# Effect of laser-induced thermotherapy on liver metastases

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**Laser-induced thermotherapy, or laser ablation, is an established minimally invasive percutaneous technique of tumor ablation. It is performed routinely in hepatic tumors and in other indications. Most patients treated with laser-induced thermotherapy suffer from liver metastases from primary tumors, particularly colorectal cancer. In this review, the local control rate, including morphological response and local recurrence, is evaluated. Survival data, including median survival time and 1-, 2- and 3-year survival, are discussed; treatment complications are also explored. The method of treatment performance and evaluation, results, and the authors' views on the current status of treatment are outlined.**

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CONTENTS



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Metastasis is the most common neoplasm in the adult liver and, after the lymph nodes, the liver is the second most common site of metastatic spread. Liver metastases can be found in up to 80% of colorectal cancer patients and, in 25–50%, it is encountered at primary presentation [1]. For selected patients with isolated liver metastases (usually ≤4, in one lobe of the liver), surgical resection is the standard curative treatment, since it consistently provides long-term disease-free survival in a substantial number of patients [2–4].

The high incidence of new liver metastases following successful metastatic resection has spurred the search for therapeutic alternatives that will achieve survival rates similar to those attained with surgery, are less invasive and expensive, are applicable on an outpatient basis under local anesthesia and will have lower complication rates [3,5–8].

Minimally invasive treatment techniques are based on two approaches: transarterial and percutaneous. Transarterial treatment is applied through the hepatic arterial supply of the tumor, in the form of chemoperfusion, transarterial chemoembolization (TACE) and transarterial embolization (TAE). Several local percutaneous ablative therapies have proved their effectiveness for the treatment of primary liver carcinoma, such as percutaneous ethanol injection, radiofrequency ablation and microwave or ultrasound ablation; however, effective local treatment is far more difficult for liver metastases [3].

## Principle & technique

Laser-induced interstitial thermotherapy (LITT) is among the relatively new percutaneous ablation techniques that have been demonstrated to be effective. Laser coagulation is accomplished using neodymium–yttrium aluminium garnet laser light (Dornier mediLas 5060 or 5100; Dornier Medizintechnik, Germering, Germany) with a wavelength of 1064 nm. The light is delivered through 400-mm-long fibers terminated by a specially developed diffuser that emits laser light effectively to a distance of up to 12–15 mm.

The laser application kit (SOMATEX®, Berlin, Germany) consists of a cannulation needle, a guide wire, a sheath system and a special protective catheter closed at the distal end. Power applicators are 9 F in diameter and cooled internally with a room-temperature sodium chloride solution that circulates within a double lumen catheter. Cooling the surface of the laser applicator modifies the radial temperature distribution so that the maximum temperature shifts in deeper tissue layers and avoids carbonization, allowing the use of higher laser power up to 35 W. These parameters result in a more


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homogeneous tissue penetration of laser radiation. The laser systems are fully compatible with magnetic resonance imaging (MRI) units [5].

In the authors' institute, laser applicator systems are placed at the desired position under computed tomographic (CT) fluoroscopy guidance (Somatom®, Siemens, Erlangen, Germany). The multiple-application technique involves the treatment of one lesion with multiple (<5) laser applicators simultaneously (FIGURE 1). It is also possible to treat more than one lesion in the same session (FIGURE 2). The patients are then transferred to a 0.5 T closed MRI unit (Privilig; Elscint, Frankfurt, Germany). Laser ablation is performed under near real-time MR using T1-weighted gradient-echo sequence (140/12, flip angle of 80°, matrix of 128 × 256, five 8-mm sections and acquisition time of 15 s) in transverse slices, parallel to the laser applicators. This is repeated every minute in order to monitor thermal ablation. The pull-back technique involves retracting the fiber optic bundle at the end of the first laser cycle by 2 cm, followed by a second laser cycle, to enlarge the area of coagulation necrosis. Necrosis manifests as progressively deepening T1 hypointensity (FIGURE 3). After the procedure, the puncture tract is closed with fibrin glue (Tissucol DuoS®, Baxter, Unterschleissheim, Germany) [5].

