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Interventional MR: interstitial therapy

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Abstract. The rationale and results for interstitial therapies via interventional MRI in the treatment of tumors in various regions are presented. Different interstitial treatment techniques are presented based on varying technologies both for tumor ablation and treatment monitoring. Data are presented based on 335 patients, 29–84 years of age (mean age 59 years, 196 men and 139 women) with a total of 932 liver tumors, 16 head and neck tumors and 14 abdominal recurrent pelvic and lymphatic tumors. All lesions had been treated with MR-guided laser-induced interstitial thermotherapy (LITT) via 2516 laser applications and 1856 cannulations. Data in the literature are extremely varying depending on author experience, treatment technique, and the included patient material. In our patient material we were able to achieve a local tumor control of 96.7 % depending on the size of the tumorous lesion, the topographical relationship, and the applied laser parameters. The overall cumulative survival rate of patients with liver metastases was 45.74 months (median 40.97 months, 95 % confidence interval 31.42–50.52). The cumulative survival rate of the patient group with hepatic metastases of colorectal carcinoma was 42.71 months (median 39.33 months, 95 % confidence interval 33.26–45.37). In patients with head and neck tumors a relevant reduction in clinically relevant symptoms such as pain, swallowing disorders, or nervous compression was achieved in 11 of 15 patients treated with LITT. In 14 soft tissue tumors, such as pelvic tumor recurrence and lymph node metastases, a local tumor control was obtained in 68 % of lesions. Interstitial therapies under interventional MRI guidance, such as LITT, results in a high local tumor control with an improved survival rate.

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Introduction

Magnetic-resonance-imaging-based guidance control and monitoring of minimally invasive intervention has developed from a hypothetical concept to a practical possibility. Magnetic-resonance-guided interstitial therapy in principle is defined as a treatment technique for ablating deep seated tumors in the human body. Compared with conventional surgical interventions, these techniques may help to reduce health care costs and shorten patient recovery times. More recently, attention has focused on the delivery of thermal energy creating thermoablative lesions. For the guarantee of a safe treatment procedure temperature dissipation must be monitored in the target tissue.

Current interstitial thermoablative modalities include laser interstitial therapy (LITT), radio-frequency (RF) thermoablation, focused ultrasound, and cryotherapy. Increasing interest in interstitial therapies as means of cancer treatment has intensified interest in noninvasive methods of monitoring temperature distributions in vivo, since the biological efficacy of thermal-ablation techniques is strongly dependent on the temperature achieved in all parts of the tumor [1]. Interventional MRI using MR thermometry allows noninvasive monitoring of interventional thermal procedures inside the human body with high spatial and temporal resolution. In comparison with CT- or ultrasound-guided therapies implementation of a laser or radio-frequency generator in the MR environment is a far more demanding task. A new application of MRI to map the spatial and temporal distribution of the effects of RF, laser, or cryotherapy on tissues has been studied in several working groups [2, 3]. The temperature dependence of MR relaxation mechanism and the high sensitivity of MR changes in the mobility and distribution of tissue water make it particularly suitable for the demonstration and control of thermal energy deposition in tissue, thus forming the basis for the use of interventional MRI in interstitial therapies [2, 4, 5]. The laser-induced interstitial thermotherapy is based on clinical concepts of contents and methods of the classical hyperthermia. With the tissue coagulation additionally achieved by this treatment, the thermoeffects exceed the exclusively hyperthermic effect of classical hyperthermia [4].

Interstitial hyperthermia via laser technology with the insertion of the light-conducting quartz-fiber into tumor was described first by Bown in 1983 [6]. Whereas this method of energy delivery is invasive, its advantages are that there is little back-scattering and impact loss as light strikes tissue, and in order to reach a specific point within an organ, the surface is not heated by the use of a thermal conduit. Laser light is produced using a Neodymium yttrium aluminum garnet (Nd-YAG, wavelength 1064 nm) delivered through a quartz fiber optic with a diameter of 400 μm with diffuse light emission. Laser light is converted into heat in the target area with an ensuing coagulative necrosis, secondary degeneration and atrophy, and tumor shrinkage with minimal damage to surrounding structures [7, 8]. The size of heated volume depends on laser power, laser irradiation time, the way it reaches the target area, and the optical and thermal characteristics of the treated tissue. Clinical studies have demonstrated that this technique is practical for the palliation of hepatic and nasopharyngeal tumors [8, 9, 10, 11]. The clinical success of the thermotherapy depends on the optimal positioning of the laser applicator in the center of the lesion, an optimal "online monitoring" of thermal changes in the treated tissue and an exact documentation of the therapy effect and the local tumor control rate. A temperature increase of approximately 60 °C leads to a denaturation of the proteins, meaning coagulation and immediate death of the treated tissue [12]. Depending on type of tissue and size of lesion, tissue treated with LITT is degraded within several months or totally incorporated.

The purpose of this paper is to describe the clinical experience with interstitial MR-guided LITT for the treatment of tumors in various indications and discuss the results with those from other treatment modalities.

Methods

Treatment of tumors

All MR-guided LITT treatments are currently performed on an outpatient basis. For malignant liver tumors we have defined the following inclusion criteria: primary or secondary malignant liver tumors without the evidence of extrahepatic spread with a maximum number of five lesions and no lesion measuring more than 50 mm in diameter.

For planning of LITT all patients are evaluated with MR imaging 1–5 days before the intervention. The protocol includes precontrast T2-weighted sequence, pre- and postcontrast T1-weighted sequence, and T1-weighted gradient-echo (GRE) FLASH sequence in transversal and sagittal orientation. After the evaluation of localization, size, and contrast enhancement of the lesion, the optimal interventional access to the lesion is defined. Special attention is focused on neighboring vascular, biliary and parenchymatous structures, which could be injured during the access or the following laser intervention.

