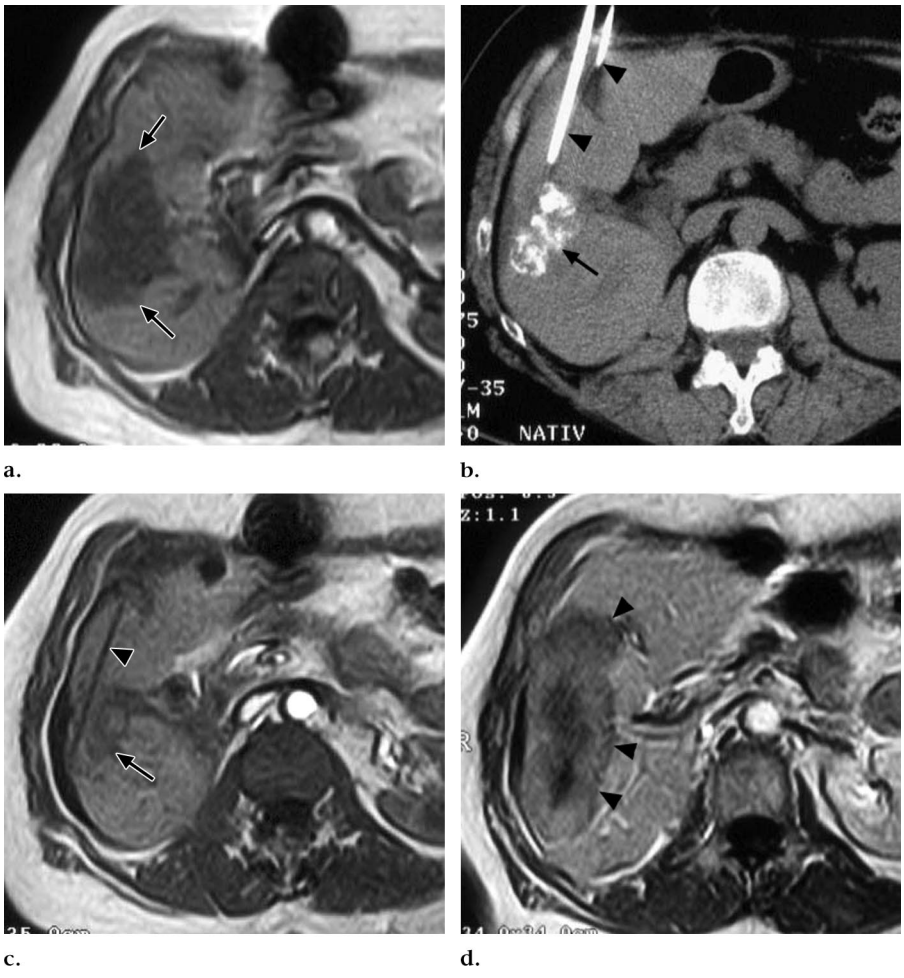

Figure 1. Images obtained in a 52-year-old man with bilobar colorectal liver metastases. **(a)** Unenhanced transverse gradient-echo T1-weighted MR image (140/12; flip angle, 80°) shows a 65 × 45-mm target lesion (arrows) in segment VI with irregular borders before treatment. **(b)** Unenhanced transverse CT scan obtained after the third course of TACE during application of the laser catheters (arrowheads) shows residual tumor lesions, with attenuating area (arrow) caused by retention of iodized oil. **(c)** Unenhanced transverse T1-weighted gradient-echo MR image (140/12; flip angle, 80°) with residual lesion (arrow). Laser catheter (arrowhead) was placed laterally during application to achieve complete ablation. During the procedure, four catheters were applied. **(d)** Gadopentetate dimeglumine–enhanced transverse T1-weighted gradient-echo MR image (140/12; flip angle, 80°) obtained 24 hours after LITT shows demarcation of the volume of the induced necrosis (arrowheads). Note the sharp delineation of the border of the induced lesion.

