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MR-guided laser-induced thermotherapy (LITT) of liver tumours: experimental and clinical data

TH. J. VOGL*, R. STRAUB, S. ZANGOS, M. G. MACK and K. EICHLER

Department of Diagnostic and Interventional Radiology, University Hospital Frankfurt, Johann Wolfgang Goethe-University, Theodor-Stern-Kai 7, D-60590 Frankfurt/Main, Germany

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MR-guided laser-induced interstitial thermotherapy (LITT) is a percutaneous, minimally invasive treatment modality for treating liver lesions/metastases, soft tissue tumours and musculoskeletal lesions. In this group, MR-guided LITT is currently performed under local anaesthesia on an out-patient basis with a specially designed saline-cooled laser application system. Nd:YAG laser (1064 nm wave length) was used for tumour ablation. Magnetic resonance imaging (MRI) using both open and closed MR units has proven clinically effective in validating the exact positioning of optical fibres. It also allows for real time-monitoring of thermal effects and the evaluation of treatment-induced coagulation necrosis. In liver tumours, percutaneous MR-guided LITT achieves a local tumour control rate of 98.7% at 3 months post-therapy and 97.3% at 6 months with metastases smaller than 5 cm in diameter. The mean survival rate for 1259 patients with 3440 metastases treated with 14 694 laser applications at the institute (calculated with the Kaplan-Meier method) was 4.4 years (95% confidence interval: 4.1–4.8 years) and median survival was 3.00 years. No statistically significant difference in survival rates was observed in patients with liver metastases from colorectal cancer vs metastases from other primary tumours. The rate of clinically relevant side effects and complications requiring secondary treatment was 2.2%. The clinical use of MR guided LITT (size < 5 cm, number < 5) is justified in patients with liver metastases of colorectal and/or breast cancers if the inclusion criteria are carefully observed. Further indications for MR guided LITT include recurrent cancer lesions in the head and neck, lung metastases and bone and soft tissue lesions.

Key words: Laser-induced thermotherapy, LITT, thermoablation, liver metastases, tumorablation.

1. Introduction

The liver represents one of the organ systems most often affected by tumour metastases. Two thirds of patients with colorectal carcinoma (CRC) have liver metastases by the time of death[1]. 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 4.5–15 months[2]. Only 5–10% of all patients with liver metastases of CRC are deemed suitable for resection. After resection, the 5 year survival time improves from 16–40%[1] but only 20–30% of patients remain free from tumour recurrence.

Hepatocellular carcinoma (HCC) is one of the most common malignant neoplasms and resection or hemihepatic resection and/or liver transplant are potentially curative treatments. In patients with a single small HCC and well-preserved liver function, surgical resection provides a 5 year survival between 47.1–60.5%. However, most HCCs are unresectable because of underlying poor liver function

*To whom correspondence should be addressed. e-mail: t.vogl@em.uni-frankfurt.de

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or tumour multi-focality[3]. For small, unresectable HCC nodules, transplantation is effective with 83% freedom from recurrence rate at 4 years. It comes with a 6% peri-operative mortality, however[4]. If there are contraindications, transarterial chemo-embolization[5, 6] and local alcohol injection[7, 8] can be used as palliative therapeutic strategies. Interstitial procedures such as MR-guided laser-induced[9–14] or radio-frequency ablation[15–21] show a high local tumour control rates.

Currently, liver resection of solitary lesions has been the only potentially curative treatment[1, 22–24]. In modern oncology, systemic treatment options like chemotherapy and immunotherapy are increasingly supplemented by regional treatment options such as surgery, radiotherapy and interventional oncological options (thermal ablation and/or locoregional chemotherapy).

Within the last decade, thermal ablation has been developed and clinically improved through the use of non-invasive imaging and improved ablation applicators. Different technologies have been developed including magnetic resonance guided laser induced thermotherapy (MR-guided LITT), radiofrequency ablation (RF), ultrasound and microwave and cryotherapy ablation. Propelled by early successes, there has been great interest in further developments in interstitial procedures such as laser coagulation or radio-frequency ablation.

