Repeated Chemoembolization Followed by Laser-Induced Thermotherapy for Liver Metastasis of Breast Cancer

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OBJECTIVE. The purpose of this study was to evaluate local tumor control and survival after use of a downstaging protocol of repeated transarterial chemoembolization (TACE) with two chemotherapeutic combinations followed by laser-induced thermotherapy in the care of patients with liver metastasis of breast cancer.

SUBJECTS AND METHODS. This prospective study included 161 patients with liver metastasis of breast cancer origin. TACE (mean, 3.5 [SD, 1.3] sessions per patient; range, 1–9 sessions) was performed as downstaging treatment to achieve the size and number of metastatic lesions that met the requirements for laser-induced thermotherapy (diameter < 5 cm, number ≤ 5). The TACE protocol was performed with either mitomycin C alone (n = 53) or mitomycin C in combination with gemcitabine (n = 108).

RESULTS. In response to TACE overall, the mean reduction in diameter based on the longest diameter of the target lesions was 27%. The difference between diameter reduction in the mitomycin C group and that in the mitomycin C–gemcitabine group was not statistically significant (p = 0.65). The mean survival time of all patients was 32.5 months, calculation starting from the first TACE treatment. The mean local tumor control period calculated as completion of therapy was 13 months, and the mean time to progression was 8 months. In the mitomycin–gemcitabine group, mean time to progression was 10.7 months, and in the mitomycin group it was 6.9 months (p = 0.5).

CONCLUSION. TACE can be used for sufficient downstaging of liver metastatic lesions of breast cancer to allow laser-induced thermotherapy. A combination of mitomycin C and gemcitabine seems to improve the reduction achieved with TACE.

Breast cancer is the most common malignant disease affecting women in Western countries and is the leading cause of cancer death among women worldwide [1]. Involvement of the liver as a site of metastatic disease implies a poor prognosis. The reported mean survival period is 4–14 months for untreated patients [2–4] and 13–25 months [3–7] for patients who undergo systemic chemotherapy. Liver resection seems to be the only cure, but many patients cannot undergo surgery because of advanced disease, the existence of a secondary disorder, or poor general condition [8]. For patients not eligible for surgical resection, local or regional treatment is an alternative for discontinuing growth of the metastatic lesions and to lengthen survival [9–11]. Although transarterial chemoembolization (TACE) is mostly considered palliative treatment of patients with advanced malignant disease, ablation methods such as laser-induced thermotherapy (LITT), radiofrequency ablation, and microwave therapy have been found to have success rates comparable to those of surgical resection [10–16]. These methods, however, are effective only for lesions of a certain size and number (for LITT, size < 5 cm, number ≤ 5) [17, 18].

Previous studies [9, 19, 20] have addressed the use of TACE as palliative therapy for liver metastasis of breast cancer. Other studies [10–12, 14–16] have concentrated on the ablative alternatives. The use of TACE as a downstaging therapy combined with LITT to decrease the size of metastatic lesions and control the tumor has been investigated with the participation of a smaller number of patients. Still, acquiring additional data in a larger number of cases, especially of liver metastasis of breast cancer, and long-term follow-up results is advantageous.

The current study was performed to assess the feasibility of the use of TACE performed
with different chemotherapeutic drug combinations as downstaging therapy before LITT and to evaluate the survival data after repeated TACE combined with LITT in the care of patients with liver metastasis of breast cancer who do not meet the criteria for LITT at first presentation. Special focus was placed on the rate of local intrahepatic tumor recurrence and the development of de novo lesions.

**Subjects and Methods**

**Patients**

From November 2001 through November 2007, 314 patients with liver metastasis of breast cancer origin were treated with TACE. One hundred fifty-three patients were not included in the study because the lesions had not decreased sufficiently in size and number for the patients to be eligible for LITT. Included in this assessment of the feasibility of the combined treatment protocol were 161 patients (mean age, 57 [SD, 1.3] years; range, 31–83 years) who were prospectively treated with 570 TACE sessions (mean, 3.5 [SD, 1.3] sessions per patient; range, 1–9 sessions) followed by LITT. Metastatic lesions remaining after TACE were ablated in 286 LITT treatments (mean, 1.8 [SD, 0.96] sessions per patient; range 1–5 sessions).