A routine hematological examination including coagulation screening, liver function tests, and tumor marker is performed. Written consent is obtained from the patient at least 24 h before the intervention. Immediately prior to the procedure pethidine (50–100 mg) is administered intravenously. After localization of the lesion on plain CT scans, the distances from the skin to the lesion and the puncture channel are measured. After anesthetizing (20 ml lidocaine 1 %) the intended puncture site, a Chiba needle is positioned percutaneously. A guidewire is introduced and the puncture channel is dilated to 7 F for a baffle catheter, in which a distally closed, thermostable plastic is introduced. The procedure is continued in the MRI unit. The patient is placed on the MR table and the laser catheter (Nd-YAG) is inserted into the thermostable plastic catheter sheath. The plastic catheter prevents the applicator from direct contact to tissue and guaranties in case of its damage a complete removal.

The laser emitter is installed in the equipment room and the laser light is transmitted to the MRI unit with a 10-m optical fiber cable. The applicator obtains the diffuse light distribution by a 10- to 20-mm-long, frosted part of the distal fiber core and by a protecting glass dome with a diameter of 1.4 mm, which is frosted on its inner surface. The optimal position of the laser applicator using a magnetite marker is established with MR imaging using the FLASH sequences in transverse, sagittal, and coronal orientation.

In order to monitor the progress of LITT two special thermosensitive MR sequences, the thermo-turbo-FLASH sequence [TR/TE: 100–500/3 ms, flip angle 15 °, field of view (FOV) 350 mm, matrix 128 × 128, slice thickness 8 mm] and the FLASH 2D sequence (TR/TE: 102/8 ms, flip angle 70 °, FOV 350 mm, matrix 128 × 256, slice thickness 8 mm) are individually optimized and repeatedly applied during therapy. The thermosequences are more sensitive for the detection of the laser-induced thermal changes in signal and morphology. The images are analyzed on-line for signal changes around the laser applicator and the border of the lesion. Signal loss around the laser tip is observed in all treated lesions and special attention is directed to signal intensity changes in normal liver parenchyma, vascular structures, and liver capsule. The time of laser irradiation varies from 5 to 35 min and the power from 8 to 30 W depending on the monitored signal changes and size of the lesion. During LITT the diameter of the area with reduced SI grows constantly and after stopping the laser power the undamaged tissue returns to the preinterventional signal intensity. Immediately after LITT contrast-enhanced FLASH 2D sequences are performed to give information about size of the coagulative necrosis and perfusion of surrounding tissue and vessels. After injection of local anesthesia (1 % lidocaine) and ethanol, the plastic catheter is removed carefully to achieve hemostasis and/or to destroy tumor cells which may have disseminated with the guidewire along the puncture channel. The puncture channel is closed with a two-component fibrin glue (Tissucol).

Patients without complaints are dismissed after a 6-h post procedure follow-up. All patients are rescanned with MRI 24 h post procedure to check for side effects such as hemorrhage, pneumothorax, fistula formation, or infection. To monitor the result of LITT follow-up examinations were obtained using the standardized MR imaging protocol every 3 months for the first 2 years after LITT.

Results

Liver

A total of 324 patients, 28–84 years of age (mean age 59 years, 196 men and 128 women) with a total of 902 liver tumors were treated with LITT. A total of 2516 laser applications and 1856 cannulations were performed in 810 treatment sessions. The patient group consisted of hepatic metastases of colorectal cancer, breast cancer, hepatocellular carcinomas and miscellaneous tumors.

One hundred ninety-nine patients suffered from metastases of colorectal cancer, and 51 patients from metastases of breast cancer. In 16 patients we treated hepatocellular carcinoma tumors, and in 58 patients miscellaneous tumors.

The complication rate is based on the number of therapy sessions. All patients tolerated the procedure under local anesthesia well. One patient died 4 weeks after treatment. This patient had developed a leakage in the jejunum after LITT of a liver metastases in the liver segment 4 a. The patient underwent surgery and died due to peritonitis and acute respiratory distress syndrome. The death was considered possibly LITT related, most likely due to a stress ulceration of the jejunum. In one case a liver abscess was observed. After two LITT treatments, 7 patients suffered from pain for more than 24 h but less than 1 week. The pain was treated with an oral analgetic drug. In 21 cases (2.48 %) subcapsular hematomas without clinical symptoms and one intra-abdominal bleeding without therapy option were verified in the postprocedure MRI study. In 60 treatments a pleural effusion (5.7 %) on the right side was documented, and in 3 patients percutaneous drainage of the effusion was performed. A local infection at the puncture site was seen in 2 patients, but no seeding metastasis was found.

The effectiveness of MR-guided LITT was evaluated both analyzing the local tumor control rate (Figs. 1, 2) and the survival data. The treated patient material is divided into three categories according to the continuous technical and clinical improvement of the LITT procedure. In phase I (patients 1–100) conventional MR-guided LITT was performed and the local tumor control rate was 71 %, and in phase-II (patients 101–175) 79 %. In phase III, patients were treated with a cooled power-laser-ablation system (Figs. 3, 4). In this patient group we were able to achieve a local tumor control rate in the 3 months of follow-up of 98.1 %, and 97.3 % in the 6 months of follow up (Figs. 3, 4, 5).