The clinical success of thermal ablation depends on optimal 'on-line monitoring' of thermal changes in the treated tissue and an exact measurement of the therapy effect. Real time MR imaging during LITT fills this need. It allows for early detection of local complications and treatment effects, such as bleeding, haemorrhage or necrosis and key MR parameter changes can be related to tumour control rate.

Laser-induced interstitial thermotherapy (LITT) is a minimally invasive, local form of treatment, the coagulative effects of which lead to tumour destruction in solid organs. Due to the comparatively high penetrative depth of the photons and the possibility of problem-free radiation transmission by fibre-optic waveguides, near infra-red lasers (NIR) are used for LITT. The institute has developed a unique saline-cooled power laser application system to increase the volume of coagulative necrosis while preventing carbonization at the tip of the laser applicator. The maximum laser power for this system is 30 W over a time period of 25 min.

The following paper will summarize experimental and clinical data for MR-guided laser induced thermotherapy of malignant liver tumours treated at the clinic, focusing on liver metastases and primary hepatocellular carcinomas[25].

LITT permits selective photothermal tumour destruction which preserves surrounding parenchymatous organ structure. The expansion of the tissue-destroying effect is dependent on the energy source. This means that the parameters must be pre-selected such that all detectable tumour, if possible, is exposed to the coagulative effect. Typically, there must also be a safety margin of at least 5–10 mm in width to take care of microscopic disease around the lesion.

Most lesions in the liver are roughly spherical in volume. Therefore, the application systems have been developed such that they create spherical volumes of tissue destruction.

2. Materials and methods

2.1. *Cooled laser device*

The system used for laser-induced thermotherapy (LITT) can be applied percutaneously or for laparoscopic or operative procedures. This permits versatile clinical application.

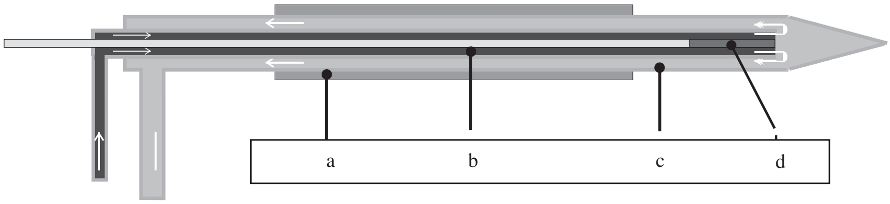

Figure 1. Illustration of the water cooled power laser system. It shows the double-tube protective catheter with the water cooling (*b*, *c*) (inflow and ouflow in blue). Laser applicator in red (*d*) (active zone) and the sheath in orange (*a*). See online version for colour figure.

The applicator is irrigated [26], which permits expansion of the laser-induced necrosis zone. The device consists of a 9 French catheter (Somatex GmbH, Berlin, Germany) with centimetre markings and a 7 French sheathed catheter (Fa. Somatex GmbH, Berlin, Germany) with irrigated double lumina. Room temperature saline is used as the irrigation fluid. A pump is integrated with the laser (irrigation rates of 30–60 ml min^{-1}). This permits reliable cooling of the applicator zone achieved (figure 1).

2.2. *Method for applying power*

The method is done in such a way as to minimize the number of insertion points. This is accomplished by inserting the applicator into the tumour area and pushing it to the deepest margin. Power is applied to the first location until coagulation occurs. The applicator is then withdrawn 1–2 cm and further power is applied. This technique can be used for elliptically shaped metastases.

Multiple applicators are also used for some circumstances. In this situation, the applicators are laid parallel to each other and are operated simultaneously. In this way, the treatment of larger malignant lesions can be speeded up substantially.

Metastases smaller than 2 cm in maximum diameter are treated with a single-power application. Lesions larger than 2 cm in maximum diameter are treated with two laser applications—a so called double power application. Lesions larger than 3 cm in maximum diameter are treated with three laser applications, etc. The disadvantage, however, is that a higher number of punctures are required to treat the larger tumours.

Tissue carbonization must be avoided in order to achieve large-volume coagulation zones and to be able to guarantee a safe application. In such circumstances, an irrigated applicator (SOMATEX, Berlin, Germany) is used, a withlaser power of 10–12 W cm^{-1} of active treatment length of applicator tip .