**Study Design and Eligibility Criteria**

The study was designed in a prospective manner and was approved by the institutional review board. Informed consent was obtained from all patients included. The enrolled patients had metastatic lesions of breast cancer, that were either in both liver lobes, locally nonresectable, or recurrent after partial liver resection. Also included were patients with existing contraindications to surgery, patients who had refused surgical treatment, and patients who had adverse reactions or no response to systemic chemotherapy. Exclusion criteria for the combined TACE–LITT protocol were poor general condition (Karnofsky rating < 70%), presence of ascites, partial or complete thrombosis of the portal vein, poor hepatic synthesis (serum albumin level < 2 mg/dL), high serum bilirubin level (> 3 mg/dL), renal insufficiency (serum creatinine level > 2 mg/dL), and respiratory or cardiovascular failure. To undergo LITT, patients had to have five or fewer lesions, none larger than 5 cm in diameter [17, 18].

**Imaging Technique**

Preintervention and follow-up examinations were performed with a 1.5-T MRI system (Magnetom Symphony, Siemens Healthcare). A body array coil was used to cover the region of interest. Initial tumor size was measured with unenhanced and contrast-enhanced MRI. The contrast material used was gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma), 0.1 mmol/kg body weight. Unenhanced and contrast-enhanced T1-weighted gradient-echo sequences (FLASH-2D) with transverse and sagittal slice orientation (TR/TE, 135/6; flip angle, 80°; field of view, 350 mm²; matrix size, 134 × 256; slice thickness, 8 mm; interslice gap, 0.8 mm) were performed in all examinations. Additional unenhanced T2-weighted breath-hold turbo-spin-echo sequences (3,800/92; flip angle, 150°; field of view, 350 mm²; matrix size, 115 × 256; slice thickness, 8 mm; interslice gap, 0.8 mm) and contrast-enhanced dynamic volumetric interpolated breath-hold examination sequences (4.5/1.8; flip angle, 15°; field of view, 350 mm²; matrix size, 128 × 256; slice thickness, 8 mm; interslice gap, 0.8 mm) were performed in both transverse and sagittal orientation. Post-TACE unenhanced CT examinations were performed with a 4-MDCT scanner (Somatom Plus 4, Siemens Healthcare) with 8-mm slice thickness.

**TACE**

After introduction of a selective catheter through the femoral artery with the Seldinger technique, the vascular anatomy of the hepatic arteries was defined. The catheter was then advanced beyond the gastroduodenal artery. Depending on the location, size, and arterial supply of the tumor, the tip of the catheter was advanced further into the segmental or subsegmental arteries. All patients underwent segmental or subsegmental chemoembolization. No patient underwent global TACE. All chemoembolization procedures were performed by one interventionalist with more than 10 years of experience in interventional radiology at the beginning of the study. The procedures were performed with an Axiom Multistar system (Siemens Healthcare).

Eligible patients received a suspension of 8 mg/m² body surface area mitomycin C alone (53 patients) or a combination of 8 mg/m² body surface area mitomycin C and 1,000 mg/m² body surface area gemcitabine (108 patients). The protocol with mitomycin C alone was used until the end of 2002, and the combined chemotherapeutic protocol was administered as of 2003. After administration of the chemotherapeutic agent or agents, a maximum of 15 mL iodized oil (Lipiodol, Guerbet) and 200–450 mg starch microspheres (200 μm) (EmboCept, Pharmacept) was injected to occlude the vessel. This step was performed under fluoroscopic control until stasis of blood flow was observed. Devascularization was confirmed with angiography.

Within the first 6 hours after chemoembolization, unenhanced CT was performed to check the distribution of embolizing material and the retention of iodized oil. Further follow-up examinations were performed with unenhanced MRI immediately before each TACE session.

The 140 patients in the study who did not meet the requirements for LITT underwent at least three TACE sessions (mean, 3.8 sessions per patient; range, 3–9 sessions) at 4-week intervals until they met the aforementioned criteria for LITT. The 21 patients who were eligible for LITT from the beginning underwent one or two sessions of TACE (mean, 1.76 sessions per patient) to maximize the ablative effect of LITT. The criteria were based on findings of previous studies [21–25] that indicated increased effectiveness of the combined treatment. Tumor size was evaluated with unenhanced MRI before the treatments.