The cumulative survival times were calculated using the Kaplan-Maier method. The overall cumulative survival rate of patients with liver metastases was 45.74 months (median 40.97 months, 95 % confidence interval 31.42–50.52; Fig. 6). The cumulative survival rate of the patients group with hepatic metastases of colorectal carcinoma was 42.71 months (median 39.33 months, 95 % confidence interval 33.26–45.37; Fig. 7). In patients with liver metastases of breast cancer cumulative survival was 50.29 months (mean 56.23 months). No statistically significant difference was documented between the survival data in patients with liver metastases of colorectal cancer and other primary tumors.

Head and neck and extrahepatic tumors

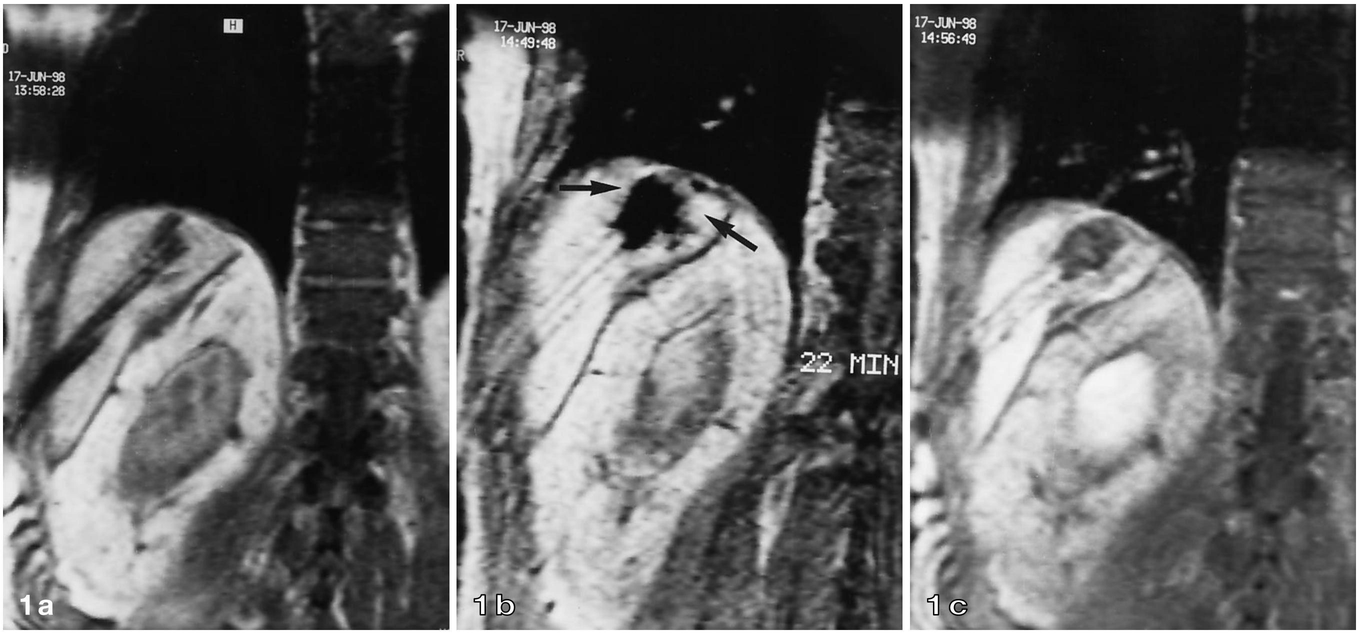
Sixteen patients (6 women and 10 men; mean age 62 years, range 57–77 years) with recurrent tumors of the head and neck were treated with MR-guided LITT. In all patients the primary tumor was located in the head and neck region. In the majority of patients there was a recurrent squamous cell carcinoma. Two patients with pleomorphic adenoma in the parapharyngeal space were treated for tumor recurrence after primary surgery.

All patients tolerated well the intervention under local anesthesia. During LITT blood pressure and pulse were measured. After 5 min of LITT treatment, 1 patient had an increasing sense of heat, but no pain. In summary, no short- or long-term side effects were observed post LITT.

Regularly the pretherapeutic T2- and T1-weighted sequences showed only a low degree of spontaneous tumor necrosis, and the solid parts of tumor were characterized by strong contrast enhancement. Magnetic resonance thermometry revealed a regional signal loss, the extent of which was dependent on the application system used and the laser energy power. The LITT procedure was judged as being successfully performed if post-procedure MRI revealed a sharply delineated necrosis exceeding the pretherapeutic tumor. Control examinations 2 days, 1 week, 4 weeks and every 3 months after LITT showed that the initial high contrast enhancement in the rim of the coagulative necrosis normalizes within 3 months.

The evaluation of subjective and objective clinical symptoms of the patients was done in each control examination. A relevant reduction of clinically important symptoms, such as pain, was observed in 11 patients, and a reduction of swallowing problems and symptoms of nervous compression in 6 patients.

