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Invited update

Percutaneous MR imaging-guided laser-induced thermotherapy of hepatic metastases

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Abstract
Background: Many primary tumors may cause liver metastases, which are generally treated with surgical resection and/or chemotherapy. After resection of liver metastases in patients with colorectal carcinoma, 5-year survival rates are achieved in 25–38%, and two-thirds of patients will experience recurrent metastases. We examined percutaneous, minimally invasive, laser-induced thermotherapy (LITT) as an alternative outpatient procedure. Local tumor control rate and survival data were analyzed prospectively.
Methods: Between June 1993 and August 2000, 7148 laser applications were performed in 1981 lesions in 705 consecutive patients and 1653 treatment sessions. The complications of the procedure were evaluated by clinical examination and magnetic resonance imaging (MRI) and computed tomography. Local tumor control was evaluated by plain and contrast-enhanced follow-up MRI using T1- and T2-weighted spin-echo and gradient-echo sequences every 3 months after treatment. Cumulative survival times were calculated using the Kaplan–Meier method.
Results: The overall rate of complications and side effects was 7.5%. The rate of clinically relevant complications was 1.3%. Local tumor control rate after 3 months was 99.3%; 6 months after laser treatment, plain and contrast-enhanced MRI documented a local tumor control rate of 97.9%. In patients treated with MR-guided LITT for unresectable colorectal liver metastases, the mean survival was 41.8 months (95% confidence interval = 37.3–46.4 months). The 1-year survival rate was 93%, the 2-year survival rate was 74%, the 3-year survival rate was 50%, and the 5-year survival was 30%. In patients treated with LITT for liver metastases from breast cancer, the mean survival was 4.3 years (95% confidence interval = 3.6–5.0 years).
Conclusion: In patients with liver metastases, local tumor destruction using minimally invasive, percutaneous LITT under local anesthesia results in improved clinical outcomes and survival rates and can be a potential alternative to surgical resection.

Key words: Laser—Laser-induced thermotherapy—Minimal invasive therapy—MRI—Liver metastases.

The liver is the most common site of metastatic disease from colorectal carcinoma, and metastases are rarely present at other sites if the liver and lung are free of tumor [1]. The liver is a common site of metastatic disease from other primary tumors as well. In 1994 in the United States, colorectal carcinoma developed in approximately 149,000 people; approximately 56,000 patients died of this neoplasm. Weiss et al. [1] estimated that at least 20% of patients with this disease will die of metastases exclusively in the liver.

In many patients, the degree of hepatic involvement is the main determinant of survival [2–4]. The median survival for patients with liver metastases from colorectal carcinoma is 4–12 months from the time of diagnosis of metastatic disease. Among those patients with a solitary metastasis, 45% are alive at 2 years, whereas only 12% are alive at 3 years.

In patients who are not candidates for hepatectomy, the palliative management of hepatic metastases remains unsatisfactory. There is a need for an efficient, minimally invasive technique that succeeds in retarding, if not halting, growth of metastases. Interstitial laser-induced thermotherapy (LITT) is a minimally invasive technique suitable for local tumor destruction within solid organs; it uses optical fibers to deliver high-energy laser radiation to

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the target lesion. Due to light absorption, temperatures of up to 130°C are reached within the tumor, leading to a substantial thermocoagulation. Magnetic resonance imaging (MRI) is used for placement of the laser applicator in the tumor and for monitoring progress of thermocoagulation. The thermosensitivity of certain MR sequences is the key to real-time monitoring, allowing accurate estimation of the actual extent of thermal damage [5–8].

This presentation deals with the actual results of local lesion control with MR-guided, minimally invasive LITT and associated survival data.

Material and methods

The LITT treatment protocol and inclusion criteria were approved by the local ethics committee, and written informed consent was obtained from all patients. We included patients who developed metastases in remaining liver after hepatectomy (36%), patients who had metastases in both liver lobes (35%), patients who had contraindications for surgery or unresectable lesions (22%), and patients refusing hepatic surgery (7%). Excluded were patients with more than five metastases, with metastases larger than 5 cm in greatest diameter, or with extrahepatic tumor spread. We treated metastases in patients who developed additional liver metastases during the follow-up period.