**Laser-Induced Thermotherapy**

After meeting the criteria for the therapy, patients underwent MRI-guided LITT 4 weeks after the final TACE session. All laser therapy procedures were performed by two radiologists with more than 15 years of experience.

Puncture was performed under CT control with local anesthesia and an IV analgesic injection of pethidine (meperidine in the United States). The application set (Power, Somatex) contained a cannulation needle, guidewire, 9-French sheathed catheter (length, 20 cm) with mandarin, flexible fiber with a diffuser tip at the distal end, and a special protective 9-French catheter (length, 43 cm), which was closed at the distal end. The protective catheter had a double lumen; the flexible fiber that delivered the laser light was in the inner lumen and room temperature saline solution was in the outer lumen constantly circulating around the fiber to cool it. This system prevented direct contact between the laser applicator and the patient. The catheter was temperature resistant and permissible for laser light.

For thermal ablation, the patient was immediately transferred to the adjacent MRI room because LITT was performed under MRI guidance. The rooms shared a common preparation area. A Nd:YAG laser emitting laser light at a wavelength of 1,064 nm was used. The laser applicators were constantly cooled and operated in continuous wave mode. They were positioned with respect to the size and location of the metastatic lesion. Multiple applicators were used for large lesions. The laser energy varied from 20 to 35 W, and the period of application was 10–35 minutes.

During a treatment, the temperature was monitored with a thermosensitive T1-weighted FLASH 2D sequence (140/12; flip angle, 80°; field of view, 350 mm²; matrix size, 128 × 200; slice thickness, 8 mm; interslice gap, 0.8 mm; acquisition time, 15 seconds) that facilitated controlled and complete destruction of the metastatic lesion and repositioning of the applicator during the ongoing treatment if any residual tissue was seen on the MR images. The endpoint of the ablation was loss.
of signal in the thermosensitive T1-weighted sequences. Immediately after coagulation, contrast-enhanced FLASH 2D sequences (140/12; flip angle, 80°; field of view, 350 mm²; matrix size, 128 × 200; slice thickness, 8 mm; interslice gap, 0.8 mm) were performed to obtain essential information about possible complications and the laser-induced necrosis. After the intervention, the puncture channel was closed with fibrin glue (2 mL Tissucol Duo S, Baxter).

After treatment, the patient was observed for 6 hours for the occurrence of adverse effects. Observation consisted of a clinical examination only. No ultrasound scan or blood sampling was performed within the first 6 hours after treatment. LITT was performed as an outpatient procedure, and after observation, the patient was discharged. Within the next 24 hours, control MRI was performed. Further examinations were performed at 3-month intervals. Patients underwent follow-up for a mean of 13.8 (SD, 17.1) months (maximum, 90 months).

Data Collection

All responses were based on findings at MRI. For measurement of the target metastatic lesion, transverse imaging was used to evaluate the longest cross-sectional diameter as the length and the associated perpendicular diameter as the width. The longest diameter also was measured on sagittal images in order to acquire the longest dimension of the lesion. The change in size was calculated with MRI, and the response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) on the basis of the longest dimension [26]. All measurements were calculated in consensus by two radiologists (more than 5 and 10 years of experience in abdominal imaging).

Information on complications and adverse effects was obtained from the imaging studies and from clinical and laboratory data provided by the referring oncologists. Data on liver toxicity after TACE treatment were collected from blood test results. Possible chemotherapy-associated steatohepatitis was diagnosed with regularly performed ultrasound by the referring oncologist. The survival rate, time to progression, and local tumor control rate were recorded.

Definitions

The survival period was defined as starting with the first TACE treatment and ending with the patient’s death or last follow-up examination in the study period. Time to progression and the period for local tumor control rate were defined as starting as of completion of therapy (the last LITT session) and ending with progression or local recurrence. For patients without progression or local recurrence, the endpoint was the last follow-up examination at the time of evaluation for this study. Time to progression included development of de novo metastasis and local intrahepatic recurrence. The local tumor control rate referred only to local recurrence in previously ablated areas.

Quantitative and Statistical Analysis

The survival rate was measured with the Kaplan-Meier method. Significance was tested with Wilcoxon’s matched-pairs test. Values of p < 0.05 were considered statistically significant.