In another group of 14 patients abdominal tumorous lymph node involvement or recurrent primary pelvic tu-



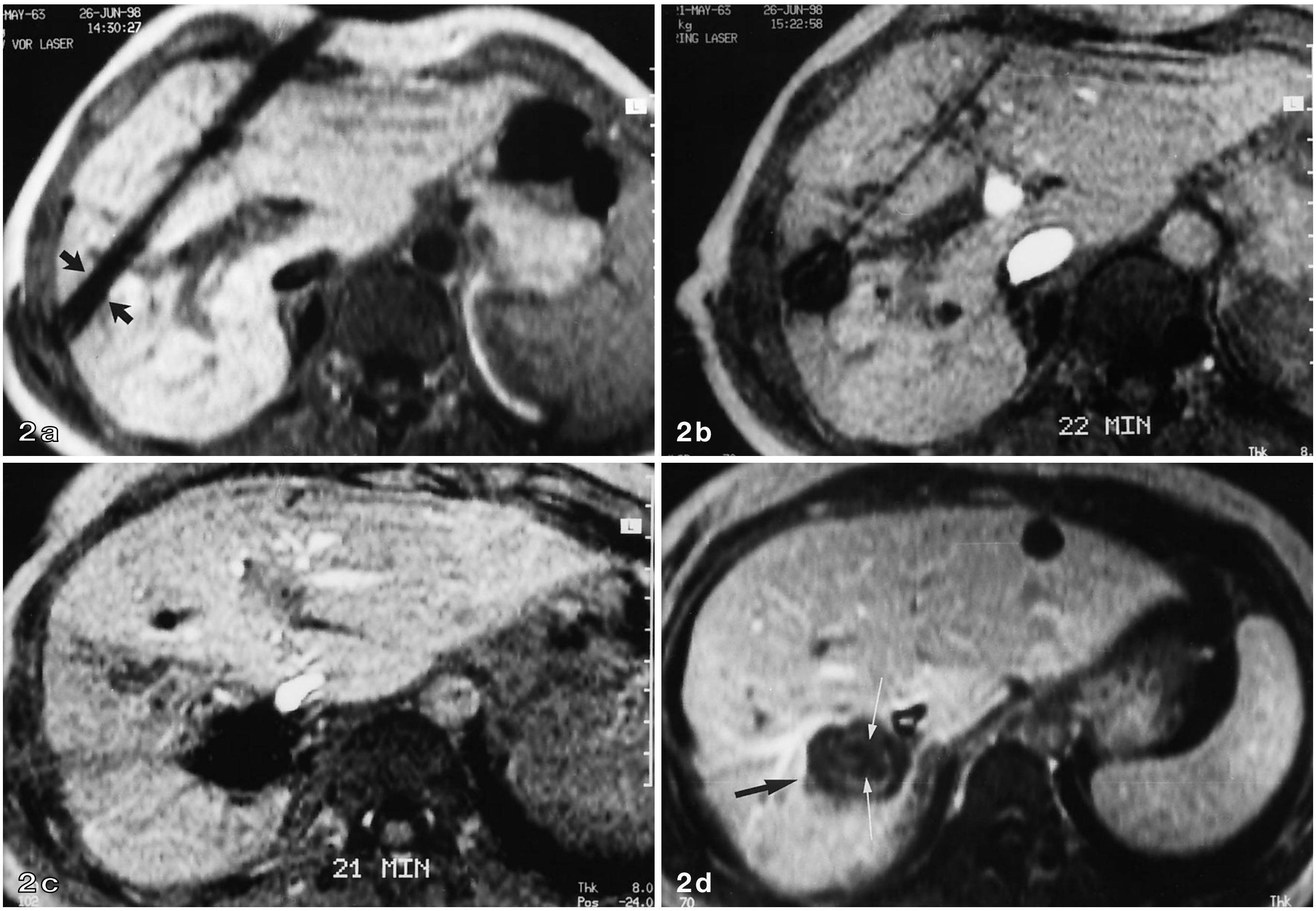
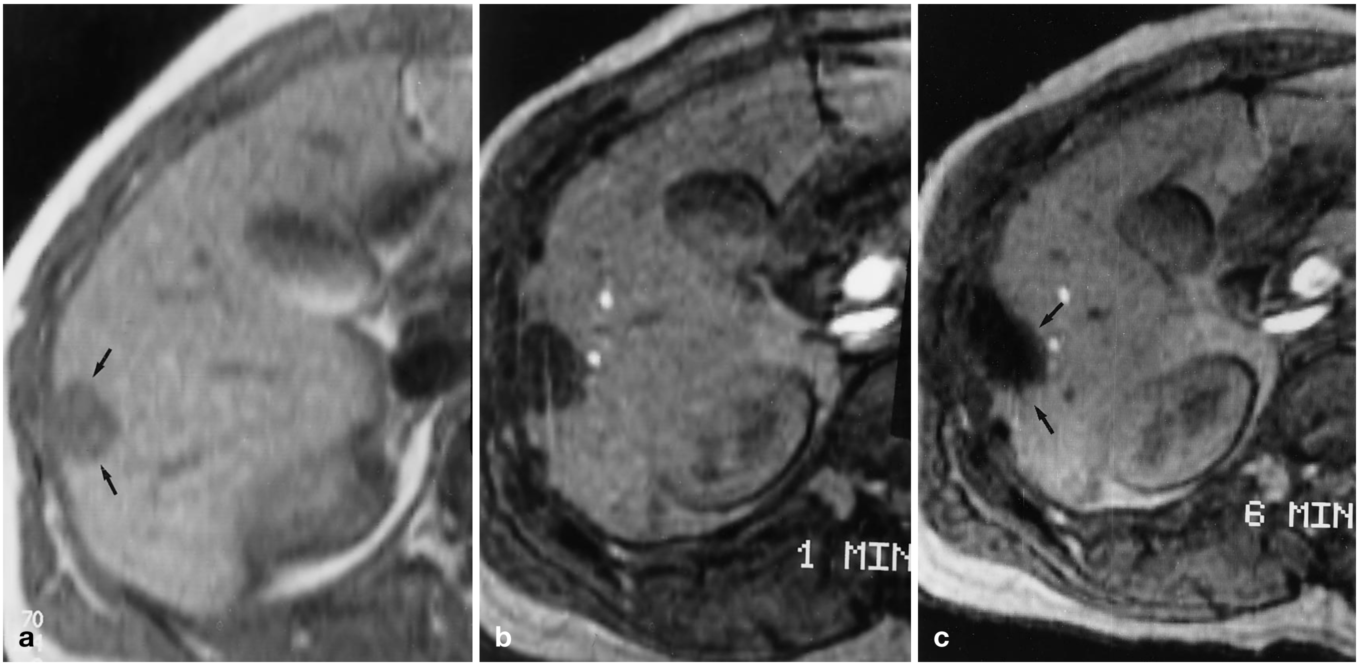