2.3. *MR imaging*

Currently, magnetic resonance imaging (MRI) and MR thermometry (MRTE) are the optimal methods for treatment monitoring. This is based on several factors such as multi-planar representation and the high soft tissue contrast of MRI.

Due to the relatively low sensitivity with regard to movement artifacts, their wide availability and speed of data acquisition, thermosensitive T1-weighted MRTE sequences are applied for the clinical implementation of LITT. The longitudinal or spin-lattice relaxation time of a tissue is temperature-dependent. Local rise in temperature results in a signal drop in the MR-image. A linear correlation has been shown between the drop in signal in the image and temperature rise (figure 2)[26].

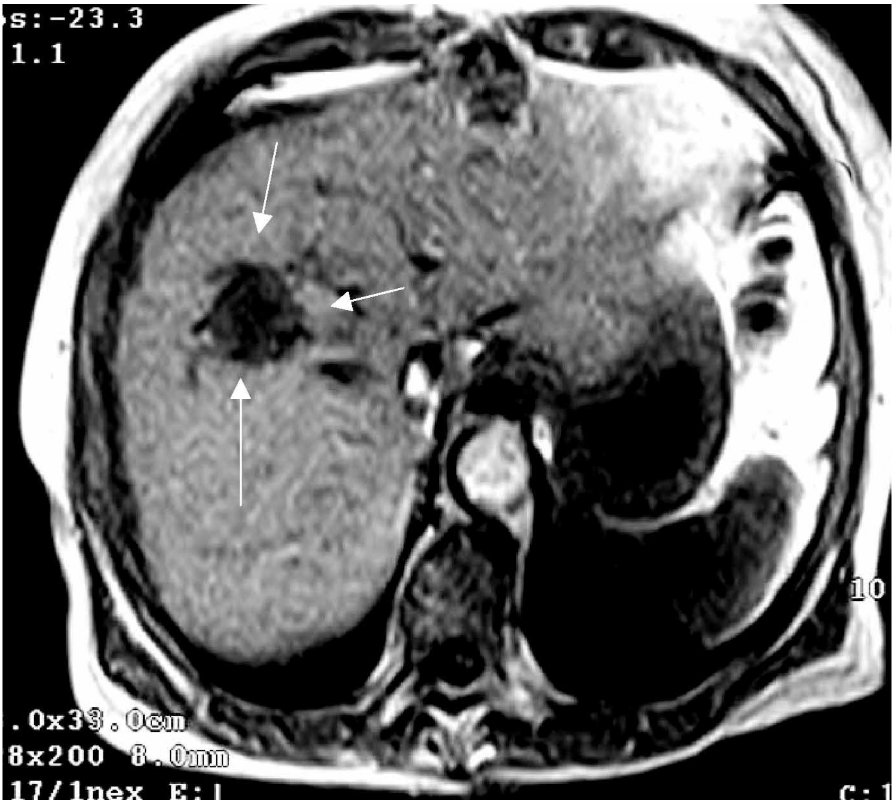

Figure 2. Patient (64-years old) with relapse metastasis from a colorectal carcinoma (initial tumour stage pT3, N1, M1). The T1-weighted thermosensitive gradient echo sequence (TR/TE/flip angle: 102/8 ms/15°) in axial tomographic orientation shows the metastasis before starting the laser.

Appropriately weighted gradient echo sequences (FLASH and Turbo-FLASH) with measuring times between 6–15 s have proved suitable to measure the laser-induced temperature changes in the range between 60–110°C. Breatholding has been used to minimize movement artifact.

The control and monitoring of the LITT is carried out during the on-going LITT treatment by MRI. The predominant aim of monitoring during LITT must be to ensure that the tumour is fully coagulated and that critical surrounding normal structures, such as major vessels or the bile duct are preserved.

