Principles and techniques of liver tumor ablation: laser induced thermotherapy

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Introduction

The liver plays a central role in the human metabolism and thus represents one of the organ systems most often affected, especially by tumor diseases. In the following the basics and data will be presented both for treatment aspects of secondary and primary liver tumors:

Two thirds of the patients with colorectal carcinoma (CRC) have liver metastases by the time of death [57]. For CRC hepatic metastases, survival is determined by the number and extent of metastases. In untreated patients with liver metastases of CRC the median survival time is from 4.5 to 15 months [57]. Only 5-10% of all patients with liver metastases of CRC are suitable for resection [23,42,43]. After resection, the 5-year survival time improves from 16% to 40%. Only 20-30% of patients undergoing liver resection will remain free from tumor recurrence [57]. Up to now the liver resection of solitary lesions has been the only potential curative treatment. However, the high rate of intrahepatic relapses and a possible potentising of the intrahepatic growth in metastases as part of the tumor stimulation process by released tumor cells is considered problematic .In modern oncology systemic treatment options like chemotherapy and immunotherapy are increasingly supplemented by regional treatment options such as surgery and radiotherapy, and interventional oncological options such as thermal ablation and locoregional chemotherapy [36,45].

Hepatocellular carcinoma (HCC) is one of the most common malignant neoplasms. In the case of hepatocellular carcinoma (HCC), when the tumor is at an appropriate stage, liver resection or hemihepatic resection or liver transplant is the essential curative treatment [7,18,40]. In patients with a single small HCC and well-preserved liver function surgical resection provides a 5-year survival ranging from 47.1- 60.5% [7,18,40]. However, most HCCs are unresectable because of underlying poor liver function or tumor multifocality. For small, unresectable HCC nodules the transplantation is effective with 83% remaining free of recurrence, and a survival rate at 4 years with a 6% peri-operative mortality. If there are contraindications, transarterial chemoembolisation is used as a palliative therapeutic strategy. Interstitial procedures such as MR-guided laser-induced thermotherapy or radiofrequency ablation show a high rate of controlling the site of the tumor.

Within the last decade thermal ablations have been developed and clinically improved. Different technologies have been evaluated like magnetic resonance-guided laser-induced thermotherapy (MR-guided LITT), radiofrequency ablation (RF), microwave and cryotherapy. For this reason, there has been great interest in further developments of interstitial procedures such as laser coagulation or radiofrequency ablation over the last few years. Laser-induced interstitial thermotherapy (LITT) is a minimal invasive locoregional form of treatment, the coagulative effects of which lead to tumor destruction in solid organs [54-63]. Due to the comparatively high penetrative depth of the photons and the possibility of problem-free radiation transmission by fiber-optic waveguides, nearly infra-red lasers (NIR) are used for LITT.

LITT provides a photothermal tumor destruction technique, permitting solid tumor configurations inside parenchymatous organs to be destroyed. The expansion of the tissue-destroying effect is dependent on the choice of radiation capacity and radiation time. This means that the parameters must be pre-selected in such a way that all tumor cells, if possible, are exposed to the coagulative effect. Besides, there must also be a safety margin of at least 5-10 mm in width.

In order to do justice to the coagulation of a 3-dimensional tumor geometry, it must be possible to heat an approximately spherical volume of tissue at the same time. For this reason application systems of defined space radiation characteristics have been developed, the distal ends of which are prepared in such a way that the result is an even circumference of radiation.

In the following we will present the experimental and clinical data for the MR-guided laser-induced thermotherapy of malignant liver tumors, focusing on liver metastases and primary hepatocellular carcinoma.

Technique of laser-induced thermometry (LITT)

Between June 1993 and May 2003 LITT was performed in 1,421 patients (741 male, 680 female, mean age 59.5 years, range 24 to 89 years) with a total of 3,122 liver metastases and 83 hepatocellular carcinomas. We included patients with different primary tumors like colorectal liver metastases, liver metastases from breast cancer, hepatocellular carcinomas, liver metastases from pancreatic cancer and a variety of other tumors.

A laser application was defined as a laser treatment at one certain position (Tab. 1). If the laser applicator was pulled back and another laser treatment was performed to enlarge the coagulative necrosis a second laser application was performed.

We also included patients with recurrent liver metastases after partial liver resection, patients with metastases in both liver lobes, patients with locally non-resectable lesions, and patients who had general contraindications for surgery or who refused surgical resection. The distribution for the different indications varied for different primary tumors.

Laser equipment and application set

Laser coagulation is accomplished using a Neodymium-YAG laser light with a wavelength of 1064 nm (MediLas 5060, MediLas 5100, Dornier Germering, Germany), delivered through optic fibers terminated by a specially developed diffusor. In the beginning a diffusor tip with a glass dome of 0.9 mm in diameter, which was mounted at the end of a 10-m long silica fiber (diameter 400 µm) was used. Since the year 2000 a flexible diffuser tip has been used with a diameter of 1.0 mm, which makes the laser applications much easier due to the fact that the risk of damage to the diffuser tip has dropped to almost zero. The active length of the diffusor tip ranges between 20 and 40 mm in length. The laser power is adjusted to 12 Watts per cm active length of the laser applicator.

The laser application kit (SOMATEX company, Berlin, Germany) consists of a cannulation needle, a sheath system, and a protective catheter which prevents direct contact of the laser applicator with the treated tissues and allows cooling of the tip of the laser applicator. The closed end of the protective catheter enables complete removal of the applicator even in the unlikely event of damage to the fiber during treatment. This simplifies the procedure and makes it safer for the patient.

The laser itself is installed outside of the MR examination room, and the light is transmitted through a 10-m long optical fiber. All patients are examined using an MR imaging protocol including gradient-echo (GE) T1-weighted plain and contrast-enhanced GD-DTPA 0.1 mmol/kg body weight (b.w). T2-and T1-weighted images are obtained for localizing the target lesion and planning the interventional procedure. The scanners are a conventional 1.5-T system (Siemens, Erlangen, Germany) and a 0.5-T system (Escint) (Fig. 8).

Imaging during therapy:

After informing the patients about potential complications, benefits, and disadvantages of LITT, consent is obtained. The metastases are localized on ultrasound or computed tomographic scans and the injection site is infiltrated with 20ml of 1% lidocaine. Under CT guidance the laser application system is inserted using the Seldinger technique. After the patient is positioned on the MRI table, the laser catheter is inserted into the protective catheter. MR sequences are performed in three perpendicular orientations before and during LITT (Fig. 8).

MR sequences are performed every 30 seconds to assess the progress in heating the lesion and the surrounding tissue. Heating is revealed as signal loss in the T1-weighted gradient-echo images as a result of the heat-induced increase of the T1 relaxation time. Depending on the geometry and intensity of the signal loss and the speed of heat distribution the position of the laser fibers, the laser power and the cooling rate are readjusted. Treatment is stopped after total coagulation of the lesion, and a safety margin from 5 to 15 mm surrounding the lesion can be visualized in MR images.

After switching off the laser, T1-weighted contrast-enhanced FLASH-2D images are obtained for verifying the induced necrosis. After the procedure the puncture channel is sealed with fibrin glue. Follow-up examinations using plain and contrast-enhanced sequences are performed after 24 to 48 hours, and every 3 months following the LITT procedure. Quantitative and qualitative parameters, including size, morphology, signal behavior, and contrast enhancement are evaluated for deciding whether treatment can be considered successful, or whether subsequent treatment sessions are required.

Laser-induced effects are evaluated by comparing images of lesions and surrounding liver parenchyma obtained before and after laser treatment with each other, and with those obtained at follow up examinations. Tumor volume and volume of coagulative necrosis are calculated using three-dimensional MR images and measurements of the maximum diameter in three planes (A, B and C).

Clinical data

All treatments can be performed under local anesthesia and are well tolerated by the patients. All patients treated between June 1993 and September 1998 (n = 278) were hospitalized for 24 to 48 hours after the intervention. All patients treated between October 1998 and now (n = 613) have been treated strictly on an outpatient basis.