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 as many as 89.3% of the patients monitored with the questionnaire, the side effects observed after TACE were mild (ie, no or few symptoms, score of 1 or 2, respectively) and included fever, abdominal pain, nausea, and vomiting for 2–7 days (Table). 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 nontargeted areas (ie, two in the stomach and one in the kidney) occurred and were also treated accordingly with oral medication. Follow-up did not reveal any

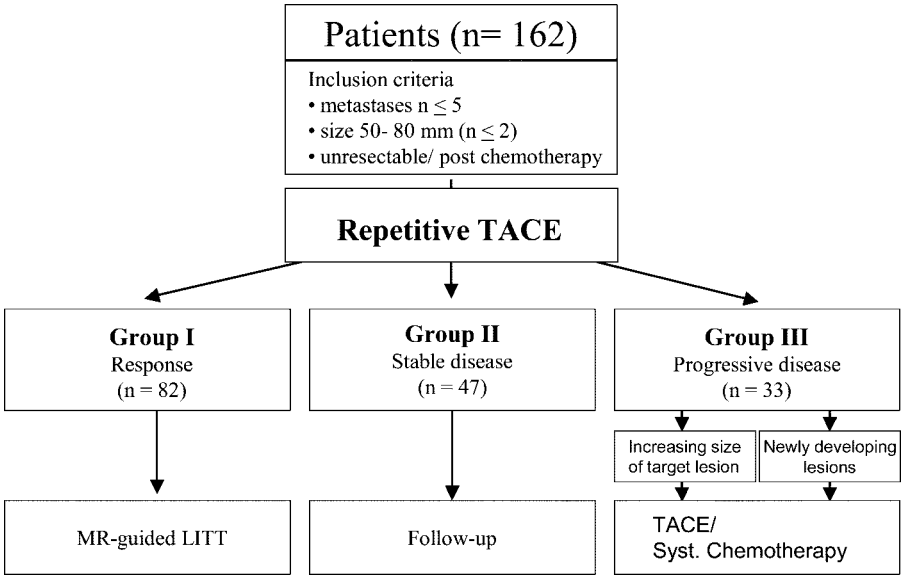

Figure 2. Flow chart of neoadjuvant study.

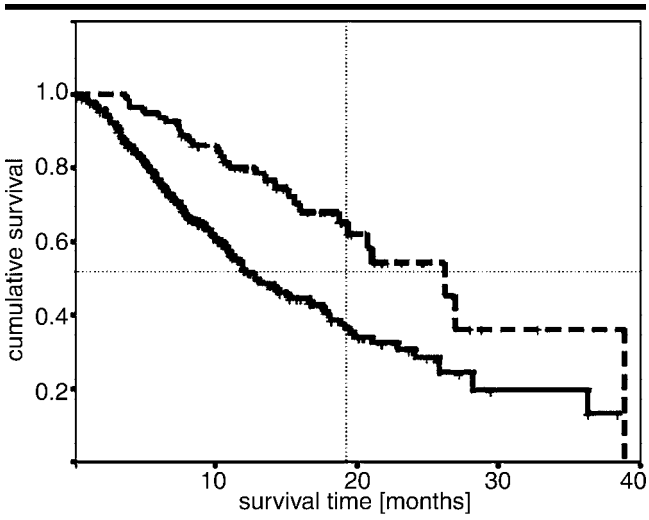

Figure 3. Graph shows survival data of patients (n = 287) with liver metastases of various primary tumors treated with TACE (solid line) and of patients (n = 82) treated with combined treatment protocol, that is, TACE followed by LITT (dashed line). Mean survival of the patients treated with TACE was 17.0 months, and that for those treated with the combined protocol was 24.9 months.

