MR guided laserinduced thermotherapy (LITT) of malignant liver and soft tissue tumors

For lasermedicine

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Summary

Objective: Presentation of MR guided laser-induced thermotherapy (LITT) for percutaneous interstitial thermotherapy of malignant liver tumours and soft tissue lesions.

Material and methods: MR-guided LITT is carried out by means of catheter systems that can be implanted percutaneously. CT or open MRI technologies are used as the control method for inserting the catheter. Irrigated application systems are available for LITT.

Findings: percutaneous LITT currently permits local tumour control of 97.2% for localised liver metastases without an extrahepatic manifestation pattern. In a patient population of 729 patients median survival times of 48.0 months for liver metastases, 41.8 months for patients with colorectal liver metastases and 46.8 months for hepatic cell carcinoma tumours have been documented. In the treatment of soft tissue tumors in the head and neck and pelvis MRI guided LITT allows an excellent local tumor control rate and reduces clinical symtoms in a palliative manner.

Conclusions: Percutaneous MR-guided LITT permits a high level of tumour control in the case of liver metastases and soft tissue tumors smaller or equal to 5 cm and a maximum number of 5 lesions with an improvement of survival data.

Key words: Liver metastases, laser ablation, thermotherapy, LITT, radio-frequency ablation.

Introduction

The liver as a large solid organ is very suitable for interventional modalities, due to a short transcostal access and its excellent functional capacity. It is the most common site of metastatic tumor deposits, especially for colorectal cancer, which 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 present liver metastases [79]. As a high number of metastases grow in the liver, new treatment protocols are currently under investigations. Laser-induced thermotherapy (LITT) has recently applied for a minimally invasive technique in local treatment of liver metastases []. Percutaneous approach avoiding laparatomy, local anesthesia, and an outpatient therapy management are the main advantages of this new kind of therapy modality.

Laser energy is transmitted via thin optical fibers resulting in a well defined area of coagulative necrosis. That means a destruction of tissue by direct heating, while greatly limiting damage to surrounding structures []. Magnetic Resonance Imaging (MRI) has proven as an ideal clinical instrument for the exact positioning of the optical fibers in the target area, real time- monitoring of the thermic effects and the subsequent evaluation of the extent of induced coagulative necrosis [].A large number of primary tumours often cause liver metastases as well as bone, lung and brain metastases. After curative sanitation of the primary tumour, the liver infestation has a decisive influence on the survival time of affected patients in many cases. The therapeutic strategy for malignant liver lesions is based on a number of factors such as the underlying primary tumour, localisation, the stage the tumour has reached, and general factors, such as age or any existing concomitant illnesses. In the case of hepatocellular carcinoma (HCC), when the tumour is at a appropriate stage, liver resection or hemihepatic resection or liver transplant is the essential curative treatment. If there are contraindications, transarterial chemoembolisation combined with a local alcohol injection is used as a palliative therapeutic strategy. Interstitial procedures such as laser-induced thermotherapy (LITT) show a high rate of controlling the site of the tumour and are currently being clinically evaluated.

Strategies for liver metastases are considerably more complex. 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 within the framework of tumour stimulation through released growths stimulating substances is considered problematical. For this reason, over the last few years there has been great interest in further developments in interstitial procedures such as laser coagulation or radio-frequency ablation.

Interstitial treatment produces a circumscribed coagulation necrosis, sparing the surrounding structures as much as possible. Percutaneous access, local anaesthesia and out-patient therapy management are the considerable advantages of this minimally-invasive procedure, which offers a curative or palliative treatment option to patients who are already under a great deal of stress.

In the following overview, we will present the methods, findings and treatment strategies for interstitial therapeutic measures for malignant liver and soft tissue tumours, focusing on liver metastases and the primary hepatocellular carcinoma.