Evaluation of the MR thermometry data during MR-guided laser-induced thermotherapy demonstrates that metastatic tissue is very sensitive to heat, showing earlier and more widespread temperature distribution of the delivered thermal energy than does surrounding liver parenchyma. The area of obviously decreased signal intensity during LITT treatment is identical with the area classified as coagulative necrosis on MR images 24 hours after laser treatment. In the minority of cases the size of the coagulative necrosis obtained 24 hours after LITT treatment is larger compared to MR thermometry images. The difference is 17% in maximum (Fig. 2).

The mean number of treated metastases per patient is 3. The evaluation of the application details is presented in Table 2. The localization of the metastases with respect to the different liver segments shows a quite homogenous distribution of the metastases in the different liver segments taking in account the different volumes of the liver segments (Fig. 3).

The mean number of inserted laser applicators for the treatment of one metastasis with a reliable safety margin with respect to the size of the metastases is shown in (Fig. 5, 6).

The approach to the lesion depends on the localization of the lesion (figure 6). Transpleural approaches are avoided in all cases. The most common approach to lesions located in liver segments 7 and 8 is the angulated

lateral approach. The most common approach for lesions located in liver segments 2 and 3 is an approach from ventral. An approach is classified as dorsal, lateral or ventral if the angulation of the puncture direction is more than 15° from the scan plane. A transpleural approach is avoided in all cases, therefore the approach to most of the lesions in liver segments 7 or 8 is a lateral angulated approach. The mean energy for metastases with a diameter of 2 cm or smaller is 48 KJ, for metastases between 3 and 4 cm the mean energy is 140 KJ. The mean values of the applied energy are statistically significantly higher in liver metastases from colorectal carcinoma versus liver metastases from breast carcinoma and hepatocellular carcinoma.
The volume of the induced coagulative necrosis 24 hours after LITT treatment exceeds the volume of the initial tumor significantly ($p < 0.001$). During follow-up examinations the volume of the induced necrosis is getting smaller again due to resorption and shrinking of the lesion. In the 3-month control the volume of the coagulative necrosis is already roughly half of the initial volume of the necrosis, but still larger than the initial tumor volume. Evaluation of the MR thermometry data during MR-guided laser-induced thermotherapy demonstrates that metastatic tissue is very sensitive to heat, showing earlier and more widespread temperature distribution of the delivered thermal energy than does surrounding liver parenchyma (Fig. 7). Online MR-thermometric changes correlates exactly with the findings from contrast-enhanced T1-weighted sequences obtained after therapy. The mean volume of necrosis 24 hours after LITT treatment is 60 ml (range: 3 ml to 460 ml). After 3 months the mean volume of necrosis is 40 ml (range: 2 to 230 ml) due to shrinking of the lesion. The number of treated metastases and laser applicators is shown in Table 1. Plain and contrast-enhanced MRI is performed in all cases for verifying the obtained necrosis.

Side effects and complications

All patients tolerated the intervention well under local anesthesia. Clinically relevant complications such as bleeding, infection, or pleural effusion were observed at the following rates (based on the number of treatment sessions): pleural effusion, 1.1%; intraabdominal bleeding, 0.1%; liver abscess, 0.4%; 30-day mortality, 0.1%; pneumothorax, 0.1%; injury to bile duct, 0.1%; and bronchial-biliary fistula, 0.07%. The overall complication rate was 1.5%. However, except for the two patient who died within 30 days after the procedure, complications were not severe and could be treated either by drainage or puncture (pleural effusion, abscess) or percutaneous bile duct reconstruction by placing a stent. One patient died 4 weeks after treatment. This patient developed leakage in the jejunum following LITT of a liver metastasis in segment 4a. The patient underwent surgery but succumbed to peritonitis and acute respiratory distress syndrome. The death was considered possibly LITT-related, most likely due to stress ulceration of the jejunum. A second, 72-year-old patient died within 30 days after laser treatment, probably due to sepsis. Unfortunately this could not be proven as no autopsy was performed. One case of intraabdominal bleeding was self-limiting and no treatment was necessary.
Imaging during LITT revealed a small, nonsymptomatic subcapsular hematoma in 1.9% of patients. Local infection at the puncture site was seen after treatment in two patients and treated with intravenous antibiotics. No seeding of metastases was found in our patients.

Local tumor control rate and survival data:

The local tumor control rate was determined using plain and contrast-enhanced MR images obtained 3 and 6 months after LITT treatment. Reflecting the development of the laser application systems and the increased experience of the physicians, the patients were divided into two groups for evaluation of the local tumor control rate. In group 1 (treated from June 93 to September 96, n=58 patients) the local tumor control rate was 70.4% in the 3-month follow-up control was 70.4%. In group 2 (n=119), treated from October 1996 to September 1997 the local tumor control rate after 3 months was 79.4%. In group 3 (treated between October 1997 and May 2001, n=335) the local tumor control rate after 3 months was 97.6%. In group 1 we observed a local recurrence of the treated lesions in 29.6% and 20.6% of the cases, respectively. This resulted in additional treatments of these lesions for definitive tumor destruction. The contrast-enhanced MRI control study 6 months after the laser treatment demonstrated a local tumor control rate of 45.1% in group 1, 64% in group 2 and 98.5% in group 3. This shows that MR-guided LITT results in definitive tumor destruction even in long-term follow-up. During the further follow-up period of up to 6 years after the laser treatment, plain and contrast-enhanced MRI revealed no local recurrence later than 6 months after initial treatment. In the late follow-up period MRI documented only scar tissue without any pathologic contrast enhancement.
Survival curves were evaluated using the Kaplan-Meier method. The mean cumulative survival rate of patients with colorectal liver metastases was 3.8 years (95% confidence interval 3.4 - 4.1 years) (Fig. 9). The 1-year survival rate was 93%, the 2-year survival rate was 73%, the 3 year survival rate was 50%, and the 5-year survival was 28%. Maximum survival was 83.4 months. Patients with 1 or 2 initial metastases (mean survival 4.0 years, 95% confidence interval: 3.6 - 4.5 years) showed a superior survival to patients with 3 or 4 initial metastases (mean survival 2.8 years, 95% confidence interval: 2.6 - 3.3 years). However, the differences were not statistically significant when assessed with the log rank test, the Tarone ware test and the Breslow test for equality of survival distribution (log rank test p=0.13, Tarone Ware p=0.14, Breslow test p=0.17). Patients with metachronous metastases showed superior survival compared with patients who had synchronous metastases (metastases developed more than 6 months after detection of primary tumor) (p=0.11) (Fig. 10,11). In our patient collective we found a nearly equal distribution of synchronous and metachronous liver metastases. There were no statistically significant differences with regard to gender or size of treated metastases (p>0.05).
In the evaluation according to the primary lymph node stage it can be seen that patients with a N0 or N1 primary

lymph node stages have superior survival compared to N2 and N3 patients. The mean survival in patients with N0 and N1 lymph node stage was 4.1 years (95% confidence interval: 3.6 - 4.6 years). The mean survival in patients with N2 and N3 lymph node stage was 3.5 years (95% confidence interval: 2.7 - 3.3 years).

Discussion

Liver metastases are the most common tumors in Europe and the United States and are twenty times more common in Africa, Japan and Eastern countries. The liver is the most common site of metastasis. Colorectal cancer is the third leading cause of death in Western communities, outnumbered only by lung and breast cancer. At the time of death, approximately two-thirds of patients with colorectal cancer have liver metastases. Survival in metastatic liver disease depends on the extent of liver involvement and the presence of metastatic tumors. In several studies, liver metastases from colon carcinoma which were confined to one lobe and involved an area of less than 25% of the liver caused death in 6 months when untreated [28]. When 25% to 75% of the liver was involved, survival was 5.5 months; and when more than 75% of the liver was involved, death occurred in 3.4 months.