Fig. 1. a A 78-year-old patient with liver metastases in the dome of the liver. FLASH 2D sequence MR thermometry before LITT. The MR thermometry reveals two applied laser application systems in a lesion directly beyond the dome of the liver. **b** Magnetic resonance thermometry 22 min post LITT. Verification of the laser-induced thermo changes in the dome of the liver. Note the sharp borders of the laser-induced changes *(arrows)*. **c** FLASH 2D sequence, gadolinium enhanced, post LITT. The gadolinium-enhanced post-contrast sequence reveals the laser-induced necrosis as a nonenhancing area under the dome of the liver

Fig. 2a–d. A 47-year-old patient with liver metastases of a colorectal cancer. Verification of MR thermometry using the power laser application. **a** FLASH 2D sequence plain. Note the applied laser application system *(arrows)*. **b** Magnetic resonance thermometry 22 min post LITT. Verification of the laser-induced necrosis near the capsule of the liver. Note the homogeneous extension and the round aspect of the laser-induced changes. **c** Additional treatment of a lesion in segment 7 post LITT. Verification of the laser-induced necrosis post LITT. d Twenty-four-hour control post LITT of the liver metastasis. Note the *dark structures* as nonenhancing areas due to necrosis *(white arrows)*, and note the *peripheral contrast-enhancing structures* due to hypervascularization *(black arrows)*



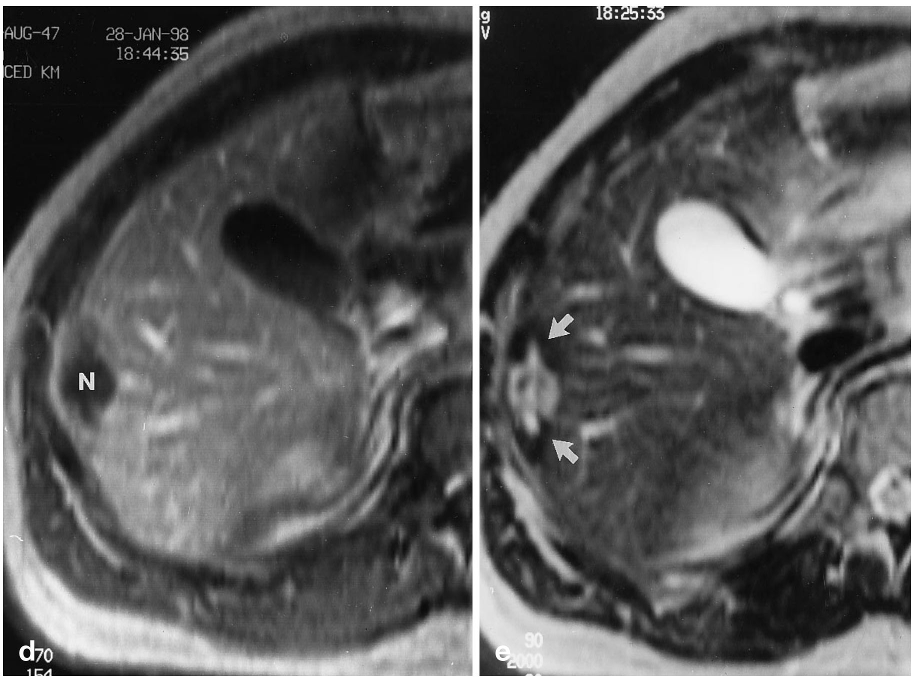


Fig. 3. a A 48-year-old patient with recurrent liver metastases of colorectal cancer. FLASH 2D sequence, T1-weighted, preinterventional gradient-echo sequence reveals a 18 × 15-mm lesion in segment 6 *(arrows)*. **b** Magnetic resonance thermometry, 1 min after laser application. Note the already visualized signal loss in the metastasis 1 min after laser application. (Power laser system). **c** Magnetic resonance thermometry, 6 min after laser application. The total area of the lesion is characterized by significant signal loss *(arrows)*. **d** T1-weighted gradient-echo sequence (FLASH 2D) post Gd-DTPA. The gadolinium-enhanced MR sequence reveals the laser-induced necrosis *(n)* as a hypointense area. **e** A T2-weighted spin-echo sequence post laser-induced interstitial thermotherapy (LITT). The T2-weighted sequence reveals within a lesion *(arrow)* a central area of hyperintensity due to coagulation. Note the peripheral zone of hypointense structures due to the laser-induced effects on the liver tissue

mors had been successfully treated using MR-guided LITT. In this minor group of patients we had been able to reduce clinical symptoms in 68 % of the patients. Also the local tumor control rate in the 3-month control studies was 68 %.