Laser application techniques

LITT makes available a photothermal tumour destruction technique, permitting solid tumour configurations inside parenchymatous organs to be destroyed. The expansion of the tissue-destroying effect is dependent on the choice of the radiation capacity and radiation time. This means that the parameters must be pre-selected in such as way that all tumour cells, if possible, are exposed to the coagulative effect and there must also be a safety margin of at least 10 mm in width. At the same time it must be taken into account that within the immediate vicinity of a tumour there may be other sensitive structures which must not be damaged. Selecting the right laser is based on the following points: an optimal depth effect in a tissue, which is determined by the absorption properties of water and haemoglobin, can be achieved with a wave length between 1060 and 1200 nm. ND:YAG and semiconductor lasers of the wavelength 1060 nm or 900 nm fulfil these requirements. The ND:YAG laser is the solid state laser used most often and comes with a wavelength of 1064 nm. The laser can be both pulsed and operated continuously and supplies output power of up to 100w. The tissue-dependent penetration depth of the photons is an essential parameter of the absorption in different depths of tissue layers. The range of the resulting increase in temperature is not restricted to the optical penetration depth, but is substantially extended by thermal conduction processes. Normal cells are less sensitive as regards thermal exposition, malignant cells show a significantly higher sensitivity. The altered metabolic status of malignant cells with pronounced hypoxia causes this high sensitivity.

In order to do justice to the coagulation of a 3-dimensional tumour 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 characteristic have been developed, the distal ends of which are prepared in such a way that the result is an even circumference of radiation. With the conventional applicators almost spherical coagulation zones with a diameter of 20 – 25 mm can be achieved. Apart from the applicator geometry, the radiation capacity and radiation time are crucial parameters for the dimensions of the coagulation zone, as are the specific tissue properties such as optical parameters or perfusion rate.

The temperature-dependent effects of the laser light on the tissue are defined as enzyme induction, oedema formation and membrane relaxation in a temperature range of 40 to 45°C. From 60°C protein denaturation takes place, from 80°C collagen denaturation as far as drying and over 150°C carbonisation.

Applicators and application techniques

Tissue carbonisation must be avoided at all costs in order to achieve large-volume coagulation zones and to be able to guarantee a safe application. The critical value is a power density of approx. 5 watts/cm^2. Depending on the applicator this means laser power of 3-10 watts. At this point the migration of the photons deep into the tissue through absorption into the resulting "carbon layer" is impeded and only "a hot spot" is produced. The only heat diffusion that is still active limits the LITT zone to a small volume (diameter of 1 cm). In order to avoid this carbonisation effect which greatly reduces the volume, a dome-shaped applicator ("scattering dome") was developed. The optimised radiation characteristic of the scattering dome applicator used here is used to achieve a maximum penetration depth of the photons into the tissue. Because of absorption and convection processes occurring there, additional heat propagation results in deeper tissue layers and hence a virtual "expansion" of the applicator, through which the diffusion processes of the heat propagation become dominant. It is technically easy and also more effective to adapt the scatter applicator to the given therapeutic situation (fig. 1). Radiation times over a period of 30 minutes do not lead to any substantial additional expansion of the damaged tissue volume (diffusion equilibrium).

Application techniques

An essential step in clinical laser-induced thermotherapy (LITT) is the development of application systems that can be applied percutaneously, and can also be used for laparoscopic or operative procedures. First a conventional system was available, consisting of a scattering dome applicator, a sluicing system and a thermostable sheathed catheter, via which the LITT applicator can be positioned sterile and as required (fig. 1b).

By further developing the irrigated application system [3] a further expansion of the laser-induced necrosis was achieved and hence an optimisation of the treatment. This system has been developed from a 9 French sluicing system with centimetre markings and a 7 French sheathed catheter with irrigated double lumina. A sterile common salt solution at room temperature is a proven irrigation medium. With a pump system integrated into the laser, irrigation rates of 30 to 60 ml per min can be reached and thus a reliable cooling of the applicator zone achieved.

The following application techniques permit further treatment optimisation: for the mono-application an application system is placed in the lesion by percutaneous access and after an application of heat it is removed again.