Therapeutic alternatives in the treatment of liver metastases include surgery, local ablation as LITT, RF ablation, cryotherapy [10,16,21], microwave ablation [3460 and ethanol injection [3,6,11,31] or oncologic strategies such as systemic or locoregional chemotherapy [19,36]. As a high number of tumors grow in damaged liver parenchyma with reduced hepatic functions, it is important for all methods which damage tumor cells to preserve functional reserve capacity, delaying terminal organ failure for as long as possible.

Therefore many local ablation techniques were developed in order to improve the survival of the patients [57]. Nowadays, the most common technique is RF ablation. Radiofrequency waves (RF waves) have been used since the 1960's for treating intracerebral tumors, controlled stereotaxically. For some years RF treatment has also been used for treating soft tissue, focusing on the treatment of malignant liver tumors. As with LITT a coagulation necrosis is caused through a local temperature increase. Wavelengths between 300 to 500 kHz are introduced into the tissue through mono- or bipolar antennae systems resulting in the target area heating up to temperatures of 90°C, caused by high tissue resistance. In previous studies monopolar systems were used almost exclusively. The necessity for an external second electrode on patients makes an uncontrolled energy flow outside the required target zone possible in theory, as burns cannot be safely ruled out. Bipolar application systems integrate both poles in one applicator. Cooling the tip of the applicator in RF treatment was introduced to increase the size of the induced necrosis up to 5 cm in diameter.

In 1996 Rossi et al. treated 11 patients with 13 metastases using mono- and bipolar systems and the multi-applicator technique. Despite the fact that the tumors were under 3.5 cm in size, one year after the operation only one patient was tumor-free and the relapse rate was around 55%. The findings for the 39 patients with HCC were better, as a relapse rate of only 10% and mean survival times of 44 months have been calculated [45].

In 1997 Solbiati et al. published a study of 29 patients with 44 liver metastases (size 1.3-5 cm) of colorectal, stomach, breast, and pancreatic carcinomas. Among them were 20 patients with solitary lesions. The operation took place using cooled systems, and a complete tumor ablation was achieved in 91% of cases. At the 3- and 6-month check-up 66% of the treated lesions were still inactive. A survival rate of 100%, 94% and 86% after 6, 12, and 18 months was documented [52]. Livraghi tried an approach using conventional systems and simultaneous irrigation with NaCl solution with 14 patients with 24 liver metastases (1.2 to 4.5 cm in size) but only 52% of the lesions were inactive after six months [33].

In 1999 Livraghi et al. presented a direct comparison of RF therapy (42 patients, 52 lesions) with percutaneous alcohol injection - PAI - (44 patients with 60 tumors) in treating hepatocellular carcinomas [32]. This was the first direct comparison of these two different treatments in similarly structured patient populations. 80% of tumors were removed completely using PAI and 90% using RF (no statistical significance). The main advantage of RF therapy proved to be the smaller number of treatment sessions (1.2 versus 4.8). On the other hand a higher complication rate (2% serious, 8% less serious complications versus 0% for PAI) was documented [15]. Side effects with regard to punctures are relevant here, e.g. pneumothorax or hemothorax (2%), injury of the bile ducts and the gall bladder, intraperitoneal bleeding (8%) and also pleural effusions. Depending on the procedure some cases had to be upgraded from local to general anaesthesia due to severe pain during the energy application.

Our data in a large population of 891 patients with liver metastases from different primary tumors, mainly colorectal carcinomas show a very high local control rate (over 97% in 3- and 6-month control studies) and a very low local recurrence rate. LITT treatment can be performed easily under local anesthesia on an outpatient basis in metastases up to 5 cm in diameter with a 1-cm safety margin, which is very important for a low recurrence rate. Multiple applications can be performed simultaneously.

The wide range of the values of the energy which was applied to the metastases indicates that there is a high variance in heat distribution. Sometimes a couple of minutes are enough to treat a metastasis with a reliable safety margin and sometimes applications times of 30 minutes and more are necessary to get same necrosis in another metastasis of the same size. Therefore reliable nearly online monitoring of treatment is absolutely necessary in order to avoid over- or undertreatment of the metastases. Due to the fact that laser ablation is fully compatible with MRI, which is the most reliable method for thermometry, MRI is very well suited for monitoring thermal ablation like LITT.

The survival rates achieved, which represent the most relevant success criterion for a treatment, are slightly superior in patients with metastases from a colorectal carcinoma or a carcinoma of the breast to those in surgically resected patients. It must be considered, however, that a surgical resection was not or was no longer an option among most of the patients being treated due to metastatic relapse after surgical resection or a bilobibular pattern of infestation. In spite of this it was possible to achieve survival rates comparable to surgical resection among these patients, who are actually in a group with a worse prognosis. Compared with the extensively published historic survival data after surgical metastatic resection, LITT offers a very good further treatment option. Due to the survival data and local tumor control rates achieved so far, in our opinion randomized studies comparing LITT with chemotherapy solely in the case of patients who fulfil the inclusion criteria for LITT are no longer ethically tenable.

In the modern oncological concept of treatment the internationally defined terms of "clinical benefit", "performance status" and "quality of life" are of the utmost importance. That applies predominantly to patients suffering from local and generally advanced tumors that are no longer curative. Above all, however, intensive chemotherapy, systemic or regional, with marked toxic side effects severely affects the quality of life in the majority of cases. Looking at it from this background all the more attention must be paid to the treatment concepts described here, because minimally invasive techniques are applied which adversely affect patients less and shorter-term. Consequently the prerequisites are given to integrate these new procedures into oncological treatment programs which have been carried out up to now. LITT, which has been used for the past eight years in the clinical routine, can play a great part in modern oncological treatment concepts.

At this time, liver resection is considered to represent the only potentially curative strategy in the treatment of colorectal liver metastases. About 40% of the surgically treated patients survive for three years and 25% of them are alive at five years [4,6,14-16]. Repeated liver resections can be performed and can still achieve a 3-year survival rate of 30%. Clinical conditions, the presence of lesions in a central location, lesions in both hepatic lobes, or poor clinical status preclude surgical treatment. In an analysis of a population of 1,568 patients with metastases confined to the liver which were surgically resected, there was a 5-year survival rate of 28% and a 5-year disease-free survival rate of 15% [6]. Nordlinger et al. demonstrated that factors associated with increased risk of recurrence and death were related to the primary tumor, metastases, and the surgical procedure itself. By contrast there was no correlation with the location of the metastases or the extent of liver resection.

Liver resection can therefore be offered only to a small number of patients with a good chance of success: There is a demand for additional treatments to improve the success of resection and to diminish the incidence of recurrence after surgery, particularly in patients for whom surgery is not an option. Alternative methods include oncologic strategies, such as systemic or locoregional chemotherapy, and interventional techniques, including percutaneous alcohol injection, transarterial chemoembolization, microwave ablation, and percutaneous laser treatment.

Until now, most patients with unresectable liver metastases from colorectal carcinoma have received either systemic or locoregional chemotherapy. The reported mean and median survival rates in these patients are between 12.7 and 18.7 months [17]. In contrast, for patients with unresectable liver metastases who fulfill the inclusion criteria mentioned above (maximum of 5 liver metastases, each one measuring less than 5 cm in diameter), MR-guided LITT offers a mean survival of 41.8 months, which is clearly superior to systemic and locoregional chemotherapy. The results of laser treatment of liver metastases support the surgical assumption that for improved survival liver metastases should be removed or destroyed whenever possible. This results are supported by a study performed on patients with initially unresectable liver metastases from colorectal cancer treated with a three-drug chemotherapy regimen followed by surgery of liver metastases whenever possible [18]. Due to the strongly superior survival of patients who are candidates for LITT treatment compared to systemic or locoregional chemotherapy, we think that a randomized study of LITT versus chemotherapy alone is ethically unacceptable, as so far no study has been able to demonstrate a similar mean survival for patients with colorectal liver metastases who received chemotherapy alone even in a highly selected patient group.