Patients treated with LITT

Between June 1993 and August 2000, 7148 laser applications were made in 1981 lesions in 705 consecutive patients (mean age = 59 years, range = 24–89 years; 385 male, 320 female) in 1653 treatment sessions. All treatments were performed under local anesthesia. The primary tumor was colorectal carcinoma in 57%, breast cancer in 18%, hepatocellular carcinoma (HCC) in 5%, and a variety of different tumors in 20%; 1203 colorectal liver metastases in 393 consecutive patients with an average age of 60.8 years were treated between June 1993 and August 2000. Three hundred thirty-two breast cancer liver metastases were ablated in 250 treatment sessions in 127 patients.

Laser applicator kit and laser systems

The cooled power laser system for MR-guided, minimally invasive, percutaneous LITT of soft tissue tumors consists of an MR-compatible cannulation needle (length = 20 cm, diameter = 1.3 mm) with a tetragonally beveled tip and stylet, a guidewire (length = 100 cm), a 9-F sheath with stylet, and a 7-F double-tube thermostable (up to 400°C) protective catheter (length = 40 cm) with a stylet, which enables internal cooling with saline solution. Cooling of the surface of the laser applicator modifies the radial temperature distribution so that the maximum temperature shifts into deeper tissue layers [7].

For LITT treatments we now use up to six laser systems (Dornier MediLas 5100 and 5060) simultaneously. These laser systems are equipped with light-guide-protection system (LPS).

Imaging protocol

MRI was used for treatment planning and follow-up examinations in all patients. For treatment planning, imaging studies were performed before LITT using a standard imaging protocol including T2-weighted and T1-weighted spin-echo or gradient-echo (FLASH-2D) sequences, plain and enhanced with gadolinium-DTPA (0.1 mmol/kg body weight). Follow-up examinations using contrast-enhanced MRI were carried out within 48 h after the intervention and then every 3 months.

Qualitative and quantitative evaluation and survival

Laser-induced effects were evaluated by comparing images of lesions and surrounding liver parenchyma obtained before and after laser treatment and with those obtained at follow-up examinations. Tumor volume and volume of coagulative necrosis were calculated using three-dimensional MR images. Survival rates were calculated using the Kaplan–Meier method.

Results

Complications

The overall rate of complications and side effects was 7.5%. The rate of clinically relevant complications was 1.3%. The most common side effect of LITT treatment was reactive pleural effusion (7.3%); puncture was necessary in 0.9%. Intrahepatic abscess was observed in 0.4% and one pleural empyema in 0.1%; both were treated by drainage. Subcapsular hematoma was found in 3.1%, intrahepatic bleeding in 0.1%, and intrabdominal bleeding in 0.2%. None of these required treatment. Further complications included local infection in 0.2% and injury to the bile duct in 0.1%. Three patients died within 30 days; only one death was possibly related to LITT.

Local tumor control

Local tumor control rate was determined using plain and contrast-enhanced MR images obtained 3 and 6 months after LITT treatment (Fig. 1). Reflecting the development of the laser application systems and the increased expe-