Alternatively, the puncture, applicator positioning and laser ablation monitoring can all be performed in an 0.2 T open MRI unit (Concerto, Siemens, Erlangen, Germany).

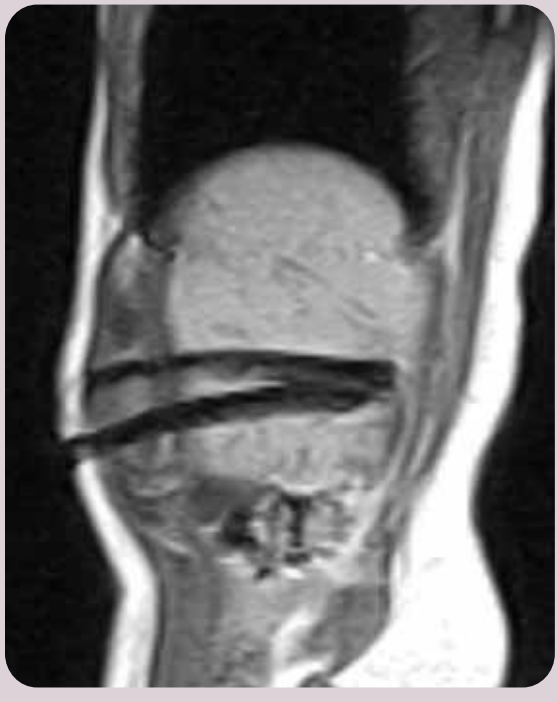

**Figure 1. Multiple applicators during magnetic resonance thermal monitoring.** A sagittal fast low angle shot (FLASH) gradient T1WI of the liver parallel to the applicators for monitoring thermotherapy.

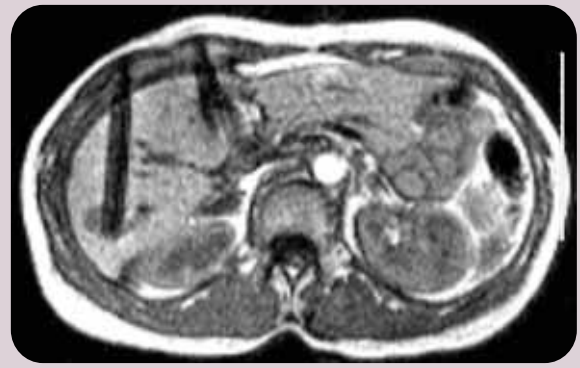

**Figure 2. Axial fast low angle shot (FLASH) gradient T1WI of the liver.** Multiple applicators used to ablate two separate lesions in segments 5 and 6 of the liver simultaneously.

The entire LITT treatment can be tolerated under local anesthesia using 20–30 ml of 1% lidocaine (AstraZeneca, Wedel, Germany) and intravenous analgesics (pethidine [10–80 mg], Aventis, Frankfurt, Germany, and/or piritramid [5–15 mg], Janssen, Beerse, Belgium) and sedatives (Midazolam [2–10 mg]; Merkle, Blaubeuren, Germany). The mean duration of ablation is 20 min (range: 2–55 min). Thermal imaging results in an adaptation concerning the duration of ablation. The pull-back and repositioning of the laser fiber is calculated on the basis of thermal imaging since the heat deposition in the tissue cannot be predicted. Thus, a certain amount of energy can result in completely different volumes of coagulation necrosis [5].

### Indications & contraindications

The indications for LITT are recurrent liver metastases after partial liver resection, metastases in both liver lobes, locally nonresectable lesions, general contraindications for surgery or refusal to undergo surgical resection [3,9]. Patients are discussed in a tumor board with oncologists, surgeons and radio-oncologists. Excluded patients are those who initially have more than five lesions, lesions with greatest diameter larger than 5 cm or known extrahepatic tumor spread not including lymph node metastases removed during primary colorectal tumor resection [3]. Some other possible contraindications are poor coagulability, liver insufficiency and contraindications for MRI [9].