Complications and Side Effects Evaluated with a Questionnaire after TACE in Patients Treated with Combined TACE and LITT

Side Effect	Incidence (%)	
	No to Few Symptoms	Moderate to Marked Symptoms
Abdominal pain	57.1	42.9
Nausea	82.2	17.8
Vomiting	89.3	10.7
Fever*	86.4	13.6
Lethargy	38.4	61.6

Note.—Number of patients was 82. Symptoms were rated with a scale as follows: none, score 1; few, score 2; moderate, score 3; and marked, score 4.

* Fever was indicated with a temperature of greater than 38.5° C.

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 (Fig 4, a–d). In seven (8.5%) patients, minor complications such as pain, pleural effusion, or subcapsular hematoma were noted.

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

DISCUSSION

The majority of patients with liver metastases have 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 survival of 28–46 months and a 5-year survival rate ranging from 24% to 38% (16). The survival of untreated patients with liver metastases is 7–8 months (17,18).

Thus, new forms of treatment aimed at improving survival, such as several minimally invasive techniques available for treatment of secondary malignant hepatic tumors that may replace or augment surgical resection, are needed. Promising minimally invasive ablation techniques include LITT, radiofrequency ablation, microwave ablation, or cryoablation (19–26). Until now, all procedures were limited by the size (diameter, ≤5 cm) of the metastases; in the case of hypervascular lesions, the procedures were limited by 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. Several groups studied techniques with respect to thermal ablation combined with intravenous chemotherapy or chemoembolic materials applied through an arterial access.

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

TACE has been developed as a palliative treatment for unresectable liver tumors, because liver metastases are almost exclusively supplied by the hepatic artery