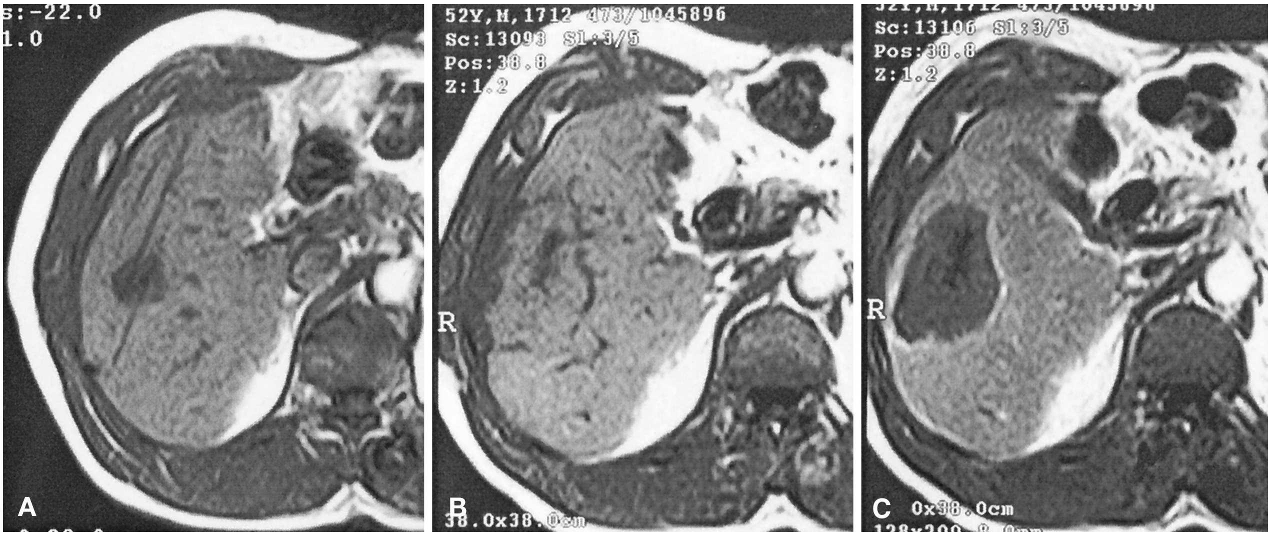


Fig. 1. A T1-weighted plain GRE sequence demonstrates a liver metastases of a colorectal cancer in liver segment 6 with two laser fibers before LITT treatment. **B** T1-weighted plain GRE sequence obtained 3 months after LITT treatment demonstrates the induced coagulative necrosis. Note the slightly hyperintense pattern of the necrosis due to hemorrhagic diffusion into the necrosis and the hypointense border due to granulation tissue. **C** T1-weighted contrast-enhanced GRE sequence obtained 3 months after LITT treatment demonstrates the induced coagulative necrosis. Note the safety margin of necrosis surrounding the initial lesion and the border enhancement due to granulation tissue.

rience of the physicians, the patients were assigned to two groups for evaluation of the local tumor control rate. In group 1 (treated June 1993 to December 1997, $n = 130$ patients), the local tumor control rate in the 3-month follow-up control was 77.8%. In group 2 ($n = 575$, January 1998 to August 2000), the local tumor control rate after 3 months was 99.2%. In group 1, we observed 22.2% recurrence of the treated lesions. This resulted in additional treatments of these lesions for definitive tumor destruction in group 2. Even 6 months after the laser treatment, plain and contrast-enhanced MRI demonstrated a local tumor control rate of 98.2%. This shows that MR-guided LITT results in definitive tumor destruction even in long-term follow-up. During the subsequent follow-up period up to 6 years after the laser treatment, plain and contrast-enhanced MRI showed no local recurrence 6 months after initial treatment. In the late follow-up period, MRI documented only scar tissue without any pathologic contrast enhancement.

There were no statistically significant differences ($p > 0.05$) between the local control rates of the various histopathologic tumor types. The same holds for the various positions of the lesions with regard to the segmental topography of the liver.

Survival rate

In patients treated with MR-guided LITT for unresectable colorectal liver metastases, the mean survival was 41.8 months (95% confidence interval = 37.3–46.4 months). The 1-year survival rate was 93%, the 2-year survival rate was 74%, the 3-year survival rate was 50%, and the 5-year survival was 30% (Fig. 2A). There was a trend for patients with one or two initial colorectal liver metastases (mean survival = 50.4 months, 95% confidence interval = 44.4–56.4 months) to have better survival than patients with three or more initial metastases (mean survival = 34.8 months, 95% confidence interval = 31.2–38.4 months). However, the differences were not statistically significant when assessed with the log-rank test and the Tarone ware test statistics for equality of survival distribution ($p = 0.14$ and $p = 0.24$, respectively).