Response to TACE was defined as follows with RECIST before LITT treatment: complete response if all target lesions disappeared; partial response if the target lesions shrank at least 30%, stable disease if there was neither sufficient increase to meet the criteria for progressive disease nor sufficient shrinkage to meet the requirements for partial response, and as progressive disease if the size increased at least 20% or new lesions were found. The responses rates of the two groups of patients were compared by Wilcoxon’s matched-pairs test.

The response to the combination of TACE and LITT was evaluated at the 6-month follow-up examination (or at the last available follow-up examination if it was performed earlier) after the laser therapy according to RECIST. The absence of enhancement and of signs of residual disease in the ablated areas after LITT was considered a complete response. Also evaluated were rate of local recurrence of previously thermally ablated lesions and the development of de novo metastasis.

Results

Findings Before and After TACE

In all 161 patients, the TACE treatments were performed successfully with no major complications observed. The MR images after the final TACE session showed statistically significant (p < 0.01) 27% reduction in the diameter of the lesions, meeting the criteria for thermal ablation with LITT. The mean diameter of the metastatic lesions before treatment was 3.36 (SD, 1.94) cm (range, 0.6–12.5 cm). After TACE, it was 2.44 (SD, 1.22) cm (range, 0.4–7.0 cm). Partial response after TACE was found in 92 patients (57.1%), and stable disease was found in 69 patients (42.9%).

With respect to the two chemotherapeutic combinations, the 108 patients receiving the combination of mitomycin C and gemcitabine had a 27.4% mean reduction in the diameter of the lesions, whereas the 53 patients treated with mitomycin C alone had a 26.9% mean reduction in diameter. The difference in reduction in diameter in the two groups was not statistically significant (p = 0.65). The diameter of lesions treated with the mitomycin C–gemcitabine combination was reduced from a mean of 3.14 (SD, 1.73) cm (range, 0.6–12.4 cm) to a mean of 2.28 (SD, 1.04) cm (range, 0.4–5.2 cm). In the mitomycin C group, the diameter decreased from a mean of 3.83 (SD, 2.29) cm (range, 0.8–12.5 cm) to a mean of 2.80 (SD, 1.48) cm (range, 0.6–7.0 cm) after chemoembolization (Fig. 1).

Findings After Laser-Induced Thermotherapy

Lesions remaining after TACE were treated with 286 LITT sessions (mean, 1.8 sessions per patient; range, 1–5 sessions). After therapy with the combination protocol, 62 patients (38.5%) had a complete response; eight patients (5.0%), a partial response (Fig. 2); and 20 patients (12.4%), stable disease. In 71 patients (44.1%), disease progression after initial stabilization was found, necessitating additional TACE treatment of 64 patients.
Chemoembolization and Ablation of Liver Metastasis

Complications

The TACE procedure was well tolerated. No fatal or major complications were found in this part of the protocol. The side effects after TACE were mild (no or few symptoms) in the form of fatigue, fever, abdominal pain, and nausea and vomiting. This complex of symptoms is known as postembolization syndrome. Twelve patients (7.5%) had chemotherapy-associated steatohepatitis in the follow-up period. All patients were discharged on the day after treatment.

Regarding the LITT procedure, the rate of complications requiring further intervention was 3.7% (six cases), but even those complications were not severe (four cases of pleural effusion, two cases of biloma) and were managed with drainage or aspiration. The most common side effect of LITT was reactive pleural effusion, occurring in 101 of 286 LITT treatments (35.3%) or 57 of 161 patients (35.4%). Intervention by aspiration was necessary in only four cases. In 15 patients (9.3%), biloma developed after a LITT treatment; two of these patients needed drainage. Subcapsular hematoma occurred in 11 patients (6.8%) and small basal lung atelectasis in 17 patients (10.6%). None of these conditions required further treatment. No deaths related to the treatments occurred. No seeding of metastasis along the cannulation track was found.