### Results

Several centers have documented their achieved results using this line of treatment. The authors' patient series involved applications made in 5105 lesions in 1650 consecutive patients. The local tumor control rate in the 3-month follow-up control was 99.2%. After 6 months, a local tumor control rate of 98.2% was observed. There are no statistically significant differences between the local control rates of the various histopathological tumor types. This is also true for the various positions of the lesions with regard to the segmental topography of the liver. The mean survival is

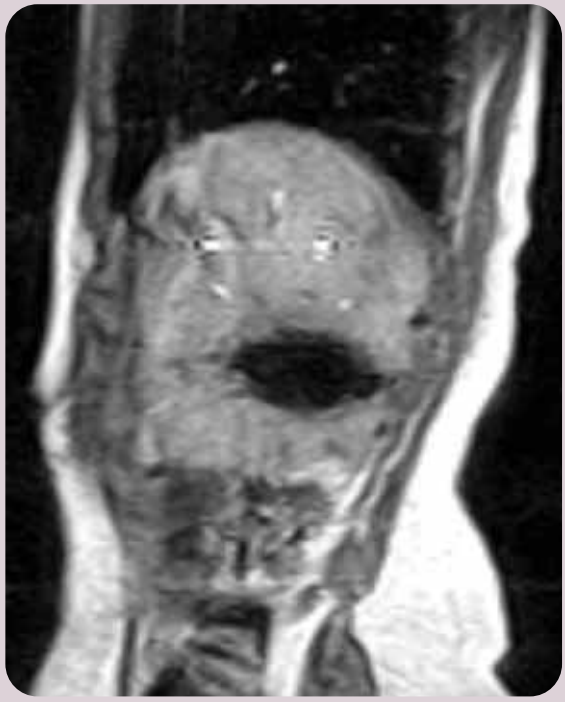

Figure 3. Deep T1 hypointensity of the tumor noted during magnetic resonance-monitored thermotherapy, which is a sign of successful coagulation necrosis.

41.8 months in patients with unresectable colorectal liver metastases and 51 months in patients with breast cancer [6], calculated from initiation of treatment.

The overall rate of complications and side effects is 7.5%; the rate of clinically relevant complications is 1.3%. The most common side effects of LITT treatment are reactive pleural effusion, intrahepatic abscess, pleural empyema, subcapsular hematoma (FIGURE 4) and intrahepatic and intra-abdominal bleeding. Less significant complications include local infection at the puncture site and bile duct injury [5,6,10].

As an update, the authors reviewed the results in 603 patients with colorectal metastases, in which 1801 lesions were treated. In an 11-year follow-up, the mean survival rate for all patients, with calculations started on the date of diagnosis of the metastasis, was 4.4 years (median survival: 4.5 years). The 1-, 2-, 3- and 5-year survival rates were 94, 77, 56 and 37%, respectively. Median survival was 3.5 years [3].

Several factors may influence the size and morphology of the areas of induced necrosis, including tumor geometry and adjacent structures, such as arteries, portal and hepatic vein, and the biliary tree, as well as tumor relation to the liver capsule. Also, patients who were judged as surgical candidates prior to LITT presented with better survival rates compared with patients who were not considered for surgery.

In the study by Mensel and colleagues to evaluate LITT effectiveness in central lesions, 23 patients with 28 central malignant liver tumors, including 27 metastases and one hepatocellular carcinoma (HCC), were included. Central lesions pose the problem of difficult access and larger surrounding vessels, causing more heat loss. Complete ablation was achieved after the first treatment session in 71.4% of patients. The effectiveness rate during follow-up was 78.6, 71.4 and 64.3% after 3, 6 and 9 months, respectively. The 1-, 2-, 3- and 4-year survival rates were 90, 72, 60 and 40%, respectively; the median survival was 46 months. Major complications occurred in one patient (hemorrhagic pleural effusion), while minor complications occurred in ten patients (43.4%) [10]. There were no mortalities (30-day mortality) related to the procedure. In accordance with these findings, the success of LITT in the authors' studies was not influenced by the location of the lesion [3,5].