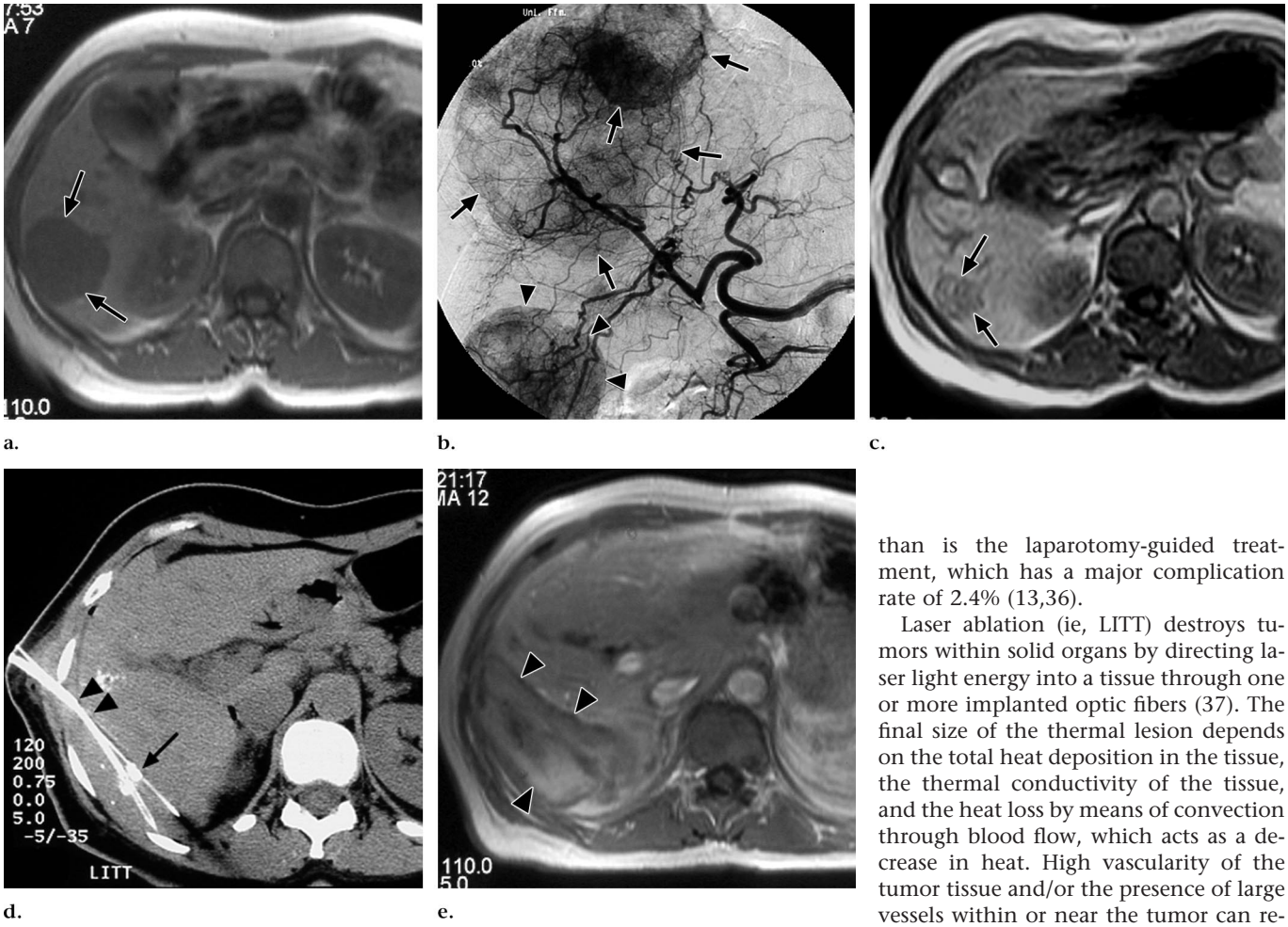

Figure 4. Images obtained in a 62-year-old woman with newly developed liver metastases of colorectal carcinoma. **(a)** Transverse gradient-echo T1-weighted MR image (135/6; flip angle, 80°) shows a large liver metastasis (arrows) in segment VI. In the coronal orientation, the lesion was 55 mm in diameter. **(b)** Frontal angiogram obtained during the first course of TACE reveals the hypervascularity of the target metastasis (arrowheads) and the additional target lesions (arrows) that were not shown in **a**. **(c)** Unenhanced transverse gradient-echo MR image (140/12; flip angle, 80°) obtained after the third course of TACE shows a 50% decrease in tumor volume (arrows). **(d)** Unenhanced transverse CT scan obtained after the third course of TACE during the application of the laser catheters (arrowheads) shows residual tumor lesions with attenuating area (arrow) caused by retention of iodized oil. **(e)** Contrast-enhanced transverse MR image (135/6; flip angle, 80°) obtained 24 hours after LITT demonstrates ablated volume (arrowheads), characterized by a low signal intensity area surrounded by a hyperintense rim. Area of necrosis is larger than original lesions.

(4,28), whereas the portal vein supplies up to 75% of the liver parenchyma. In chemoembolization, embolization of the hepatic artery reduces the blood flow, creates ischemia, and increases the contact time between the chemotherapeutic agent and the tumor cells (29). Subsegmental chemoembolization enhances the local effect on the neoplasm while it minimizes further damage to the surrounding liver tissue (29).

The same results were observed in patients with primary hepatocellular carcinoma. TACE combined with other local therapeutic options (ie, percutaneous ethanol injection or radiofrequency ablation) increases the effectiveness of the treatment, and better results were reported with the combination treatment 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 with TACE, was used for total ablation of the treated liver metastases (Fig 4). With a major complication rate of as much as 1%, this is a less invasive and less traumatic treatment than is the laparotomy-guided treatment, which has a major complication rate of 2.4% (13,36).

Laser ablation (ie, 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 means of convection through blood flow, which acts as a decrease 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, and these factors may lead to treatment failure or early recurrence.