Survival Analysis

The mean survival period after combined TACE and LITT, calculated as of the first TACE treatment, was 32.5 (SD, 21.6) months (range, 5–101 months). In the group who underwent LITT and did not have progressive disease, the mean survival period was 35.9 (SD, 23.5) months (range, 5–101 months). The progressive disease group had a mean survival period of 28.1 (SD, 18.0) months (range, 6–93 months) ($p < 0.01$) (Fig. 3). The 1-year survival rate was 88.8%, the 2-year survival rate was 55.9%, the 3-year survival rate was 36.6%, and the 5-year survival rate was 13.7%. Patients treated with mitomycin C had a mean survival period of 45.11 (SD, 27.97) months (range, 5–101 months), and patients treated with the mitomycin C–gemcitabine combination had a mean survival period of 26.26 (SD, 14.02 months) (range, 5–63 months) (Fig. 4). The
survival difference between the two groups was statistically significant ($p < 0.01$).

**Local Tumor Control and Time to Progression**

Overall local tumor control calculated from completion of combined therapy with respect only to absence of local recurrence in previously ablated areas was in a mean of 13.1 (SD, 15.9) months (range, 0–90 months). In the group with progressive disease after LITT (new liver metastasis during follow-up), the mean local tumor control was 11.0 (SD, 13.4) months (range, 0–65 months). In the group without progressive disease, the mean local tumor control was 14.7 (SD, 17.6) months (range, 3–90 months). The difference between the two groups with respect to local tumor control was not statistically significant ($p = 0.29$).

In the group of patients receiving the mitomycin C–gemcitabine combination, the mean local tumor control rate was 10.3 (SD, 11.8) months (range, 0–57 months). In the group receiving only mitomycin C, the mean local tumor control rate was 18.6 (SD, 20.9) months (range, 0–90 months). The difference between the two groups with respect to local tumor control was statistically significant ($p < 0.01$).

During follow-up, progression was found in 71 patients, three of whom (1.9% of the 161) had local recurrence of previously ablated lesions and 69 of whom (42.9% of the 161) had new metastasis, including one patient who had a local recurrence. Only 64 of these patients underwent additional TACE treatment.

The mean time to progression calculated from the date of the last LITT treatment was 8.2 (SD, 12.29) months (range, 0–69 months). In the group of patients receiving the combination of mitomycin C and gemcitabine, the mean time to progression was 10.7 (SD, 9.0) months (range, 0–54 months). In the group of patients treated with mitomycin C only, the mean time to progression was 6.9 (SD, 16.89) months (range, 0–69 months). The difference between the two groups was not statistically significant ($p = 0.54$).

**Discussion**

Liver metastasis of breast cancer origin is life limiting, and the patient needs treatment. Surgical resection of parts of the liver is considered the only potentially curative therapy, but the condition of only 24% of patients is suitable for resection [8]. The other patients need therapeutic alternatives, that is, minimally invasive interventional techniques. Promising techniques are radiofrequency ablation, LITT, microwave ablation, and cryoablation.

Laser coagulation is limited by the size of the metastatic lesions to be treated owing to the large ablation zones developed in the procedure. A safety margin of 1 cm from the tumor is necessary to reduce the risk of leaving residual tumor tissue. Thus the maximum size that can be ablated with LITT is 5 cm [17, 18]. Therefore, decreasing the size of large metastatic lesions of the liver with TACE is a good method to allow LITT of metastatic lesions that are too large for LITT alone. Chemoembolization has proved to be an appropriate method for reducing the size of metastatic lesions [9, 19, 20].

Combining TACE with MRI-guided LITT ablation increases the effectiveness of treatment. With embolization of the hepatic artery, the thermal effect of ablation increases because the cooling effect of blood flow is delayed. Several authors [21–24] have found that the interruption of hepatic artery blood flow significantly increases the coagulation volume produced by ablation. Therefore, with chemoembolization therapy before LITT, fewer laser applications are necessary to achieve large ablation volume. Whelan et al. [25] found that the cooling effect of blood flow preserves viable cells around larger vessels in the ablation area as the result of local underheating. This effect can be prevented by performance of TACE before LITT. Because of the increased effectiveness of the combined treatment, a small group of patients in our study underwent one or two TACE sessions before LITT even though they were eligible for LITT from the beginning. Another therapeutic combination for downstaging liver metastasis to allow ablation treatment was described by Hoffmann et al. [14]. With selective internal radioembolization with $^{90}$Y microspheres, liver metastasis was downstaged to an extent that allowed subsequent radiofrequency ablation.