Fiedler and colleagues evaluated the relationship between lesion size and effectiveness. This was 100% for metastases less than 2 cm in diameter, 71% for metastases between 2 and 3 cm, 46% for metastases between 3 and 4 cm and 30% for metastases greater than 4 cm [11]. This is in agreement with the authors' findings, as shown in TABLE 1.

### Dicussion

Surgical resection offers the best curative results in liver metastases. Recent series have described 1-year survival rates of 71–88%, 3-year survival rates of 21–46%, 5-year survival rates of 25–37% and 10-year survival rates of 20–22%. Mean survival times of 25–35 months were achieved. However, less than 20% of patients are candidates for resection. Perioperative mortality data range from 4.4 to 10.0%. A total of 65–80% of patients have a relapse, with half of the relapses occurring in the liver [2,3]. Nevertheless, repeat liver resection can be performed and may result in improved survival of selected patients. Surgical treatment is contraindicated in the presence of lesions close to vital structures or in both hepatic lobes, and in patients with poor general clinical status [3].

Systemic chemotherapy with 5-fluorouracil (5-FU) produces a response rate of approximately 20% and a 2-year survival rate of 20%. Recently, it was demonstrated that the addition of irinotecan and oxaliplatin to 5-FU-based regimens resulted in superior response rates (40–50%) as well as longer median survival times (15–17 months) [12].

The morphological response achieved by regional chemoperfusion in colorectal liver metastases during the last 5 years ranges from 29.7 [13] to 56% [14]. Median survival with chemoperfusion ranged from 10.6 [15] to 62.6 months [16]. Comparable results were encountered using TACE and TAE. Median survival ranged from 8.5 months in uveal melanoma metastases [17] to 69 months in neuroendocrine metastases [18]. Morphological responses ranged from 9 to 79% in neuroendocrine metastases [19,20]. These results are so variable owing to the various chemotherapeutic agents, embolizing material and treatment protocols applied. There is no universally accepted scheme to achieve optimal results.

Radiofrequency ablation is effective in ablation of liver metastases with respect to survival rates [21–23]. Solbiati and colleagues reported a median survival of 36 months in patients with colorectal

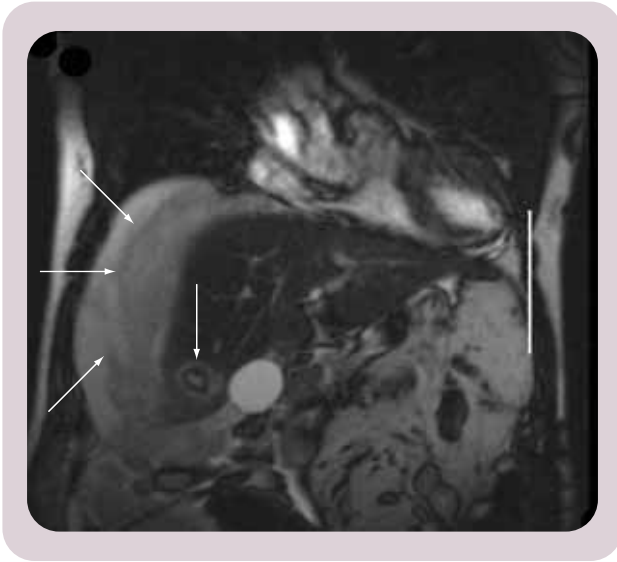

Figure 4. Coronal T2WI of the liver after a laser-induced thermotherapy session showing a subcapsular hematoma overlying the lateral surface of the liver (arrows). The patient developed shock manifestations and was successfully stabilized by selective embolization of the bleeding artery. The ablated metastatic lesion is seen at the inferior liver surface (sagittal arrow).

liver metastases treated with radiofrequency ablation. A high local recurrence rate ranging from 21.6% for metastases up to 2.5 cm to 68.4% for lesions larger than 4 cm was reported [24]. With microwave ablation, the reported recurrence rate was 15% [25].

Survival after LITT is clearly superior to survival after systemic chemotherapy [16] and equal to survival after surgery. Local tumor control in the authors' studies was better than that reported with other minimally invasive therapies.