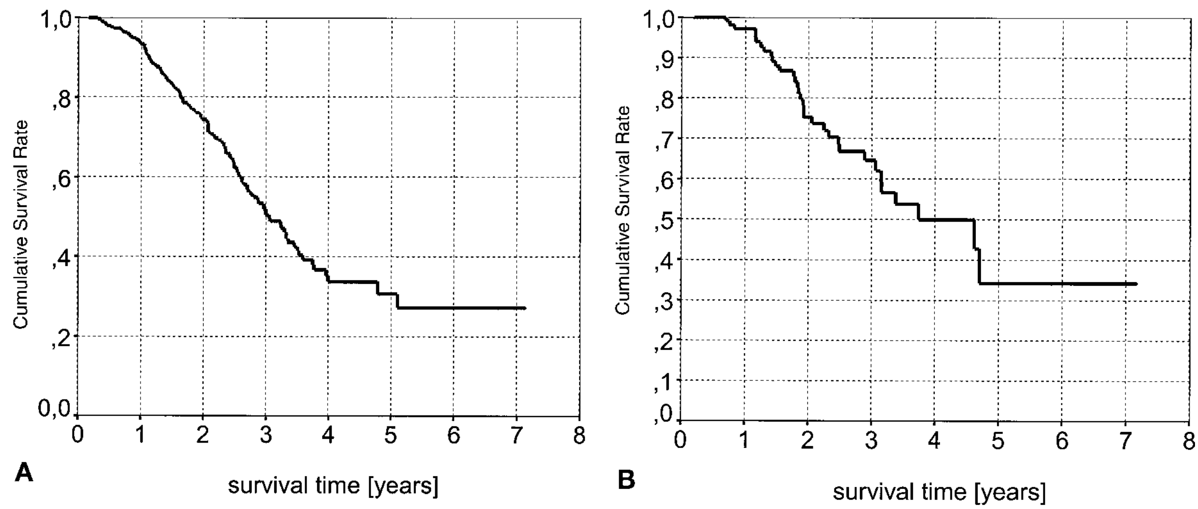
In patients treated with LITT for liver metastases of breast cancer, the mean survival was 4.3 years (95% confidence interval = 3.6–5.0 years). The 1-year survival rate was 97%, the 2-year survival rate was 75%, the 3-year survival rate was 65%, and the 5-year survival was 34% (Fig. 2B).

In all patients treated with LITT for liver metastases, the mean survival was 4.0 years (95% confidence interval = 3.7–4.4 years). The 1-year survival rate was 92%, the 2-year survival rate was 73%, the 3-year survival rate was 54%, and the 5-year survival was 36% (Fig. 2C).

Survival did not differ significantly ($p > 0.05$) between male and female patients or between patients with colorectal metastases and those with metastases of other primary tumors.

Discussion

The liver is one of the most common sites of metastases in patients with cancer. Survival of patients with meta-



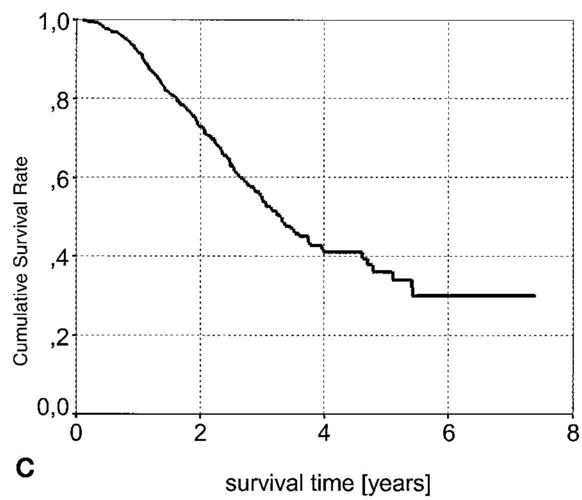


Fig. 2. A Survival data of all patients (n = 393) treated with LITT for colorectal liver metastases (n = 1203). **B** Survival data of all patients (n = 127) treated with LITT for colorectal liver metastases (n = 332). **C** Survival data of all patients (n = 705) treated with LITT for liver metastases (n = 1981).

static liver disease depends on the extent of liver involvement and the presence of metastatic tumor elsewhere.

There are two general ways of treating metastatic liver tumors: systemic and locoregional including surgical resection. In at least 50% of patients with metastases from colorectal cancer, the liver will be the sole or predominant site of metastatic disease. For these patients, the question is whether systemic or locoregional therapy will be more beneficial. One trial, performed by the Mayo Clinic and North Central Cancer Treatment Group, demonstrated a survival advantage for patients receiving fluorouracil–leucovorin [9]. Even if such regimens confer survival advantages, the study demonstrated that remissions do not endure.