2.4. *Treatment planning*

For treatment planning and control before and after LITT, T1 and T2-weighted spin echo and gradient echo sequences are used (figure 3). These images give a baseline for the planning software. Simulations of laser treatment using a software program LITCIT version 4.3 (Lasermedizin, Berlin, Germany) on a PC are performed. These computer-aided treatment planning simulations, which have been validated against *in vivo* comparative tests, are available for further treatment optimization. Predicted irreversible damage distribution and migration of the thermal field can be represented at the same time as progress of the treatment. The simulations allow for

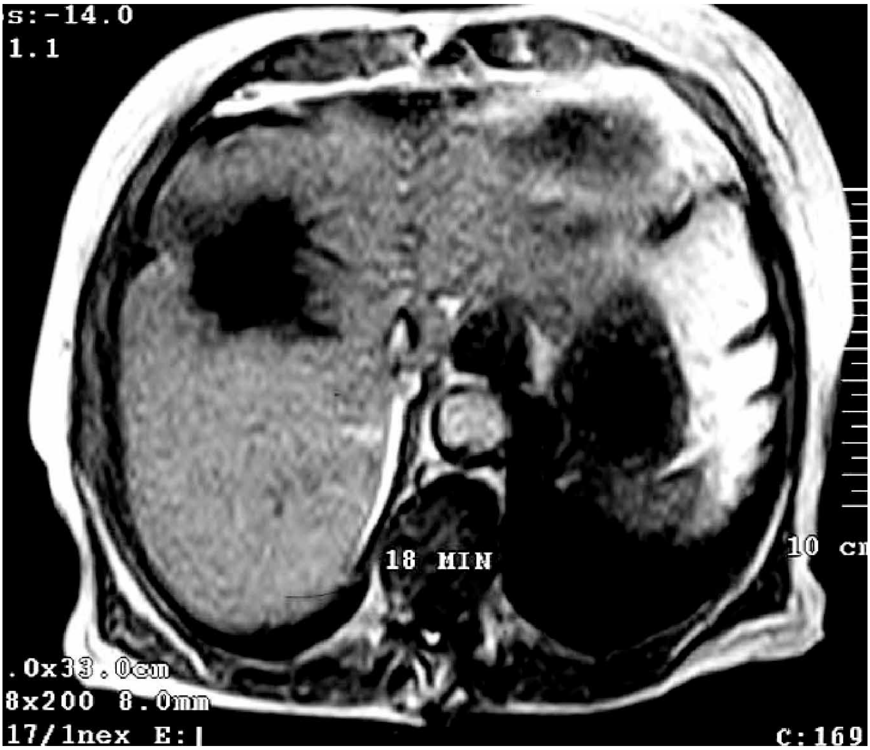

Figure 3. T1-weighted thermosensitive gradient echo sequence in axial tomographic orientation in an advanced phase of the intervention 18th min of this patient. Clear drop in the signal intensity in the heated area.

calculation of the optimum parameters for laser energy and exposure time for each individual fibre before actually carrying out the treatment.

Implementing and evaluating computer-aided thermoplanning for LITT applications is costly, however, because the expected irreversible damage zone depends on various parameters in a complex way. Important factors include laser energy, irradiation time, applicator characteristics, optical and thermal tissue parameter such as tissue perfusion and adsorbtion rates. Initial applications of this kind of system lead one to expect a further improvement in precision during the treatment.

2.5. *Clinical application*

The following criteria have been defined for selection of appropriate patients with malignant liver tumours for LITT Inclusion Criteria:

(1) Liver metastases ≤ 5 cm in diameter;
(2) Number of lesions < 5;
(3) Primary tumour must be completely resected;
(4) Informed consent from the patient in writing after a verbal and written explanation at least 24 h before the operation;
(5) Full awareness and 18 years of age; and
(6) The lesion must be verified with a morphological image.

2.6. *Exclusion criteria*

(1) Existence of extrahepatic metastatic spread;

(2) Absolute contraindications for an MRT examination; and

(3) Coagulation status more than 50% below normal values.