The clinical success of MR-guided LITT depends on many factors. First, optimal positioning of one or more laser application systems in the lesion must be ensured, as determined in three dimensions. The real advantage of MR over CT and ultrasound lies in 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, permitting nearly real-time documentation of LITT effects. Monitoring of these effects during ongoing therapy is advantageous for a number of reasons. The technique can be used to assure 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 re-positioned under MR guidance during the same treatment session. This technique allows safe destruction of metastases and well controlled coagulation of a safety margin surrounding the lesion. Monitoring also minimizes destruction of healthy tissues, thus enhancing the safety of the procedure, particularly in the vicinity of vital structures such as large vessels or the central bile ducts in the liver. MR provides unparalleled topographic accuracy, due to its excellent soft-tissue contrast and high spatial resolution. This allows early detection of complications.

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 veins, and the biliary tree. The relationship of the tumor to the liver capsule is an essential factor in planning treatment of the lesion.

The major advantage of MR-guided LITT is that it can easily be performed under local anesthesia in outpatients with a low complication rate. Long-term studies yielded a local tumor control rate that depended largely on the technique used and the experience of the interventional group performing the procedure. In our series, the local tumor control rate after MR-guided laser-induced thermotherapy was 99.2%, including power laser and multiapplicator techniques. One imaging system serves in the planning, targeting, monitoring and control of the disease.

Additionally, the factor of a lower degree of therapeutically induced liver regeneration with a lower factor of possible tumor stimulation has to be discussed.

In summary, MR-guided LITT is a safe and effective treatment modality for oligonodal colorectal liver metastases. Our data show that MR-guided LITT allows a local tumor control rate of 97% and more after 3 months and 98% after 6 months, even in nonsurgical candidates. Although the intention of LITT was originally a palliative one, its favorable survival rates compared to those obtained with surgical resection of liver metastases, based on analyses of large surgical series [1-8] with a clearly lower complication rate, are most encouraging. These data form the basis for an extension of the indication to surgical candidates if there are no more than 5 metastases with a maximum diameter of 5 cm.

Table 1

Distribution of the metastases and laser applications in patients with colorectal liver metastases.

	Mean	Median	min.	max.
Number of metastases	3.2	2.0	1	21
Number of laser applicators per metastases	2.28	-	1	6
Number of laser applicators per patient	7.6	6	1	34
Treatment session per patient	2.7	2	1	13

Table 2

Documentation of the application data for the total patient material including all patients with malignant liver lesions. The number of applicators represents the number of applicators per patient. The number of applications indicates how many LITT treatments were performed per patient (An LITT treatment with one laser applicator at one certain location is one laser application. If the laser fiber is pulled back in order to enlarge the volume of coagulative necrosis a second laser application will be performed. One LITT session is the LITT treatment performed on one day with 1 to 7 laser applicators simultaneously. One LITT round includes all LITT sessions which are necessary to get all visible metastases treated. If new metastases are detected by MRI during follow-up control studies 3 months after initial LITT treatment or later, these lesion will be treated again by LITT. This was counted as a second LITT session.

parameter	mean	Median	Minimum	Maximum
age	59.5	60.0	28.4	88.7
applicators	6.8	5	1	34
applications	11.4	9	1	56
metastases	2.8	2	1	21
LITT session	2.4	2	1	13
LITT-round	1.5	1	1	9
applicator per met.	2.5	2	1	9
session per met.	1.05	1	1	3
energy per met.	104 KJ	82.9 KJ	5.9 KJ	502.4 KJ

Figure 1

Documentation of the distribution of the indications for LITT treatment for all patients (all), patients with colorectal liver metastases (colorec.), liver metastases from breast cancer (breast), hepatocellular carcinoma (HCC), and patients with liver metastases from pancreatic cancer (pancr.).

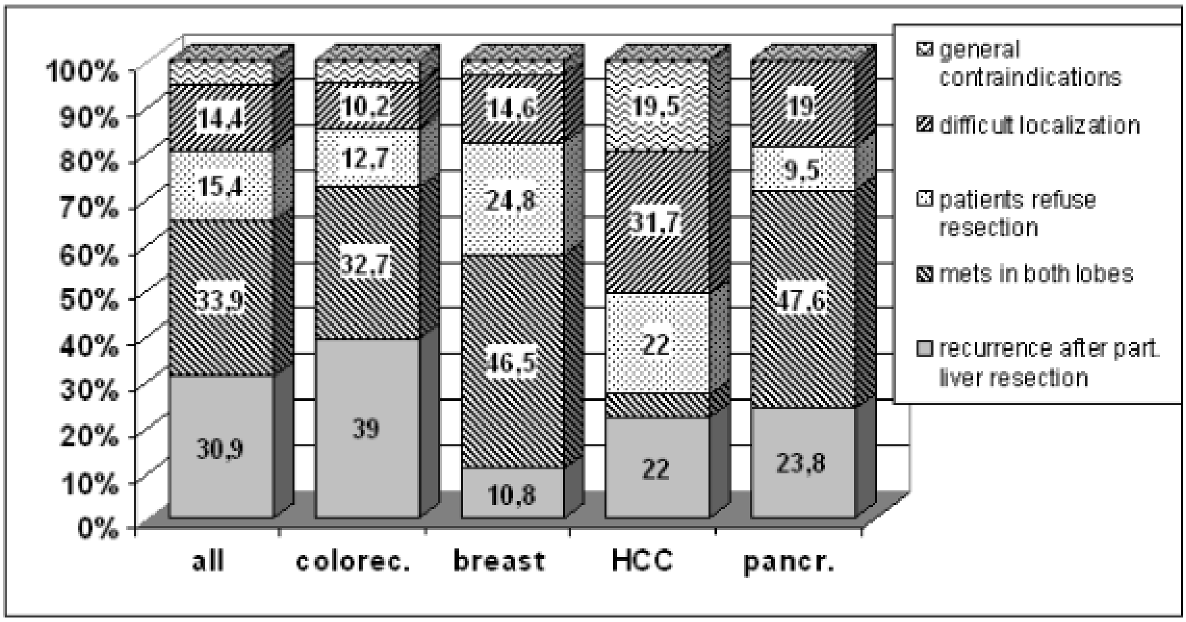


Figure 2

The graph shows the total number of treated metastases per patient, including recurrent metastases during follow-up examinations.

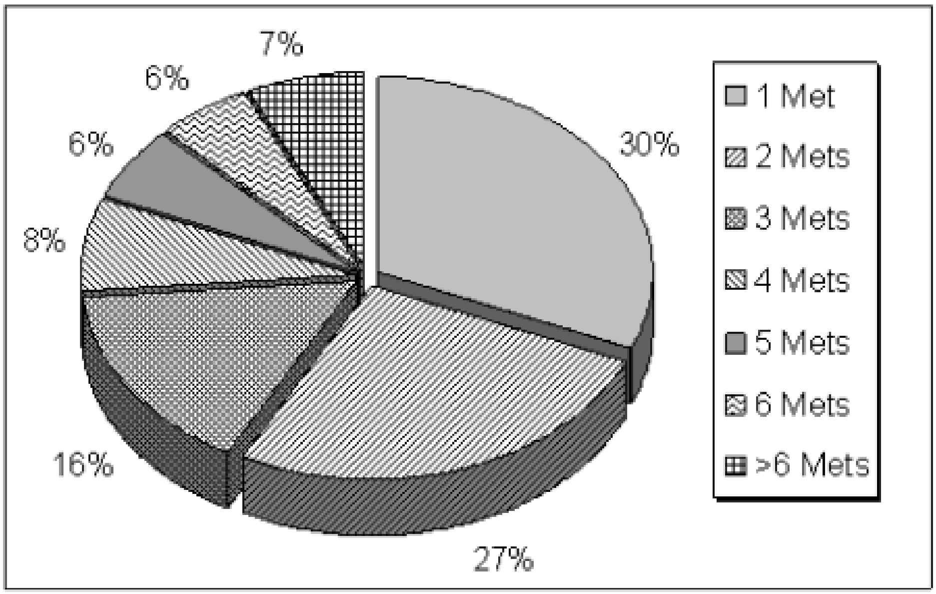


Figure 3

The graph shows the distribution of the treated metastases with respect to the different liver segments.