The survival period after resection to manage liver metastasis of breast cancer origin is 34–42 months, the 5-year-survival rate ranging from 34% to 42% [8, 27–32]. Our data show the mean survival time among patients with breast cancer liver metastasis who underwent TACE and laser ablation was 32.5 months from the beginning of chemoembolization therapy. The combined treatment therefore has comparable results in that the patients treated were not surgical candidates because of disease expansion or poor clinical condition. The survival time of untreated patients with liver metastasis is 3.8–14 months [2–4]. The median survival period among patients with unresectable liver metastatic lesions of breast cancer who undergo systemic or regional chemotheraphy is 13–25 months [3–5, 7].

![Fig. 3—Kaplan-Meier survival curves show survival of patients divided into two groups. 1 = patients without progression after laser-induced thermotherapy (mean survival time, 35.9 months), 2 = patients with progressive disease after laser-induced thermotherapy (mean survival time, 28.1 months).](image)

![Fig. 4—Kaplan-Meier survival curves show survival of patients divided into two groups. 1 = patients treated with mitomycin–gemcitabine combination (n = 108; mean survival period, 26.26 months), 2 = patients treated with mitomycin (n = 53; mean survival period, 45.11 months).](image)
Different chemotherapeutic combinations were used in our study. The patients who received a combination of mitomycin C and gemcitabine had a greater reduction in tumor size, 27.4%, than those in the mitomycin C group, 26.9%, but the difference was not statistically significant \( (p = 0.65) \). The comparison of the two chemotherapy groups showed that all 12 patients (7.5%) with chemotherapy-associated steatohepatitis were treated with the mitomycin C–gemcitabine combination. This phenomenon must be evaluated in further studies.

Concerning the comparison of survival rates in the two chemotherapy groups, a statistically significant difference was found in favor of mitomycin C alone. This difference may be due to the study design and may not represent the actual. The follow-up time for the mitomycin C–gemcitabine group was shorter, a maximum survival time of 63 months. The maximum survival time of the mitomycin C group was 101 months, but the follow-up period was more than 9 years. This finding is supported by the fact that at the time of evaluation, 60 of 108 patients (55.6%) receiving mitomycin C and gemcitabine were alive whereas only 16 of 53 patients (30.2%) treated with mitomycin C were alive. We assumed that survival of the mitomycin C–gemcitabine group would have exceeded that of the mitomycin C group if the follow-up period had been longer. This finding is indicated in the Kaplan-Meier curve (Fig. 4). Likewise, with respect to local tumor control, a statistically significant difference was found in favor of mitomycin C, but again, this finding might have been affected by the different follow-up times. The maximum local tumor control period at the time of evaluation was 90 months for the mitomycin-only group but only 57 months for the mitomycin–gemcitabine group, without local recurrence at the time of evaluation for this study.

The combination of TACE and LITT is a good treatment option, leading to a median survival time of 32.5 months. TACE is associated with less systemic toxicity than is systemic chemotherapy, and LITT serves as an end therapy to improve survival and local tumor control. These results support the surgical theory that liver metastatic lesions should be destroyed or removed for improved survival.

Because of the complications of our treatment protocol in comparison with the results reported in major surgical series, the combination of TACE and LITT, because it had no treatment-related mortality and only a 3.7% rate of major complications, is a safe option compared with the operative mortality rate of 0–6% and the major complication rate of 4.7–12.9% for surgical treatment of liver metastatic lesions \( [8, 27–32] \).

Surgical resection is associated with a high rate of intrahepatic recurrence due to release of growth factors after tissue injury \( [23] \). These proliferation-promoting effects appear to a lesser extent after LITT because of the minor loss of the liver parenchyma. Albrecht et al. \( [23] \) found that 2 days after surgical resection or laser therapy, the messenger RNA expression level of hepatic growth factor was almost twice as high after surgery as after laser therapy. This finding was reflected in the comparison of progression times. After hepatectomy, a median time to progression of 10–36 months is observed in 58.3–76% of patients \( [8, 27–32] \). In our study, the mean time to progression was 8 months (range, 0–69 months) in 44.1% of the patients even though we treated patients at an advanced stage of disease in which metastasis was present both lobes of the liver.

TACE and LITT can be performed on an outpatient basis. This capability compares favorably with surgery because patients who undergo hepatectomy stay in the hospital a mean of 8–11 days after the operation \( [8, 27–32] \). In accordance with the global definition of cure suggested by Pagani et al. \( [6] \) that cure does not necessarily mean eradicating every tumor cell but means causing no major side effects and lengthening life of good quality, the combined therapeutic protocol without hospitalization and major complications is a major benefit.