The clinical success of MRI-guided LITT is based on a number of factors. One imaging system serves in the planning, targeting and monitoring of therapy and follow-up of the disease. Optimal positioning of one or more laser application systems in the lesion can be ensured in three dimensions. The main advantages of MRI over CT scan and ultrasonography include the heat sensitivity of the MR sequence and the possibility of visualizing and quantifying the degree of induced necrosis of the malignant and surrounding parenchymal structures. It allows rapid acquisition of temperature maps, which allow near real-time documentation of LITT effects.

Monitoring of these effects during ongoing therapy is advantageous for the following reasons: the technique can be used to ensure that the entire lesion has been treated; and if there is residual tissue within the lesion that has not been treated, the applicator can be repositioned with MRI guidance during the same treatment session. This technique allows safe destruction of metastases and well controlled coagulation in a safety margin surrounding the lesion.

Monitoring with MRI also helps minimize destruction of healthy tissues, thus increasing the safety of the procedure, particularly in the vicinity of vital structures, such as large vessels or the central bile ducts in the liver. MRI enables early detection of complications owing to its unparalleled topographic accuracy, excellent soft-tissue contrast and high spatial resolution [3].

In the authors' practice, LITT treatment is performed with a conventional closed MR imager. Therefore, the needle is placed with CT guidance instead of MRI guidance. Another advantage of CT-guided needle placement is quicker image update and more precise visualization of the needle. This might be considered by some as a potential limitation of the LITT procedure if it is difficult to coordinate two modalities (CT and MRI); however, with an open MR imager, this problem is avoided [26,27].

In the authors' opinion, CT guidance alone is inferior to combined CT and MRI guidance since thermal changes can be better visualized with temperature-sensitive MR sequences.

The high rate of intrahepatic recurrences after resection and the possibility of potentiating intrahepatic growth of metastases as a result of a release of growth factors after resection must be discussed. In the authors' opinion, these effects are less relevant for LITT owing to the obviously minor loss of liver parenchyma after LITT compared with after liver resection. Stimulation of growth factors probably has no influence on local tumor control at the ablation or resection site but does have an influence on the development of new intrahepatic metastases.

As a result of being able to place multiple application systems, the authors were able to induce coagulation necrosis that exceeded the volume of the tumor. All inserted laser application systems can be operated simultaneously since there is no interference between multiple-inserted laser applicators. In the authors' opinion, this is the reason for such a low local recurrence rate in comparison to that after radiofrequency ablation [2,3]. The data published by Pacella's group are based on an easier technique [28,29]. In this technique, fine needles are applied under ultrasound guidance. The survival data compare favorably with those of radiofrequency [28,29].

Although the intention for LITT was originally palliative, its favorable survival rates compare with those obtained with surgical resection of liver metastases, while it also demonstrates lower morbidity and mortality rates [3,8,9]. Surgery can be combined with LITT in the same treatment plan, thus reducing the resected portion, while LITT is used to treat residual lesions in the spared portion. LITT also can be applied in coordination with TACE, which is applied first to achieve downsizing of metastases, enabling them to be treated by LITT (FIGURE 5) [30].

Table 1. Local tumor control data at 3 and 6 months after laser-induced thermotherapy correlated to lesion size.

| Size of metastases (cm) | Local recurrence rate at 3 months | Local recurrence rate at 6 months |
|---|---|---|
| 0–2 (n = 474) | 1.4 (3/213) | 2.3 (5/213) |
| 2–3 (n = 539) | 2.5 (4/162) | 4.3 (7/162) |
| 3–4 (n = 327) | 3.2 (2/63) | 3.2 (2/63) |
| >4 (n = 294) | 1.9 (1/52) | 1.9 (1/52) |

Numbers in brackets are raw data. Only those patients are measured who had their follow-up in the authors' department. No significant difference was noted. Data from [3].

These data suggest that, in the next few years, the indication for LITT rather than surgery can be extended to all patients with colorectal liver metastases, including surgical candidates with no more than five metastases with a maximum diameter of 5 cm. By applying LITT, less healthy liver tissue is sacrificed and more hepatic reserve is salvaged. Keeping in mind the possibility of recurrence of metastases, this approach gives the patients better prospects.