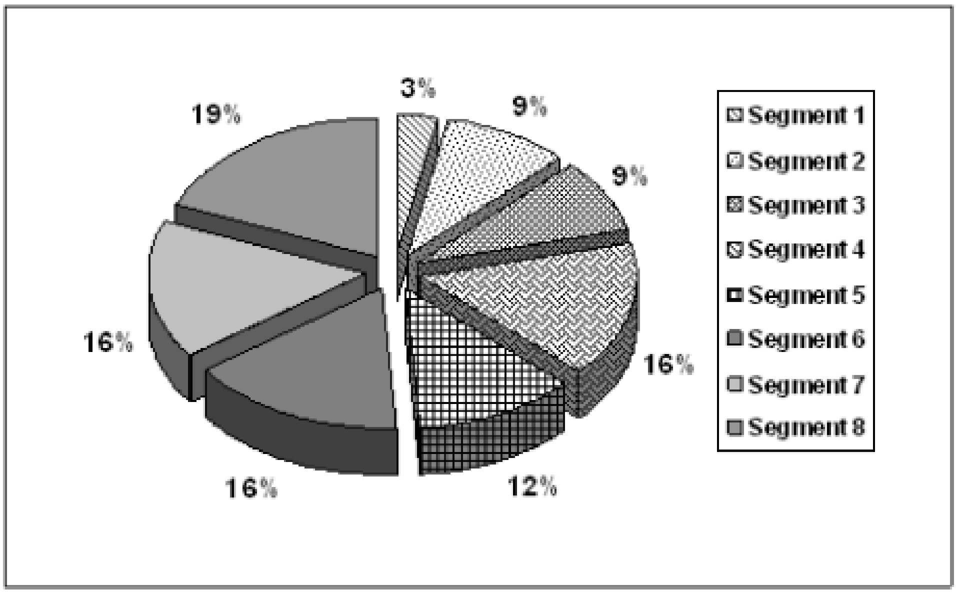


Figure 4

The graph shows the distribution of the liver metastases with respect to the localization of the lesion. A localization was classified as "easy" if the lesion was sufficiently surrounded by normal liver parenchyma without relationship to any of the other listed structures. A lesion was classified as "paracaval" if there was a contact to the vena cava inferior. Other important relationships were the liver capsule, the gall bladder, the bowel and the central portal vein structures (including the central bile ducts). A lesion was classified as subcardial, if the lesion was located in liver segment 2 and the distance between the lesion and the pericard was less than 8 mm.

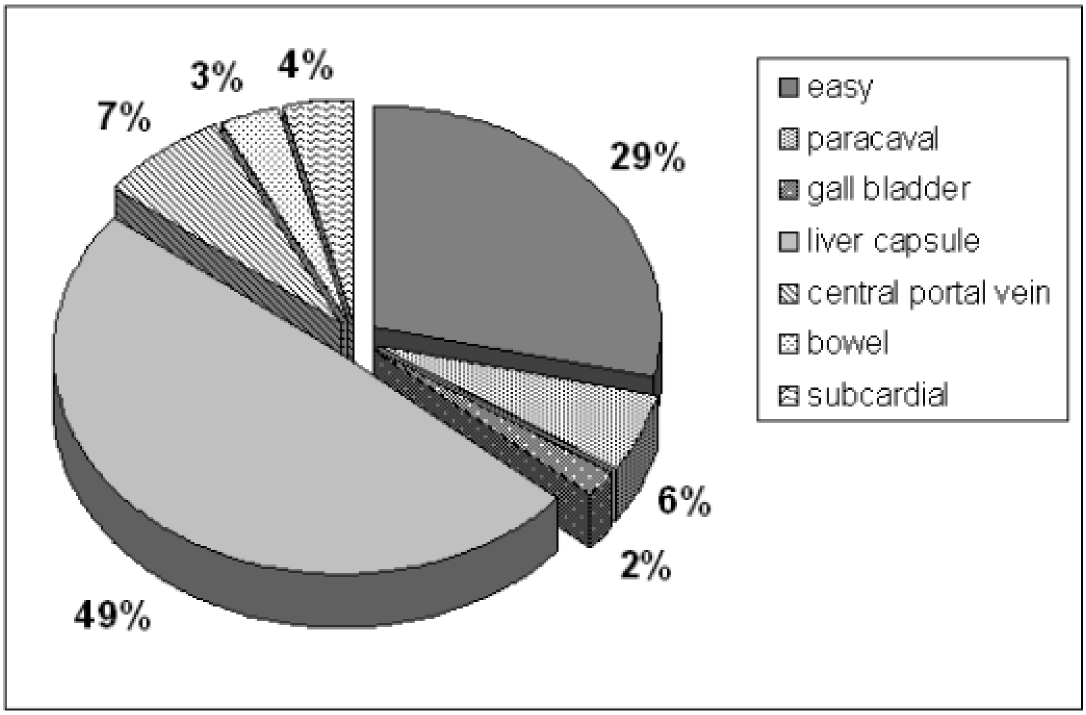


Figure 5

The graph show the number of laser applicators which were inserted for the treatment of one single metastasis with respect to the size of the metastases. PA = power laser applicator.

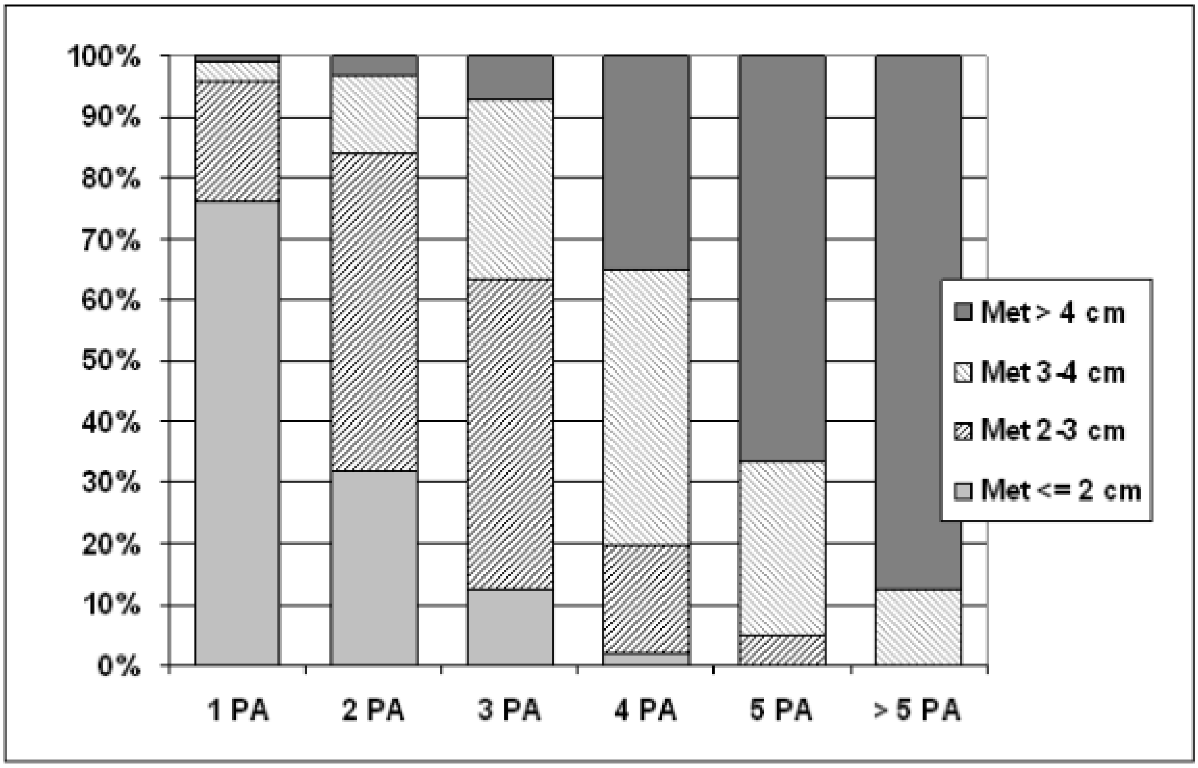


Figure 6

The diagram presents the different approach to the lesion with respect to the different liver segments. An approach was classified as dorsal, lateral or ventral if the angulation of the puncture direction was more than 15° from the scan plane. A transpleural approach was avoided in all cases. Therefore the approach to most of the lesions in liver segments 7 or 8 was a lateral angulated approach.