Discussion

Clinical applications of MR-guided interventional techniques have to be divided into diagnostic and therapeutic procedures. Much of the effort in the development of MR-guided therapy has concentrated on local cancer treatment through percutaneous MR-guided thermal or chemical tumor ablation. These techniques have significant potential to produce complete destruction of local tumors. With growing experience in interventional MR many groups have turned to MR as an effective means of guidance for percutaneous destruction of neoplastic tissue [6, 13, 14, 15]. Chemoactive agents include absolute alcohol and various chemotherapy drugs. Most attention has focused on the delivery of thermal energy creating thermoablative lesions. Through the combination of MR-image monitoring of tumor destruction with minimally invasive methods for tumor destruction these new techniques have the potential to guide and visualize directly an ablative procedure for achieving complete tumor destruction.

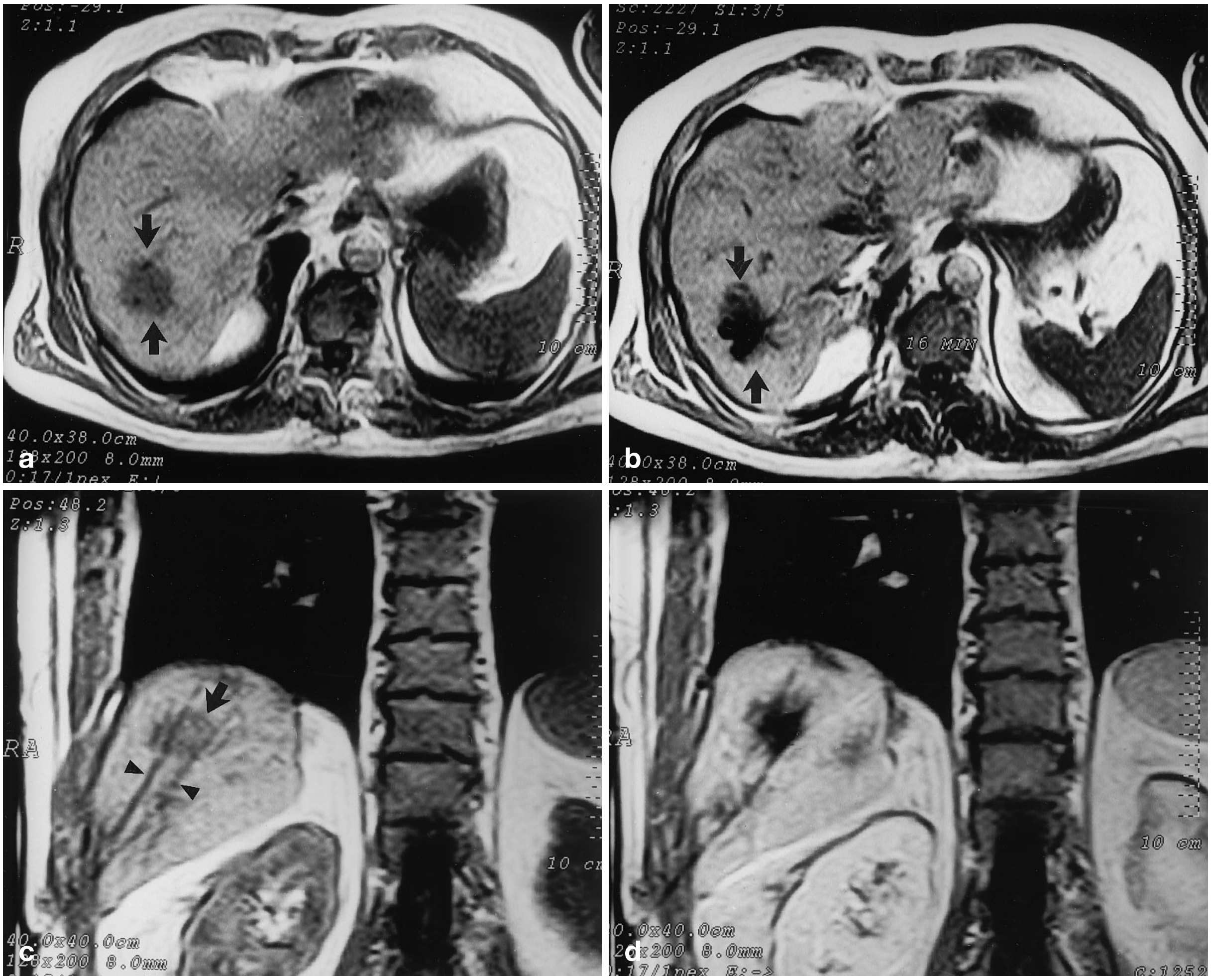


Fig. 4. a A 57-year-old patient with liver metastases of colorectal cancer. FLASH 2D sequence before LITT. The plain sequence reveals a 30 × 35-mm lesion in segment 7 *(arrow)*. **b** Magnetic resonance thermometry 16 min post LITT reveals a significant signal loss within the lesion *(arrows)* partially surrounding the original size of the metastasis. **c** Coronal MR thermometry before LITT. Verification of two laser application systems *(arrowheads)* transversing the liver metastasis *(arrow)*. **d** Magnetic resonance thermometry 16 min post LITT. Verification of the coronal extension of the laser-induced changes in the MRI

The addition of MR temperature monitoring and necrosis confirmation to interstitial thermal ablation was initially made in brain tumors using both laser and RF generators [15, 16]. Temperature-sensitive MR sequences enable accurate on-line monitoring of heat deposition, although the relationship of MR signal changes to tissue temperature is a complex phenomenon. So precise MR measurement of temperatures is difficult, and a phased transition from viable to necrotic tissue might also be imaged using changes in the tissue relaxation parameters, T1 and T2.