3. Results

3.1. *Local tumour control rates*

The local tumour control rate after LITT has been defined as: (1) imaging verification that visible tumour was completely ablated at the time of treatment and (2) no local recurrences in the heated zone, as assessed using follow-up imaging and physical examination. At 3 and 6 months post-treatment, all patients were assessed for local tumour control using unmodified and contrast-enhanced MRI. T1-weighted MR sequences are performed to verify the amount of induced necrosis. Successfully treated metastases in the unmodified T1-weighted sequence typically showed an increased signal intensity that appears similar to low-grade haemorrhage. Local tumour control was of 98.7% and 97.3%, respectively, at these follow-up times. It is believed that the excellent local tumour control is the result of the optimized application technique. Emphasis on coagulation of a 10 mm safety margin is apparently effective in achieving short-term local control of both gross and microscopic tumour at the tumour borders. The data demonstrate that a follow-up MR examination 24 h after LITT provides essential information on the dimensions of the coagulation zone. Contrast-enhanced MRI elucidates induced coagulation necrosis portrayed as hypo-intense zones in comparison with the surrounding hepatic tissue. Enhancing solid portions of the liver are defined as residual tumour tissue. T2-weighted images areas of coagulation necrosis regularly showed a moderate increase in signal intensity in the border area, probably reflecting concomitant oedema. Both the initial complete destruction of the tumour and the coagulation of an appropriate safety margin of 10 mm around the metastasis are crucial for the success of LITT treatment, as shown in figure 4.

At the 3 and 6 month follow-ups, the size and morphology of the ablated zone and reactive changes are estimated and compared with the pre-therapy images. Success was defined as regression of lesion size and reduction in signal intensity vs the last follow-up images.

3.2. *Survival data*

The cumulative survival rate of patients treated with LITT has been calculated using the Kaplan-Meier method. Here, the cumulative survival rate, both for the period from the first LITT treatment, and the period of the initial diagnosis of the metastatic lesion(s) was calculated (figure 5). The mean cumulative survival time calculated from the time of the initial diagnosis of the metastasis/metastases was 4.4 years (95% confidence interval: 4.1–4.8 years); and median survival was 3.00 years. No statistically significant differences in survival rates were seen between groups of patients treated with colorectal cancer metastases vs metastases from other primary tumours.

The patients tolerated the LITT well with a local anaesthetic and systemically applied low dose of analgesics. Within the framework of clinical tests and the imaging treatment check-ups, the following side effects and complication rates, referring

Figure 4. T1-weighted spin echo sequence in axial tomographic orientation after the administration of gadolinium-DTPA (0.1 ml kg^{-1} body weight). Immediate expansion of the necrosis and, hence, documentation of the complete ablation of the tumour tissue is seen in this case of the 64-year old patient..

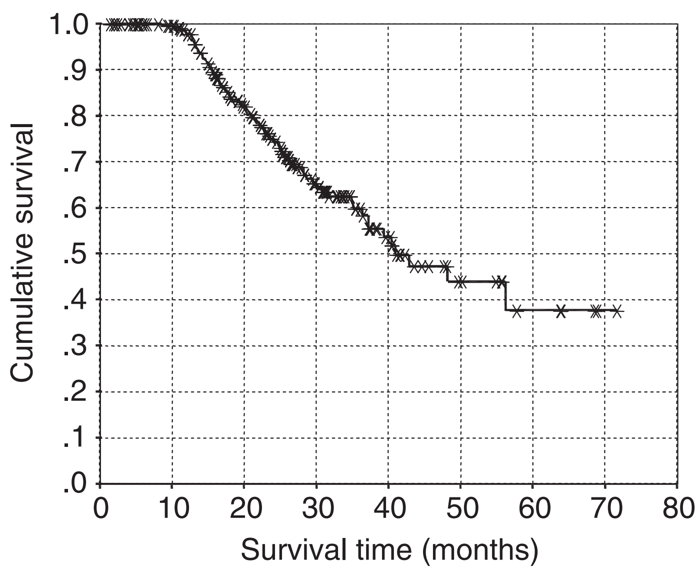

Figure 5. In a total of 1259 patients with 3440 metastases, treated with 14 694 laser applications the mean survival rate was 4.4 years (95% confidence interval: 4.1–4.8 years), median survival was 3.00 years after the first LITT.

to the number of LITT sessions, were documented. Pleural effusion (7.28%), subcapsular haematoma (1.9%), intra-hepatic abscess formation (0.42%) and local infection at the puncture site (0.31%). These patients were successfully treated with intravenous antibiotics. With the exception of the complications listed above, all side effects and complications were not clinically relevant and could only be detected in images on the check-up MRI after 24 h.

One patient with a central relapse metastasis after an extended hemi-hepatectomy was treated. He had infiltration of the bile ducts, which was documented by MRI. An intensive explanation was given to the patient about a possible treatment strategy, which consisted of removing the metastasis thermoablatively as far as the biliary passage and then treating the biliary passage with a stent via the PTCD access. It was possible to remove the metastasis completely using this technique.