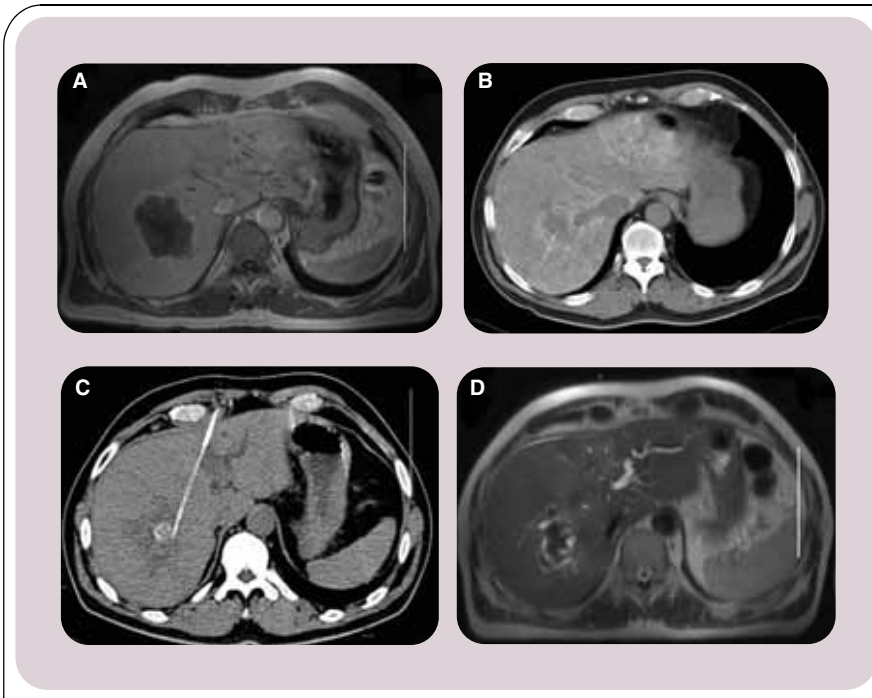


Figure 5. Downsizing of colorectal liver metastases using transarterial chemoembolization (TACE) followed by laser-induced thermotherapy (LITT). (A) Postcontrast T1WI showing a large right hepatic lobe metastatic mass in a patient with colorectal carcinoma that was not treatable by LITT. (B) The same lesion after three TACE sessions showing lipiodol retention and size reduction. (C) First LITT session to ablate the lesion. (D) Follow-up T2W magnetic resonance image after LITT, showing necrotic lesion with no evidence of recurrence.

### Expert commentary

Thermoablation is an evolving field in interventional oncology. The minimal invasive character and the reproducible clinical results of the treatment can be well documented and fixed in the area of oncology. There are various techniques for performing thermal ablation, including radiofrequency ablation, cryoablation and LITT. Currently, MRI-guided LITT is an optimal therapy method for liver metastases, providing a high local tumor control rate, a low rate of complications and side effects and an improved survival rate.

### Five-year view

Within 5 years, we are convinced that thermal ablation will be included in clinical oncology protocols. There will be three major indications: curative thermal ablation of liver metastases; low-volume liver metastases in the liver; and thermal ablation in combination with chemotherapy and regional chemotherapy.

### Key issues

- Laser-induced thermotherapy (LITT) is an effective method of treating liver metastases.
- Application can be guided by computed tomography (CT) or magnetic resonance imaging (MRI).
- Thermal ablation is monitored by MRI.
- The process is minimally invasive and can be performed in an outpatient setting under local anesthesia.
- Local control and survival data are comparable with surgery and significant complications are infrequent.
- LITT can be applied in coordination with surgical resection and transarterial chemoembolization.
- The indications for LITT may well increase in the near future to involve more patients who were previously only treatable surgically.

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•• Very important and unique reference to discuss combined TACE and LITT treatment, which is successfully used in the authors' institute.


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