The RF thermotherapy is not a new therapeutic modality; it has been used with great success for over three decades within the neurosurgical community [16]. Using RF thermal ablation the transfer of electrical energy to tissue results in the deposition of heat secondary to the increased resistivity of the intervening tissue substrate to the passage of rapidly alternating current. Interstitial thermotherapy is the attractive treatment option due to the long experience with that treatment technique and the readily accessible equipment [17, 18]. A major contribution of MR imaging for interstitial RF thermotherapy is its outstanding ability to monitor the zone of thermal tissue destruction during the procedure.

New software and hardware modifications could overcome the disadvantages of inherent imaging interference caused by the RF, recent improvements include the development of a water-cooled RF electrode. Current experience in MR-guided RF thermotherapy includes the RF ablation of brain lesions, RF thermotherapy of hepatic lesions, and the initial clinical experience in extrahepatic abdominal lesions.

Cryotherapy is based on the contact or proximity of a cryoprobe to a target tissue [19, 20]. The major advantages of this ablation technique are the induction of a therapeutic effect due to ice formation in or near the target tissue. Additional advantages are based on the missing toxic products during cryotherapy and in the low risk of bleeding in cryotherapy [21, 22]. At present, MR-guided interstitial cryotherapy remains experimental; currently, problems of temperature-resistant materials and probe design are being solved.

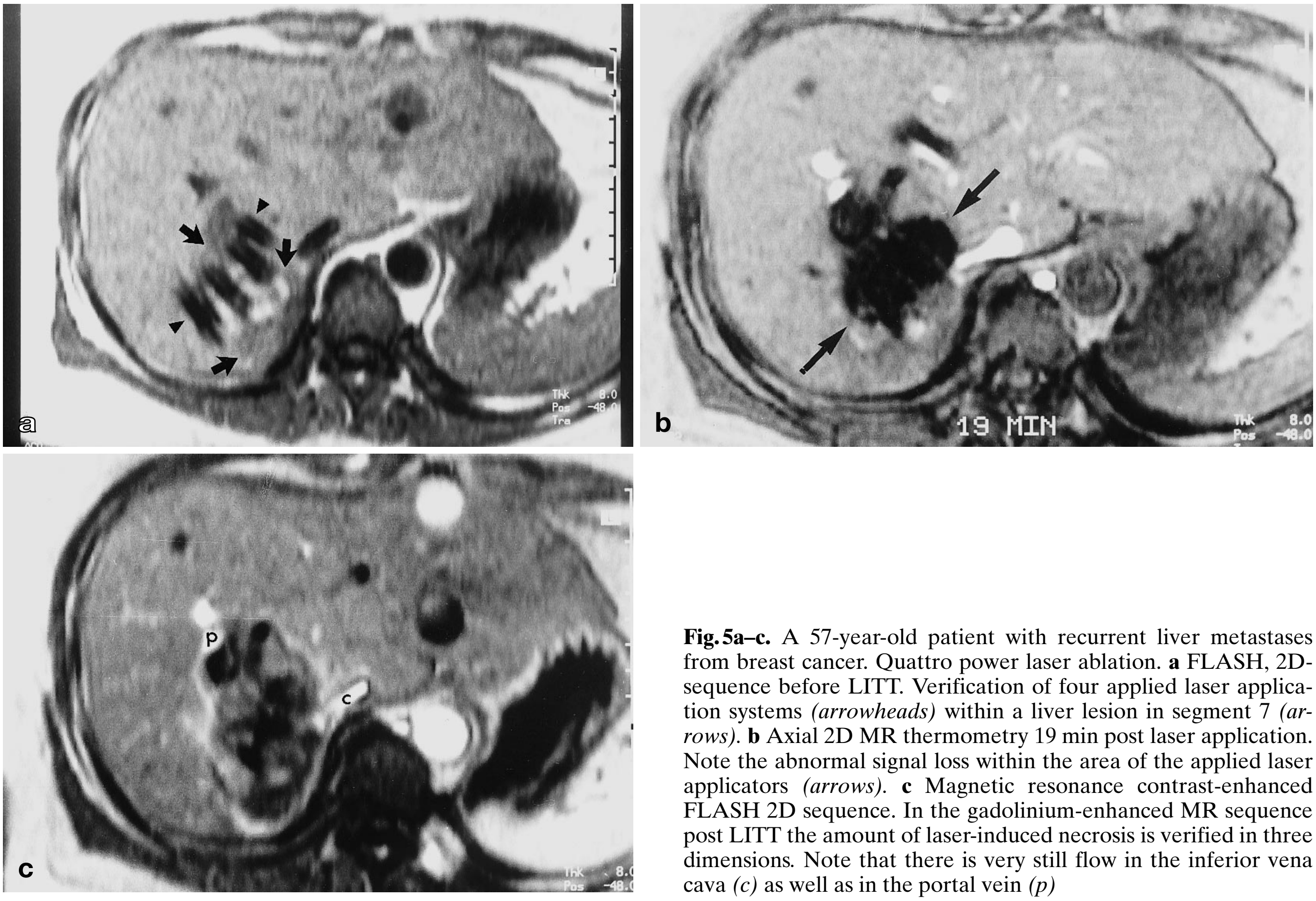


Fig. 5a–c. A 57-year-old patient with recurrent liver metastases from breast cancer. Quattro power laser ablation. **a** FLASH, 2D-sequence before LITT. Verification of four applied laser application systems *(arrowheads)* within a liver lesion in segment 7 *(arrows)*. **b** Axial 2D MR thermometry 19 min post laser application. Note the abnormal signal loss within the area of the applied laser applicators *(arrows)*. **c** Magnetic resonance contrast-enhanced FLASH 2D sequence. In the gadolinium-enhanced MR sequence post LITT the amount of laser-induced necrosis is verified in three dimensions. Note that there is very still flow in the inferior vena cava *(c)* as well as in the portal vein *(p)*