Currently, hepatic resection is the only potentially curative therapy for patients with colorectal cancer metastatic to the liver. Many uncontrolled studies have reported 5-year survival rates of 20–40% for patients who underwent resection of metastases [10–12]. Even in highly selected patients, this represents a remarkable result because the 5-year survival rate in patients with medical treatment of metastatic colorectal cancer is very low.

Palmer et al. [13] followed a group of 30 patients with unresectable liver metastases who refused to undergo further treatment. In 24 patients (80%), less than 25% of the liver was involved. Fourteen had synchronous metastases, and 16 had metachronous tumors. The mean interval from diagnosis of primary disease to diagnosis of metachronous metastases was 16 months. The overall mean survival was 16 months, overall median survival was 12 months, and mean survival from diagnosis of the primary tumors was 25 months.

Stangl et al. [12] followed 1099 consecutive patients with colorectal liver metastases, 566 (51.5%) of whom received no treatment for their hepatic metastases, 340 (31%) underwent hepatic resection, 123 (11.2%) received regional chemotherapy, and 70 (6.4%) received systemic therapy. Thirty-four patients died within 30 days as a result of postoperative complications or advanced disease; 48 were excluded because they developed a second primary cancer. After hepatic resection, 60% of all patients survived 2 years, and 32% of all patients survived 5 years (median survival = 30 months). In patients who underwent regional or systemic chemotherapy, median survival rates were 12.7 and 11.1 months, respectively. In the untreated group, 31.3% of the patients were alive at 1 year, 7.9% at 2 years, 2.6% at 3 years, and 0.9% at 4 years.

Failures after resection unfortunately outnumber cures, and disease most frequently recurs within the liver parenchyma. Sugihara et al. [14] reported recurrence in 64 of 109 patients (59%) whose metastases from colorectal cancer were completely resected. Recurrence developed most commonly in the liver (34 of 64 patients) and the lung (20 of 64 patients). The peritoneum was affected in 12 patients. Findings in a more recent study [15] confirmed these results; hepatic recurrence was most often not in proximity to the surgical margin. In this series, the mean interval between resection and detection of recurrence was 17 months. This confirms the suspicion that many patients who undergo resection harbor metastases too small to be detected with cross-sectional imaging techniques.

Surgery is the only known cure for hepatic metastases of colorectal carcinoma to the liver, but the morbidity associated with hepatic resection is quite high at 15–43% [11, 16]. Even after apparently successful surgery with complete removal of metastases, the disease frequently recurs. Over the past 5–10 years, therefore, interest has focused on several minimally invasive, interstitial techniques such as LITT, radiofrequency evaluation, cryoablation, and focused ultrasound.

Laser photocoagulation involves heating a tumor with low-power laser light delivered through optical fibers (Nd:YAG). Pilot studies [17–19] using different approaches and techniques have shown that this is a very promising method for treatment of liver tumors.

A number of studies [18–23] have shown that MRI is an appropriate method for monitoring temperature changes of tissue.

The large patient group presented here shows that MR-guided LITT can offer a number of potential treatment benefits. First, MRI provides unparalleled accuracy in topographic assessment because of its excellent soft tissue contrast and high spatial resolution. This is important for initial detection of metastases and early detection of recurrence. Second, the temperature sensitivity of the thermo-turboFLASH and FLASH-2D sequences can be used to monitor the temperature elevation in the tumor and surrounding normal tissues, thus increasing the safety of the procedure. On-line MRI during LITT, therefore, allows monitoring of treatment effects such as necrosis and early detection of local complications such as hemorrhage. Third, recovery times, length of hospital stays, and the risk of infection and other complications can be reduced when compared with conventional surgery. Successful implementation of such minimally invasive procedures would significantly reduce costs in comparison with surgical procedures.

Our study yielded an overall cumulative survival rate that is comparable to data obtained from the literature after hepatic resection and better than the data of patients who received chemotherapy or no treatment.

In conclusion, our experience with MR-guided LITT in the treatment of liver metastases shows that it yields survival and local tumor control rates comparable to those of hepatic resection. LITT can be performed on an outpatient basis and is well tolerated under local anesthesia.

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