A method of modifying the size and morphology of the necrosis is a multi-application with unifocal access ("pull-back" technique). The applicator is withdrawn through the single percutaneous access point after the end of the first heat application by 1 to 2 cm in the puncture track and a further heat application is carried out.

As well as mono-applicators, multi-applicators are also used (multi-applications with multi-focal access). Here 2, or even up to 4, applicators are laid parallel and operated simultaneously. Prerequisites are the corresponding number of laser devices or beam splitters. In this way the treatment of larger malignant lesions can be speeded up substantially. The disadvantage however is the higher number of punctures required.

Treatment monitoring

According to findings so far magnetic resonance tomography (MRT) and the MR thermometry (MRTE) is the optimum imaging procedure for treatment monitoring.

This is based on several factors such as multiplanar representation and the high soft tissue contrast of MRT.

Because numerous image characterising MRT parameters such as perfusion or diffusion are temperature-dependent, in principle sequences that emphasise these parameters can be used for non-invasive temperature measuring. These parameters include the diffusion coefficient of the water, the photon resonance frequency or chemical shift and the T1 relaxation time. 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 in the area of the liver. The longitudinal or spin-lattice relaxation time of a tissue is temperature-dependent, in that a local rise in temperature results in a signal drop in the MRT-image. In vivo examinations and the findings of our team and other teams showed a virtually linear correlation between the drop in signal in the image and the temperature. Appropriately weighted gradient echo sequences (FLASH and Turbo-FLASH) with measuring times between 6 and 15 seconds in breathholding technique have proved suitable to represent the laser-induced temperature changes in the range between 60 to 110°C.

Before and after LITT a test certificate of T1 and T2-weighted spin echo and gradient echo sequences is used for treatment planning and control. In addition contrasting agent aided (0.1 mmol GD-DTPA per kg of body weight) T1 weighted sequences are used (fig. 3).

Computer-aided treatment planning, which has been expanded through in vivo comparative tests, is available for further treatment optimisation. This makes it possible to calculate the optimum parameters for radiation capacity and radiation time for each individual fibre before actually carrying out the laser treatment. The progress of the current temperature and irreversible damage distribution can be represented at the same time as the progress of the treatment by means of real-time simulation, so that by means of magnet resonance tomography indirect "monitoring" is available as an extension of virtual on-line monitoring. 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. Influencing factors are laser capacity, radiation time, applicator characteristics, optical and thermal tissue parameters such as tissue perfusion and blood flow. Initial applications of this kind of system lead us to expect a further improvement in precision during the treatment.

Indications

The primary therapy goal is defined as the local tumor control in patients with restricted hepatic malignant tumor deposition. A majority of patients is suffering from liver metastases of colorectal cancer, but also solitary hepatic manifestations from other primary tumors, like breast cancer, carcinoids and others are treatable. According to our inclusion criteria patients who are eligible for this treatment have less than 5 lesions with a maximum diameter of 50 mm, are unfit for surgical resection, do suffer from irresectable tumors in both hepatic lobes or refuse surgical resection. Patients after a partial resection of one hepatic lobe developing a new lesion in the remaining liver part are also suitable for this therapy. Basic requirements for this treatment are the complete resection of the primary tumor and absence of extrahepatic metastases.

LITT of liver tumors:

- max. 5 lesions
- max. diameter of 50 mm
- patients with tumor recurrence after surgery, radiatio or chemotherapy
- new metastases after liver resection
- no response to chemotherapy
- metastases in both liver lobes
- lesions in high risk locations, e. g. near the bile duct
- LITT as replacement of the oncological therapy in case of patient refusal

LITT of soft tissue tumors:

- Tumor recurrence in the head and neck region
- Tumor recurrence in the pelvis
- Lymph node metastases in the abdomen, the head and neck region and the retroperitoneum

Criteria for Exclusions

- extensive extrahepatic tumor spread
- contraindications for MRI (pace-maker)
- ascites, apparent infections, coagulation disorders
- diffuse and multiple pattern of metastasis