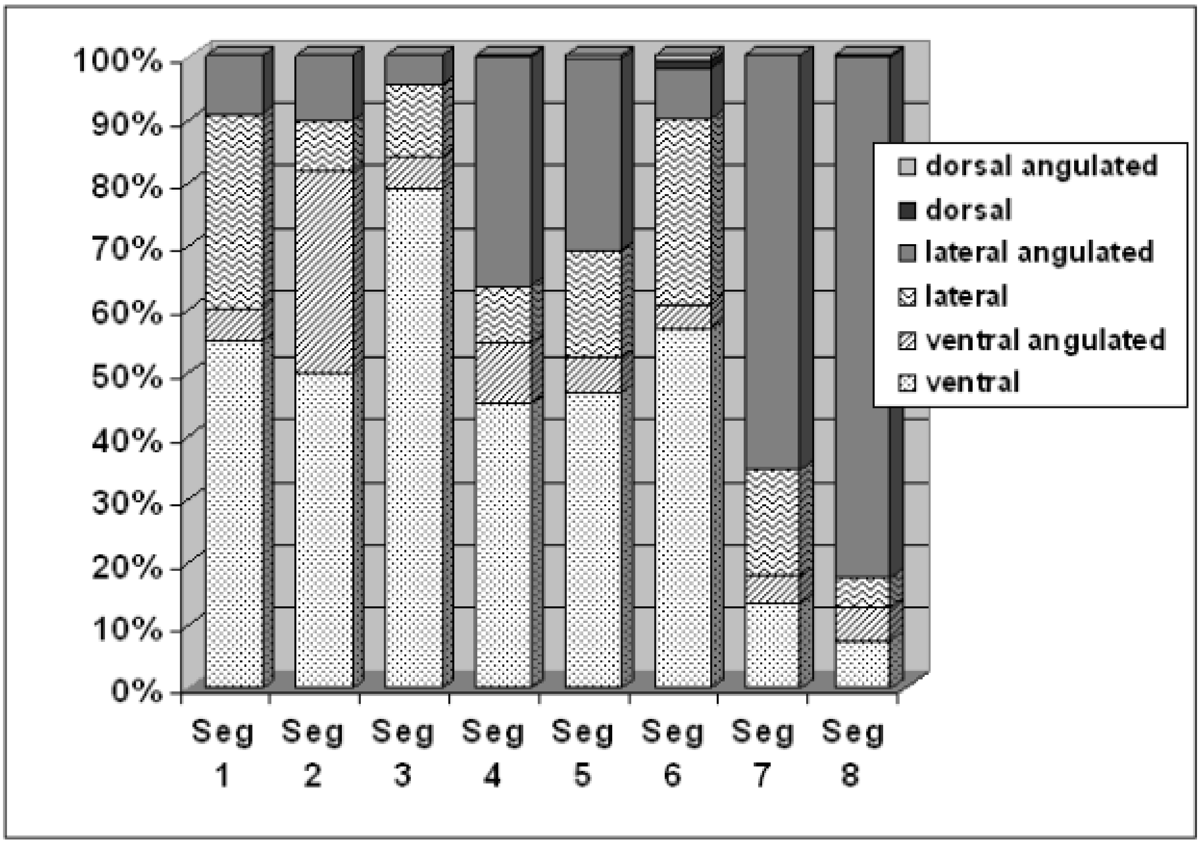


Figure 7

The graph shows the applied energy per metastasis for colorectal cancer liver metastases, liver metastases from breast cancer and hepatocellular lesion for metastases 2 cm or less in diameter, metastases between 2 and 3 cm, metastases between 3 and 4 cm and metastases larger than 4 cm in diameter. Values are expressed as mean plus/minus standard error of mean, which is the measurement of how much the value of the mean may vary from sample to sample taken from the same distribution. It is the standard deviation of the distribution of all possible means, if samples of the same size are repeatedly taken.

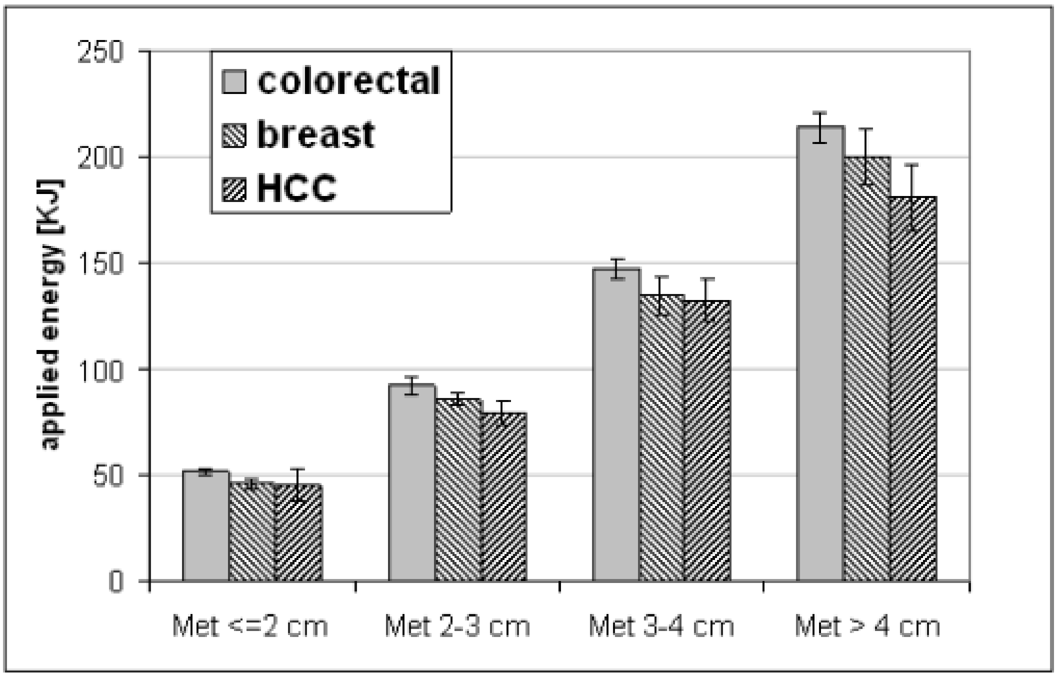


Figure 8

40-year-old patient with liver metastases of a colorectal cancer

Figure 8a

Transverse noncontrast T1-weighted GE image (TR/TE = 110/5) obtained 3 weeks before laser treatment shows a liver metastasis (arrows) in segments 7/8 with a maximum diameter of 2.5 cm.