No seeding of metastases along the cannulation tract was found in the patients. One patient died 4 weeks after treatment after developing a 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. A second patient died, presumably due to sepsis, unfortunately this could not be proven as no autopsy was performed.

Including these two fatalities, the overall complication rate was 2.2% and considered acceptable, given the benefit achieved in the majority of patients.

4. Discussion

The most frequent primary tumour with virtually exclusively hepatic metastatic spread is colorectal carcinoma. Consequently, colorectal carcinoma is the second most common cancer behind bronchial carcinoma amongst the male population and third after breast and lung cancer among women. The risk of developing an intestinal cancer clearly increases after the age of 40 for both sexes[27].

Seventy-three per cent of patients with hepatogenic metastatic spread are free of metastases in other organs[28]. This indicates that, for many of those affected, the intensity of hepatic infestation is the first determining factor for survival time. Stangl and team observed 1099 patients in this context. Those who received no treatment ($n = 484$) survived on average 7.5 months. The 1, 2, 3 and 5 year survival rates were 31%, 7.9%. 2.6% and 0.9%. For those patients who were surgically resected ($n = 340$), the 5 year survival time was 32%. Those who were administered systemic ($n = 70$), regional chemotherapy ($n = 123$) had a median survival time of 12.7, 11.1 months. However, no patients survived longer than 4 years[24].

The current gold standard for treatment of liver metastases is surgical resection. Current studies with very large patient numbers have been made by Scheele *et al.*[1] and Nordinger. Of a population of 1766 patients with HCC, recorded from 1960–1993, who had hepatic metastatic spread from colorectal carcinoma, 473 were eventually able to undergo a liver resection with the intention of a curative outcome. In this sub-group, taking into account the operation mortality rate (4.4 range from 11.5–4.1%), survival rates of 46%, 33%, 22% and 18% at 3, 5, 10 and 20 years were achieved[1, 29]. The surgical data have shown that, for the sucessful treatment of liver metastases and HCC nodules, it is necessary to resect a 1-cm margin of normal-appearing tissue. Because up to 60–70% of the patients had intra-hepatic tumour relapses after initial treatment, consistent follow-up checks are of the utmost importance This paper is just in press.

The findings in a population of patients with liver metastases from different primary tumours, with a majority from colorectal carcinomas, can only be compared with the other local ablative procedures to a limited extent, because in these studies mostly HCCs have been treated.

The survival rates achieved are similar among patients with metastases from colorectal carcinoma or carcinoma of the breast compared to those in surgically resected patients. It is important to note that a surgical resection was an option among most of the patients treated in the series 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. Therefore, LITT is a very favourable treatment option. Advantages of LITT have proven to be

(1) good tolerance through local anaesthesia and percutaneous access,

(2) low rate of complications,

(3) low peri-operative mortality,

(4) treatment managed on an outpatient basis,

(5) low costs in comparison with hepatectomy, and

(6) treatment can be repeated.

Disadvantages of LITT have proven to be

(1) requirement of access MR imaging facility, and

(2) need a highly skilled interventional radiologist.

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 tumours 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. Due to the survival data and local tumour control rates achieved so far, in the authors' opinion, randomized studies comparing LITT with chemotherapy solely in the case of patients who fulfil the inclusion criteria for LITT are no longer necessary.

Consequently, the pre-requisites are given to integrate these new procedures into oncological treatment programmes, which have been carried out up to now. Because the correlation between tumour mass and response to chemotherapy can be documented, in the palliative approach a laser-guided intra-hepatic metastatic removal in combination with chemotherapy may improve treatment response.

The much discussed problem of spreading tumour cells by manipulating the tumour tissue with needles, scalpels or other surgical instruments affects both the surgery and the radiological intervention in the case of resections, biopsies or therapeutic intervention like LITT. Current publications assume an incidence among percutaneous biopsies of 1/10 000–1/33 000, in which 48% of the population studied had pancreatic biopsies; however, occasional individual cases are reported in the literature[30, 31].