Comparison with alternative methods

Surgery: Surgical resection of liver metastases is still considered as one of the best options for a radical treatment of malignant tumors, but only 20% of the patients are suitable for surgical resection. Clinical conditions like the presence of lesions in both hepatic lobes or the reduced clinical condition of a patient exclude surgical treatment. Additional liver surgery is associated with a mortality rate of approximately 3-8%. But the main problem is tumor recurrence after surgical resection of up to 70%. Only in some selected cases the re-resection is possible, so that the further surgery is restricted for the majority of patients [1, 4, 6, 7, 13, 14, 21, 22, 25, 27, 28, 44, 52, 61, 63]. MR-guided LITT offers the option of several retreatment courses. For new hepatic lesions the same inclusion criteria are applied like at the time of the initial LITT.

Percutaneous alcohol injection (PAI): MR-guided ethanol ablation is used to reduce tumor bulk and cancer pain, but mostly in low risk regions and has been used especially to treat hepatocellular carcinoma (HCC). Among the limitations of this technique is the lack of an instrument for monitoring the effects induced in both normal and pathological tissue. Comparisons between interstitial laser coagulation (ILP) and percutaneous alcohol injection (PAI) to treat colorectal hepatic metastases have shown, that there were no major complications after ILP or PAI, but that pain during PAI was more severe and also the efficacy for tumor control was lower [2, 37, 40, 65, 66]. In summary alcohol injection is an accepted therapy method for small HCC-nodules, but no treatment option for metastases.

Cryosurgery: At present cryosurgery is carried out using laparatomy and ultrasound guidance. Single and multiprobe arrays are possible. Tumor tissue will be freezed less than –190 degrees and defrosted. The double freezing technique is resulting in a reliable destruction of tumor cells. Inclusion criteria are similar to LITT concerning size and number of lesions. Cryosurgery under MR-guidance has been investigated in animal studies and MR imaging is promising here for real-time monitoring of the progress of freezing and thawing during cryosurgery. Drawback is the need for laparatomy with its complications, thatsway the minimal invasive aspect is missing. Hospital stays about 7 to 10 days are normally [5, 8, 15, 33, 47, 49, 54, 60, 69, 78, 81, 82].

Radiofrequencyablation: Radiofrequency (RF) ablation is an other modality for thermal coagulation of tumor tissue. Heating is caused by a high tissue impedance between two applicator tips. Solbati demonstrated currently the feasibilty of tumor-destruction with conventional and cooled-tip monopolar RF-electrodes in patients with metastatic gastrointestinal carcinomas[67]. The studies included up to 29 patients, treated with mono- and multiprobe arrays and also with liquid cooled-tip techniques. The same inclusion criteria are applied, but there are problems with the monitoring technique. Interferences between the RF-applicators and the MRI device prevent an sufficient imaging [20, 35, 36, 38, 39, 42, 58].

Focused ultrasound: Noninvasive surgery using focused, high-intensity ultrasound beams was first proposed as a therapeutic modality for destruction of central nervous system tissue. Recently, a novel solution was demonstrated for real time monitoring of focused ultrasound using only MR imaging for visualizing the temperature elevation during sonication and for delineating regions of tissue necrosis. This promising modality is actually under in vitro evaluation for soft tissue tumors in the brain and the breast. Problems are the rapid increase of temperature and to reach larger volumes with a small focus [9-11, 24, 50, 77]. So far focused ultrasound has no indication for treatment of liver metastases due to breathing artefacts.

Transarterial chemoembolization (TACE): The transarterial chemoembolization is defined as a local hepatic deposition of chemotherapy via tumor providing vessels and a transfemoral entry for the treatment of HCC-nodules and hepatic metastases of neuroendocrine tumors. In other liver metastases there is a palliative intention to reduce tumor bulk and to decelerate tumor progression. Indication is justified due to low percentage of side effects, outpatient managment and nearly no impairment of the quality of life [41, 59].