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

The thermal effect can be substantially increased by interrupting blood flow before or during the thermal ablation. Heisterkamp et al (39) showed that the hepatic blood flow in pigs influenced the coagulated volumes produced by laser coagulation. In these experiments, the authors showed that the size of the thermal lesion with flow conditions was only 20% of the size produced with partial-flow or no-flow conditions. Likewise, Heisterkamp et al (39,40) showed that hepatic blood flow substantially reduces the size of the lesion produced by using laser coagulation. The portal venous 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 the portal vein and the hepatic artery or of the portal vein alone (41). Some investigators performed the laser treatments during total occlusion of the arterial and/or portal venous inflow, with the patient receiving general anesthesia and undergoing laparotomy (39,42,43). Other groups showed that the temporary occlusion of tumor arteries with injection of particles would be a suitable approach (44,45).

Likewise, microwave coagulation therapy was performed with ischemia induced by partial obstruction of the hepatic artery and the portal vein during laparotomy and was conducted in patients with multiple liver metastases from colorectal cancer. The survival rate of patients receiving microwave coagulation therapy with ischemic conditions was compared with that of those receiving this therapy with nonischemic conditions. The results of this comparison revealed that the group receiving microwave coagulation therapy with ischemic conditions had a higher 1-year survival rate (ie, 50%) than did the group receiving microwave coagulation therapy with nonischemic conditions (ie, 14%) (31,34,46).

Temporary hepatic venous or portal venous branch occlusion during radiofrequency ablation facilitated the treatment of large tumors or tumors that were in contact with the walls of a large vessel. This resulted in an increase in energy deposition (47) and improved heat conductivity and decreased the tumor tolerance to heat.

In a rabbit model, Aschoff et al (48) showed that the major factor that influenced the size of the coagulation area was the portal venous flow. Occlusion of the hepatic artery alone did not seem to increase the lesion size substantially.

The effectiveness of our TACE protocol for metastases is possibly based on the decrease in tolerance to heat of the tumor, caused by cellular hypoxia, and on an increase in the tumor sensitivity to heat. Thus, this technique would also be suitable for a combined protocol with radiofrequency ablation 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%–7.6%, according to some researchers (49–51).

Accordingly, the 30-day mortality rate for all sessions of LITT after TACE was only 0.8% (one case). A death from multiple organ failure after treatment was observed by Tranberg et al (43) 10 days after laser treatment of a lesion with a diameter of 8 cm. In comparison, after the combined protocol, patients had a longer recovery phase than did patients treated with LITT alone. This situation may be caused by the large size of the treated lesions and the increasing amount of tumor necrosis. 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, thus reducing the risk of bleeding during the ablation procedure that follows it. Second, TACE increases laser effectiveness because it reduces the cooling effect of blood flow through intratumoral vessels. Third, it proved advantageous to obtain a more detailed insight about the biologic data of the tumor during the 3-month courses of therapy. The disadvantages of our protocol were a slight increase in risks associated with the ablation procedure itself because of possible infection (52), as well as a higher incidence of liver infarction. Prophylactic administration of antibiotics before and after laser treatment may reduce this risk of infection.

The treated patients were an inhomogeneous population with different primary cancers who received different treatments before our treatment protocol was applied. The problems that we had with the interpretation of the collected data were an indication that further studies are needed for more controlled data to evaluate criteria such as tumor vascularization, pretreatments, or the 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 the 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, we showed that repeated TACE allows reduction in the size of liver metastases with a diameter larger than 50 mm so that safe ablation of the lesions is possible. 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 a high volume of induced necrosis, which resulted in complete tumor ablation and a sufficient safety margin (Fig 4). Although 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 allow a distinction 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 imaging–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 the destruction of focal tumors with imaging guidance in a minimally invasive way.

With increasing experience in the use of embolization and LITT, the rate of complications and mortality will be substantially 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 through an intravascular approach.

In conclusion, with TACE, liver disease can be stabilized and the size and perfusion of treated metastases can be reduced in half the patients; thus, it can influence patient survival. Combined with an ablation procedure such as LITT, TACE allows an increase in local tumor control and survival.

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