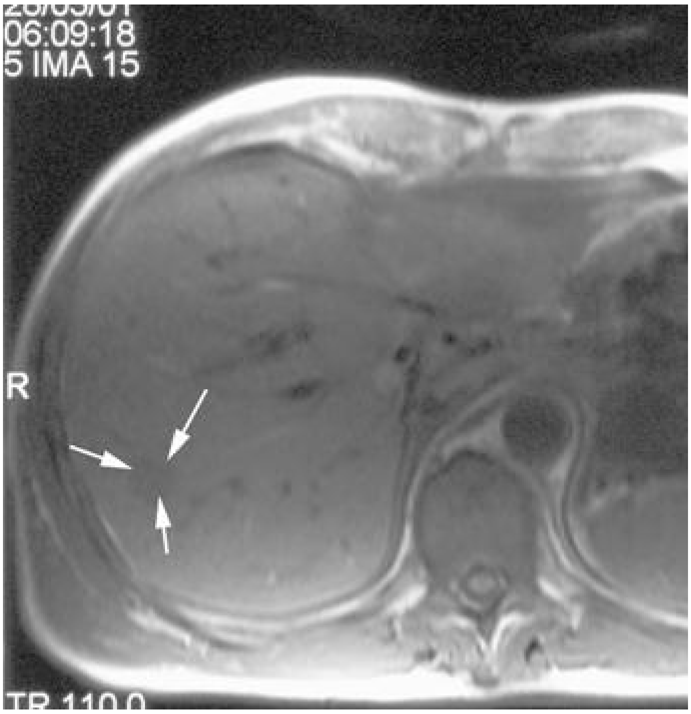


Figure 8b

Transverse contrast enhanced T1-weighted GE image (TR/TE = 110/5) 3 weeks before LITT treatment shows contrast enhancement in the periphery of the metastasis (arrows).

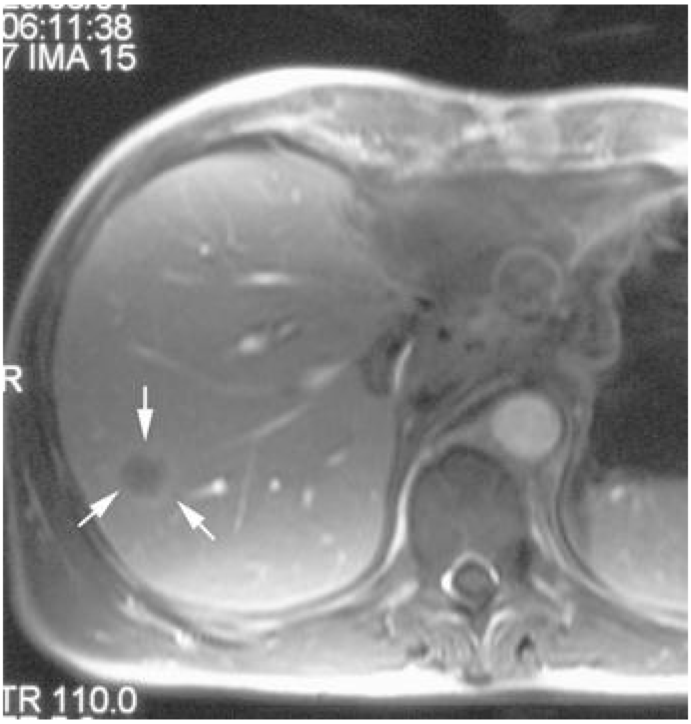


Figure 8c

CT image obtained at the day of treatment shows an obvious progression of the lesion (arrows) in segments 7/8 with a maximum diameter of 4.5 cm compared to pre-treatment images (fig 1a and b). Note the placement of 5 laser fibers (arrow heads) in the peripheral zone of the metastases.

Figure 8d

Transverse noncontrast image immediately before starting the LITT treatment shows the metastases (arrows) and the positioned laser fibers (arrow heads).

Figure 8e

Coronal noncontrast T1-weighted GE image shows the access to the metastases from caudal to cranial. For better visualization of the application systems a magnetite marker (arrows) was placed in the protective catheter. The course of two application systems is shown on this image.

Figure 8f

Transverse noncontrast T1-weighted image obtained 26 minutes after starting the laser treatment demonstrates an obvious signal decrease of the lesion and the surrounding tissue (arrows) due to the increase of tissue temperature (compare fig. 1d). The temperature in the center of the lesion is around 110°C, in the peripheral zone the temperature is around 60-70°C).

Figure 8g

Transverse noncontrast T2-weighted image obtained 24 hours after laser treatment shows the induced coagulation area (arrows) with some inflammatory changes and edema in the surrounding area (arrow heads).

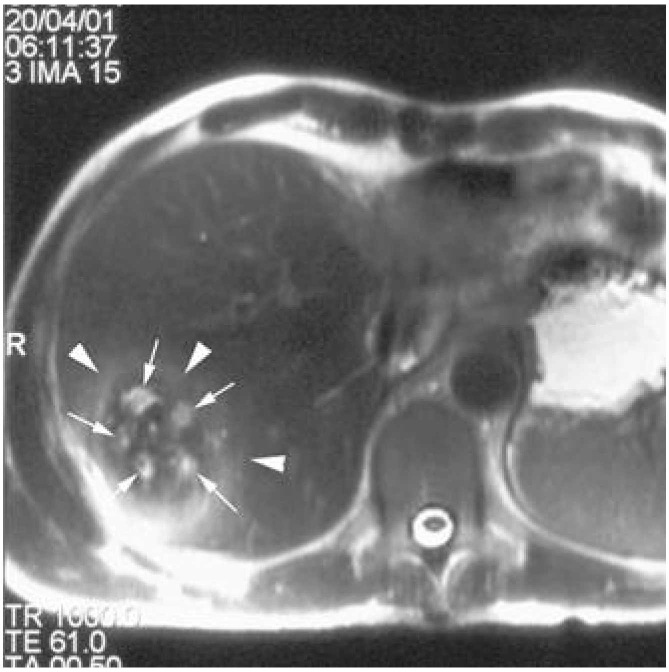


Figure 8h

Transverse noncontrast T1-weighted GE image 24 hours after LITT demonstrates the typical pattern of a coagulation area after LITT with hyperintense pattern (arrows) in the peripheral zone probably due to some slight hemorrhagic diffusion into the lesion. Corresponding to the hyperintense signal on the T2-weighted image (see fig 1g) the lesion is surrounded by a hypointense rim (arrow head) due to edema and inflammatory changes.

Figure 8i

Transverse contrast-enhanced T1-weighted image 24 hours after laser treatment shows the induced coagulation area (arrows).

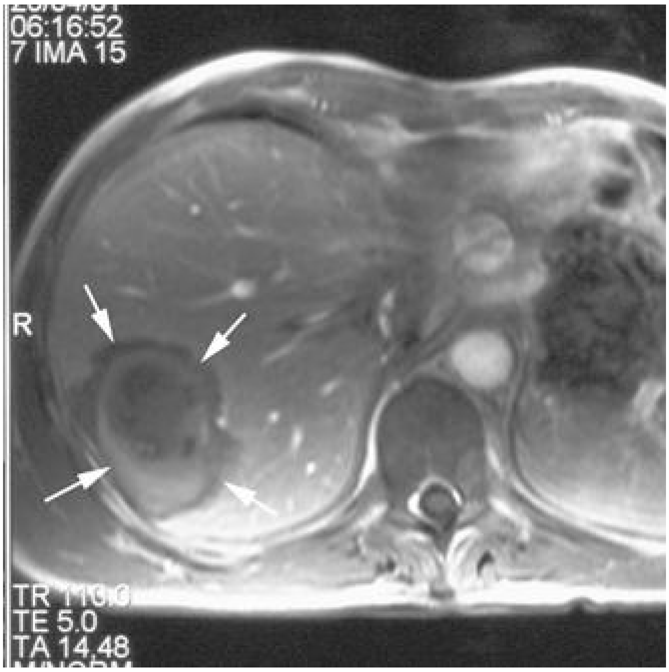


Figure 8j

Sagittal contrast-enhanced T1-weighted GE obtained 24 hours after LITT demonstrates the extension of the necrosis (arrows), which exceeds the initial tumor size by a factor of 4.

Figure 9

Survival data of all patients (n=512) treated with LITT for colorectal liver metastases (n=1556).