A comparison between our results with the combined treatment protocol and the results of single TACE treatment reported in the literature (survival time, 6–28 months) \( [9, 19, 20] \) shows a longer better overall survival time with the combined protocol (mean, 32.5 months). Previously reported results \( [10, 15, 33] \) of single LITT treatment show a mean survival time of 50 months and of radiofrequency ablation treatment show a survival time of 30–60 months, although patients meeting the inclusion criteria for ablation therapy had an earlier stage of disease than most of our included patients. After local treatment of patients with solitary metastatic lesions, the metastatic disease can be controlled for a long period, especially when adjuvant systemic chemotherapy is administered to eliminate the assumed micrometastasis, with a reported 20-year disease-free survival rate of 26% \( [6, 16] \).

A limitation of our study was that randomization was not performed. Our promising results should be further evaluated with a randomized comparison of chemotherapeutic drug combinations, more precisely, mitomycin C alone versus the mitomycin–gemcitabine combination. Another limitation was that only dimensional assessment of tumor response according to RECIST was performed, and this is not the ideal assessment of tumor response to local treatments such as chemoembolization and laser ablation. In further studies, the volume of the lesions should be evaluated. This process can be semiautomated according to the method of Keil et al. \( [34] \), in which the same results as obtained with manual evaluation are obtained in 98–100% of cases. The functional response also should be evaluated with imaging techniques such as PET and diffusion-weighted MRI.

In a previous study \( [13] \), we suggested the effectiveness of the combined treatment protocol of TACE before LITT with only mitomycin as the chemotherapeutic drug. Fourteen of 82 patients had liver metastasis of breast cancer origin. The results with the large patient group presented in the current study show that the combination of TACE and MRI-guided LITT is safe and effective therapy for liver metastasis of breast cancer and that although not statistically significant, a difference in tumor reduction in favor of mitomycin C–Gemcitabine was found. The negligibility of major side effects or complications, the minimally invasive nature, and the capability of performing the treatment on an outpatient basis makes TACE with LITT a good therapeutic alternative in the care of patients not responding to systemic chemotherapy alone and as an alternative to surgery when liver resection is contraindicated.