There is the possibility that tumour seeding can occur along the puncture channel and subcutaneously in the puncture area. Over the months, the growing masses appear in the case of CT or MRI examination or stand out through tactile findings in the course of clinical examinations. The effects of the tumour manifestations on the survival time or on further clinical progress of the affected patients have not been sufficiently examined, but seem to have no real influence. Overall tumour cell spreading must be considered as a potential complication. The procedure used of installing tissue glue via a double lumina catheter in the puncture canal seems to have a beneficial effect. In the patient population, no spreading of tumourous cells in the puncture canal has been observed so far.

5. Summary

The percutaneous interstitial thermoablation of malignant liver tumours is a treatment concept for destroying tumours palliatively and is also potentially curative.

For the hepatocellular carcinoma, a local ablative procedure instead of, or in combination with, local alcohol installation or the transarterial chemoembolization (TACE) can be used[32–35]. According to the studies, local procedures such as radiofrequency ablation and laser therapy (LITT) are promising tools for the treatment of HCC and permit reliable local tumour control.

In the case of liver metastases, the therapeutic situation must be discussed within the context of the primary tumours. Today, using MR-guided LITT for liver infestation restricted to a local area without extra-hepatic manifestations can be justified clinically. Magnetic resonance imaging proves to be an indispensable tool for monitoring and controlling percutaneous LITT. MRI is used both for monitoring and controlling complete tumour removal. Additionally, MRI is used for the follow-up process and is proven to be the optimum examination procedure in assessing very small tumour manifestations.

It is important that the long-term results of patients treated with LITT be compared to the natural history and those treated with surgical resection. It is necessary that LITT be performed as part of clinical trials in prospective randomized studies to establish long-termes outcomes.

References

1. Scheele J, Altendorf-Hofmann A, Stangl R, Schmidt K. Surgical resection of colorectal liver metastases: gold standard for solitary and completely resectable lesions. *Swiss Surg Suppl* 1996; 4: 4–17.
2. de Jode MG, Vale JA, Gedroyc WM. MR-guided laser thermoablation of inoperable renal tumors in an open-configuration interventional MR scanner: preliminary clinical experience in three cases. *J Magn Reson Imag* 1999; 10: 545–9.
3. Grasso A, Watkinson AF, Tibballs JM, Burroughs AK. Radiofrequency ablation in the treatment of hepatocellular carcinoma—a clinical viewpoint. *J Hepatol* 2000; 33: 667–72.
4. Mazzaferro V, Regalia E, Doci R, *et al*. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334: 693–9.
5. Kawai S, Tani M, Okumura J, Ogawa M, *et al*. Prospective and randomized clinical trial of lipiodol-transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: a comparison of epirubicin and doxorubicin (second cooperative study). *Sem Oncol* 1997; 24: 38–45.
6. Lufkin RB, Gronemeyer DH, Seibel RM. Interventional MRI: update. *Eur Radiol* 1997; 5: 187–200.