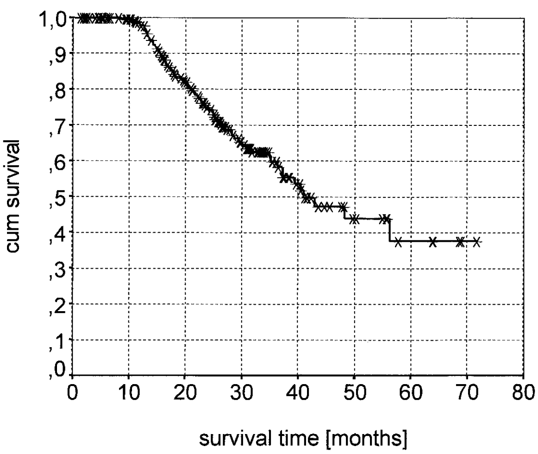


Fig. 6. Survival data of patients ($n = 324$) with liver metastases ($n = 932$) of various primary tumors treated with LITT. The mean survival was 45.74 months (95 % confidence interval: 41.21–50.26) and the median survival was 40.97 months (95 % confidence interval: 31.42–50.52)

Magnetic-resonance-guided focused ultrasound has several characteristics such that it is a mechanical wave with particle movements so that there is no interference with the process of MR data acquisition. Interestingly, the ultrasound beams can be focused and controlled providing a completely noninvasive method for energy delivery deep into the body. Via two mechanisms the ultrasound beam interacts with tissue at the target volume. Firstly, the temperature is elevated due to energy absorption from the wave, resulting in different degrees of thermal damage. Secondly, there is a phenomenon of transient or inertial cavitation. Thus far, focused high-power ultrasound beams have been well suited for noninvasive local coagulation of deep target volumes; however, more clinical testing and device development is needed prior to its routine clinical use.

Clinical laser-induced thermotherapy was first described by Bown [6]. Via LITT tissue is destroyed with near-infrared, continuous-wave laser energy being directed into tissue volume through one or more interstitially implanted optical fibers. Size and geometry of the thermal lesions cannot be predicted due to inherent tissue heterogeneities and the variability of blood flow and tissue perfusion. So the use of interventional magnetic resonance imaging has been shown to be sensitive to changes in tissue temperature. The role of LITT as a therapeutic alternative for brain tumors still has to be defined, but some preliminary reports concerning the clinical applications of LITT in brain tumors exist [15]. In these series LITT was of low intraoperative morbidity and no mortality was found. The results indicated that MR-guided LITT is a safe procedure if the laser-induced lesion is confined to the tumor margins. In all patients a marked tumor reduction could be obtained in

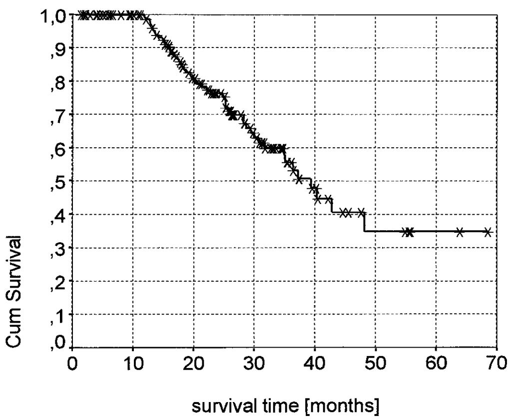


Fig. 7. Survival data of patients ($n = 324$) with liver metastases ($n = 932$) of colorectal carcinoma treated with LITT. The mean survival was 42.71 months (95 % confidence interval: 37.52–47.90) and the median survival was 39.33 months (95 % confidence interval: 33.29–45.37)

low-grade gliomas. For the treatment of patients with irresectable tumors of the liver and the head and neck region, MR-guided LITT has been developed as an alternative local ablative therapeutic modality [8, 9, 11, 13]. Especially for the treatment of liver tumors additionally RF [14, 15, 16], cryotherapy [17, 18, 19, 20], and local drug administration such as alcohol injection [21, 22, 23, 24], endotumoral chemotherapy, and regional chemoembolization are alternative therapies. Laser-induced interstitial thermotherapy performed under MRI guidance has some relevant advantages over these methods: It is a three-dimensional technique that can provide information from the treated volume, is noninvasive, requires no additional apparatus to be inserted along with the laser wave-guide fiber, and results in precise and reproducible areas of induced necrosis. In addition, optical fibers and light are not affected by the magnetic fields used for MR imaging, nor does the optical fiber disturb the MR signal. Besides the advantages of LITT, the possible side effects must be critically discussed. Depending on the relationship of the tumor to vessels or bile ducts, special attention has to be focused in order to avoid damage to these vital structures. Our results prove that via the use of on-line MR thermometry and flow analysis of vessels the rate of complications can be kept very low [4, 8].

In summary, our results show that MR-guided laser-induced thermotherapy is a safe therapeutic alternative in the treatment of tumors of the liver and recurrent head and neck tumors. Future intentions are directed towards multidisciplinary studies, analyzing in a randomized fashion the effect of the different therapeutic strategies solitary or combined on the clinical outcome and survival of the patients. Given the enormous development of interventional MRI systems, the minimally invasive tumor treatment approaches will hopefully improve the survival rate and life quality of cancer patients in the twenty-first century.

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