References


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12. Mack MG, Straub R, Eichler K, Sollner O, Leh-
11. Ishida T, Murakami T, Shibata T, et al. Percutane-
guidelines for management of metastatic breast
cancer: can metastatic breast cancer be cured? J
Natl Cancer Inst 2010; 102:456–463
5. Er O, Frye DK, Kau SW, et al. Clinical course of
malignant microwave tumor coagulation for hepatocel-
lar carcinomas with interruption of segmental
hepatic blood flow.
14. Hoffmann RT, Jacob TF, Kubisch CH, et al. Ra-
diofrequency ablation after selective internal ra-
diation therapy with yttrium 90 microspheres in
metastatic liver disease: is it feasible? Eur J Ra-
diol 2010; 74:199–205
15. Meloni MF,Andreano A,Laeske PF,Livraghi T,
Sironi S, Lee FT Jr. Breast cancer liver metasta-
ses: US-guided percutaneous radiofrequency ab-
lavation—intermediate and long-term survival rates.
Radiology 2009; 253:861–869
16. Raimondi C, Danova M, Chatzilicontiadou S,
Palmeri L, Vercelli A, Palmeri S. Role of loco-
regional treatments for patients with breast cancer
liver metastases [in Italian]. Recent Prog Med
2009; 100:424–433
17. Vogl TJ, Muller PK, Mack MG, Straub R, En-
gelmann K, Neuhaus P. Liver metastases: inter-
ventional therapeutic techniques and results—
MG. Malignant liver tumors treated with MR im-
age-guided laser-induced thermotherapy: expe-
rience with complications in 899 patients (2,520
19. Giroux MF, Baum RA, Soulen MC. Chemoemo-
bolization of liver metastasis from breast carcinoma.
20. Li XP, Meng QZ, Guo WJ, Li J. Treatment for
liver metastases from breast cancer: results and
prognostic factors. World J Gastroenterol 2005;
11:3782–3787
proving laser-induced thermotherapy of liver me-
tastases: effects of arterial microembolization and
complete blood flow occlusion. Eur J Surg
Oncol 2007; 33:608–615
22. Wacker FK, Reither K, Ritz JP, Roggan A, Germ-
er CT, Wolf KJ. MR-guided interstitial laser-in-
duced thermotherapy of hepatic metastasis com-
bined with arterial blood flow reduction: techni-
que and first clinical results in an open MR system.
laser coagulation: evaluation of the effect of nor-
mal liver blood perfusion and the application
mode on lesion size. Lasers Surg Med 1998; 23:
40–47
24. Heisterkamp J, van Hillegersberg R, Mulder PG,
Sinfofsky EL. Ilzermans J. Importance of elimi-
nating portal flow to produce large intrahepatic
lesions with interstitial laser coagulation. Br J
Surg 1997; 84:1245–1248
25. Whelan WM, Wyman DR, Wilson BC. Investiga-
tions of large vessel cooling during interstitial la-
response evaluation criteria in solid tumours: re-
vised RECIST guideline (version 1.1). Eur J Can-
cer 2009; 45:228–247
27. Caralt M, Bilbao I, Cortes J, et al. Hepatic resec-
tion for liver metastases as part of the “oncosurgi-
cal” treatment of metastatic breast cancer. Ann
Surg Oncol 2008; 15:2804–2810
28. Lubrano J, Roman H, Tarrab S, Resch B, Marpeau
L, Scotte M. Liver resection for breast cancer me-
tastasis: does it improve survival? Surg Today
2008; 38:293–299
Hepatic resection for metastatic breast cancer:
prognostic analysis of 34 patients. World J Surg
2005; 29:524–527
30. Thelen A, Benckert C, Jonas S, et al. Liver resec-
tion for metastases from breast cancer. J Surg
Oncol 2008; 97:25–29
An attempt to clarify indications for hepatectomy
for liver metastases from breast cancer. Am J Surg
2003; 185:158–164
32. Yoshimoto M, Tada T, Saito M, Takahashi K,
Uchida Y, Kasumi F. Surgical treatment of hepatic
metastases from breast cancer. Breast Cancer Res
Treat 2000; 59:177–184
33. Jakobs TF, Hoffmann RT, Schrader A, et al. CT-
guided radiofrequency ablation in patients with
hepatic metastases from breast cancer. Cardio-
vase Intervent Radiol 2009; 32:38–46
34. Keil S, Bruners P, Olsnorge L, et al. Semiauto-
mated versus manual evaluation of liver metastases
treated by radiofrequency ablation. J Vasc Interv
Radiol 2010; 21:245–251
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2. Giovan Giuseppe Di Costanzo, Raffaella Tortora, Marco Guarracino, Maria Mattera, Tian’an Jiang, Claudio Maurizio Pacella. 31. [Crossref]


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6. Michel Ducreux. Liver Metastases of Other Indications 129-160. [Crossref]

7. Onofrio Catalano, Dania Daye, Alberto Signore, Carlo Iannace, Mark Vangel, Angelo Luongo, Marco Catalano, Mazzeo Filomena, Luigi Mansi, Andrea Soricelli, Marco Salvatore, Niccolo Fuin, Ciprian Catana, Umar Mahmood, Bruce Rosen. 2017. Staging performance of whole-body DWI, PET/CT and PET/MRI in invasive ductal carcinoma of the breast. *International Journal of Oncology*. [Crossref]


10. Christina Loberg. Transarterial Treatment of Primary and Secondary Liver Tumors 285-292. [Crossref]

11. Abdullah Icgi, Enver Özkurt. Management of Isolated Liver Metastasis 681-694. [Crossref]


13. Michel Ducreux. Liver Metastases of Other Indications 89-106. [Crossref]

14. Elżbieta Senkus, Fatima Cardoso, Olivia Pagani. 2014. Time for more optimism in metastatic breast cancer?: *Cancer Treatment Reviews* 40:2, 220-228. [Crossref]


21. Thomas J. Vogl, Katrin Eichler, Stephan Zangos. Regionale Therapieverfahren bei Lebermetastasen unterschiedlicher Primärtumoren: Lokale Chemotherapie und Thermoablation 237-248. [Crossref]