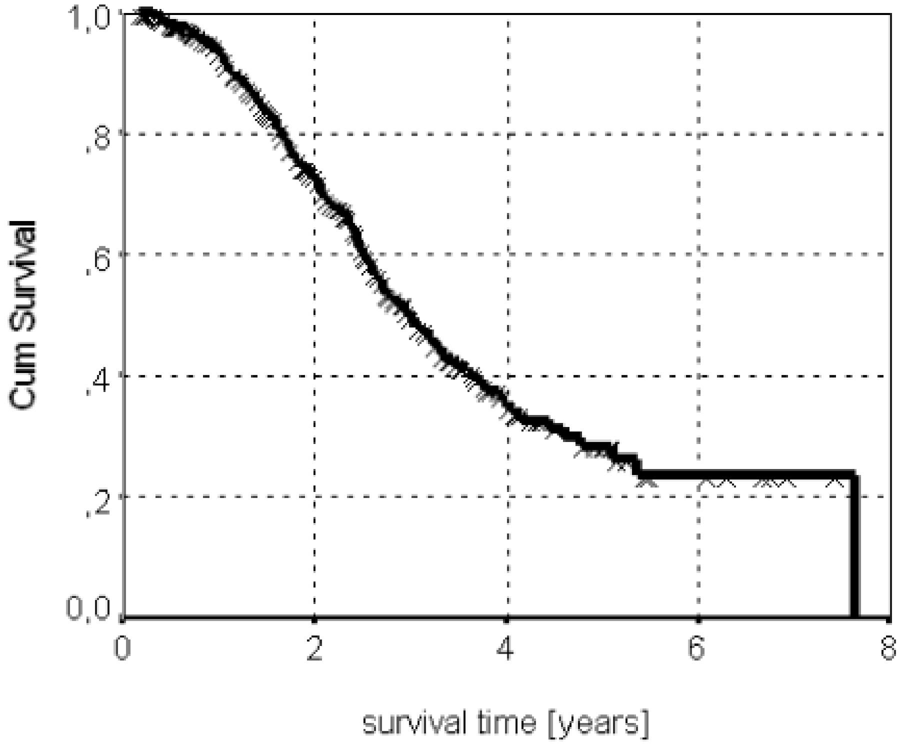


Figure 10

Comparison of survival of patients with respect to the number of initial metastases (black line = group 1 = 1 or 2 metastases, blue line = 3 or 4 metastases, red line = group 2 = more than 4 metastases).

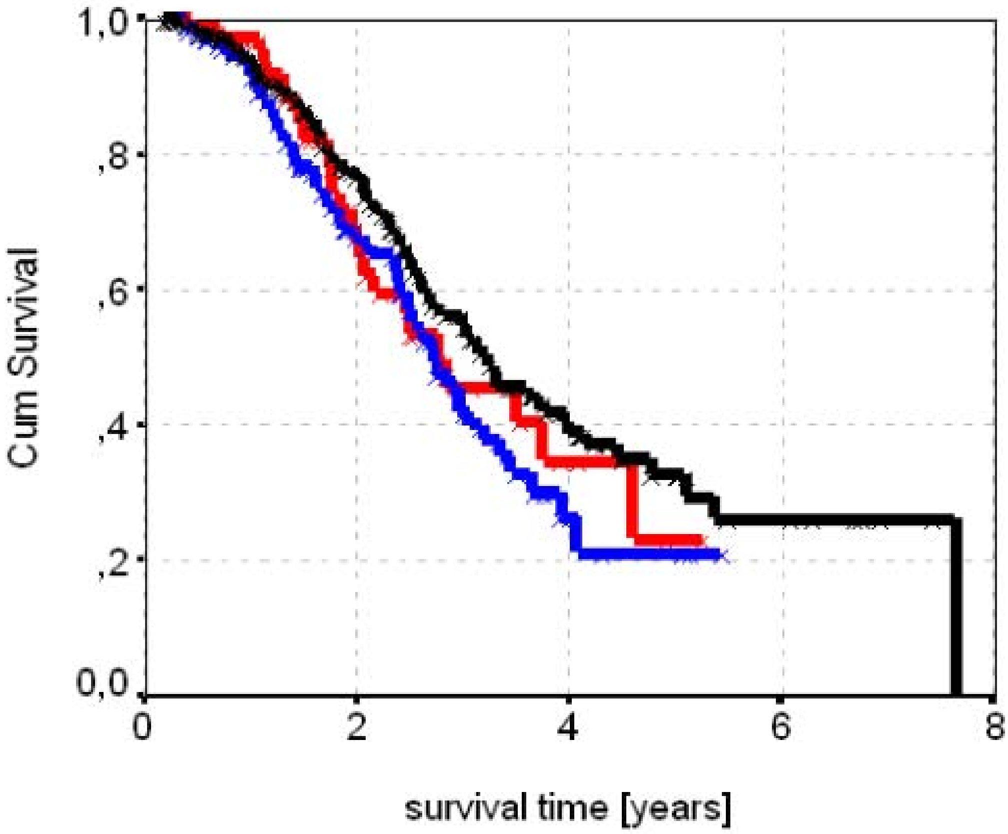
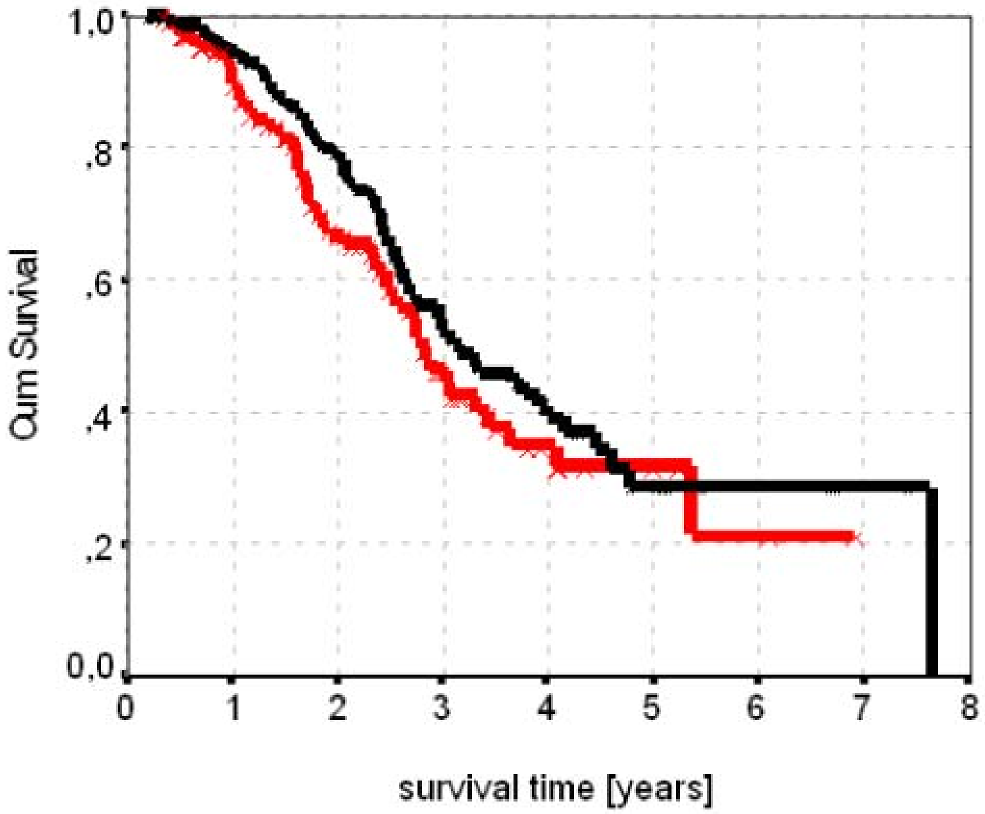


Figure 11

Comparison of survival of patients with respect to the initial staging of lymph nodes (black line = group 1 = N0 and N1 stage, red line = group 2 = N2 or N3 stage).



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