7. Livraghi T, Bolondi L, Buscarini L, *et al*. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. Italian Cooperative HCC Study Group. *J Hepatol* 1995; 22: 522–6.
8. Amin Z, Lees WR, Bown SG. Hepatocellular carcinoma: CT appearance after percutaneous ethanol ablation therapy [letter; comment]. *Radiology* 1993; 188: 882–3.
9. Vogl TJ, Mack MG, Straub R, *et al*. MR-guided laser induced themotherapy (LITT) of liver metastases: results of the multiapplicator technique versus monoapplication. *ISMRM Abstracts* 1997; 522.
10. Vogl TJ, Müller PK, Hammerstingl R, *et al*. Malignant liver tumors treated with MR imaging-guided laser-induced thermotherapy: technique and prospective results. *Radiology* 1995; 196: 257–65.
11. Vogl TJ, Mack MG, Straub R, *et al*. MR-guided laserinduced thermotherapy of liver metastases. In: Waidelich W, Waidelich R, Waldschmidt J, eds. *Laser in der Medizin/in Medicine*. Berlin, Heidelberg, New York: Springer Verlag, 1998, pp. 194–7.
12. Vogl TJ, Eichler K, Straub R, *et al*. Laser-induced thermotherapy of malignant liver tumors: general principals, equipment(s), procedure(s)—side effects, complications and results. *Eur J Ultrasound* 2001; 13: 117–27.
13. Vogl TJ, Mack MG, Straub R, *et al*. Magnetic resonance (MR)-guided percutaneous laser-induced interstitial thermotherapy (LITT) for malignant liver tumors. *Surg Technol Int* 2002; 10: 89–98.
14. Vogl TJ, Mack MG, Balzer JO, *et al*. Liver metastases: neoadjuvant downsizing with transarterial chemoembolization before laser-induced thermotherapy. *Radiology* 2003; 229: 457–64.
15. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology* 2003; 226: 441–51.
16. Livraghi T, Solbiati L. [Percutaneous treatment: radiofrequency ablation of hepatic metastases in colorectal cancer]. *Tumori* 2001; 87: S69.
17. Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the 'test-of-time approach'. *Cancer* 2003; 97: 3027–35.
18. Solbiati L, Ierace T, Tonolini M, Osti V, Cova L. Radiofrequency thermal ablation of hepatic metastases. *Eur J Ultrasound* 2001; 13: 149–58.
19. Goldberg SN, Charboneau JW, Dodd GD, 3rd, *et al*. Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. *Radiology* 2003; 228: 335–45.
20. Goldberg SN, Solbiati L. Tumor dissemination after radiofrequency ablation of hepatocellular carcinoma. *Hepatology* 2001; 34: 609; author reply 610–601.
21. Goldberg SN, Gazelle GS, Compton CC, Mueller PR, Tanabe KK. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. *Cancer* 2000; 88: 2452–63.
22. Chiappa A, Zbar AP, Bertani E, Biella F, Staudacher C. [Hepatic resection for hepatocarcinoma in the cirrhotic patient]. *Chir Ital* 1999; 51: 345–54.
23. Fong Y, Cohen AM, Fortner JG. Liver resection for colorectal metastases. *J Clin Oncol* 1997; 15: 938–46.
24. Stangl R, Altendorf Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; 343: 1405–10.
25. Hughes K, Scheele J, Sugarbaker PH. Surgery for colorectal cancer metastatic to the liver. *Surg Clin N Am* 1989; 69: 339–59.
26. Vogl TJ, Mack MG, Hirsch HH, Müller P, Weinhold N, Wust P, Phillip C, Roggan A, Felix R. *In vitro* evaluation of MR thermometry in the implementation of laser-induced thermotherapy. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 1997; 167: 338–44.
27. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. *CA Cancer J Clin* 1995; 45: 8–30.
28. Weiss L, Grundmann E, Torhorst J, *et al*. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 1986; 150: 195–203.
29. Nordlinger B, Guiguet M, Vaillant JC, *et al*. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996; 77: 1254–62.

30. Chapman WC, Sharp KW, Weaver F, Sawyers JF. Tumor seeding from percutaneous biliary catheters. *Ann Surg* 1989; 6: 708–15.
31. Loew R, Dueber C, Schwarting A, Thelen M. Subcutaneous implantation metastasis of a cholangiocarcinoma of the bile duct after percutaneous transhepatic biliary drainage (PTBD). *Eur Radiol* 1997; 7: 259–61.
32. Livraghi T, Lazzaroni S, Meloni F, Torzilli G, Vettori C. Intralesional ethanol in the treatment of unresectable liver cancer. *World J Surg* 1995; 19: 801–6.
33. Kanematsu T, Matsumata T, Shirabe K. A comparative study of hepatic resection and transcatheter arterial embolization for the treatment of primary hepatocellular carcinoma. *Cancer* 1993; 71: 2181–6.
34. Livraghi T, Goldberg N, Lazzaroni S, Meloni B, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999; 210: 655–61.
35. Vogl TJ, Mack MG, Balzer JO, Engelmann K, Straub R, Eichler K, Woitaschek D, Zangos S. Liver metastases: neoadjuvant downsizing with transarterial chemoembolization before laser-induced thermotherapy. *Radiology* 2003; 229: 457–64.
36. Vogl TJ, Mack MG, Roggan A, *et al*. Internally cooled power laser for MR-guided interstitial laser-induced thermotherapy of liver lesions: initial clinical results. *Radiology* 1998; 209: 381–85.