Systemic and regional chemotherapy: All above mentioned techniques are restricted regionally to the liver, so the adjunct use of systemic chemotherapy is essential in most cases. Protocols, doses and intervals are depending on the primary tumor and data from staging.

Results

In vitro studies:

In vitro studies using pig liver demonstrated reproducible loss of signal intensity in MRI corresponding to increasing tissue temperatures. Using an energy of 5 Watt and an application time of 12 min, the maximum diameter of the region with signal loss was 25 mm. This effect was best monitored using the Thermo-TurboFlash sequence at TI-values of 300 to 400 ms, providing a nearly linear, inverse correlation between signal intensity and temperature as well as the Thermo-FLASH-2D sequences.

A mean size of necrosis of 2 cm^3 of a ellipsoid morphology may be achieved by an application time of approximately 20 minutes and a power of 5-6 W using one applicator system. There are two possibilities of enlarging the necrosis: First the pullback-technique, which allows a more longitudinal enlargement of necrosis and second the multi-applicator-technique. The positioning of two or three applicator systems results in a necrosis size up to 17 cm^3 .

The use of an internally cooled power laser applicator at power settings between 25 and 30 Watt over 10 to 20 minutes additionally results in a significant enlargement of the obtained coagulative necrosis.

Patients:

So far from 1993 to october 2000 we treated 729 patients with a total of 1707 liver metastases of colorectal carcinoma, esophageal, gastric, pharyngeal, testicular and pancreatic tumors. A total of 7470 laser applications were performed. The laser-induced necrosis was quantified by comparing the pre- and posttherapeutic plain- and contrast-enhanced MR-images. Parameters like size, morphology and contrast enhancement were directly compared to pre-therapeutic MRI. Successful therapy is defined by a geometric shaped necrotic area without enhancement in the adequate topographic position and reliable safety margin.

Local tumor control rates for data from 1997 to 2000 are 98,1% after 3 months and 97,3% after 6 months in liver lesions smaller than 50 mm. Mean survival time for all patients is 45 months using the Kaplan-Meier method (95% confidence interval: 40,9 to 49,2 months, median 39,8 months, maximum survival 74,6 months) (fig. 1).

The most homogeneous patient group are patients with hepatic metastatases of colorectal primaries. Mean survial time is 42,6 months (95% confidence interval: 37,7 to 47,5 months, median 36,7 months) (fig. 2).

Survival did not differ significantly ($p>0.05$) between male and female patients, nor between patients with colorectal metastases and those with metastases of other primary tumors.

Complications:

All patients tolerated the procedure under local anesthesia well. The following side effects could be visualized on clinical examinations or imaging studies: pleural effusion in 7.28%, subcapsular hematoma in 2.46%, intrahepatic abscess in 0.11%, intraabdominal bleeding in 0.11% and local infection on punctering side in 0.2%. All complications except the following were clinically not relevant and only visible on imaging studies. In 0.36% of the cases the pleural effusion had to be treated by percutaneous drainage. 3 patients died within four weeks after LITT. 1 patient has operated for the suspiction of a colonic perforation.

Head and neck and extrahepatic tumors:

26 patients (8 woman and 18 men, mean age 64 years, range 57-77 years) with recurrent tumors of the head and neck were treated with 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 the procedure well under local anesthesia. No side effects were observed. The procedure was judged a being successfully performed if postinterventional MRI revealed a sharply delined nedrosis exceeding the pretherapeutic tumor. 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 other group of 14 patients abdominal tumorous lymph node involvement or recurrent primary pelvic tumors had been successfully treated using MRI-guided LITT. In this minor group of patients we had been able to reduce clinical symptoms in 68% of the patients.

Discussion

The liver is one of the most frequent deposits of tumor cells, so a lot of therapeutic strategies are accessed or are currently under investigation. At the time of death approximately two-thirds of patients with colorectal cancer do have hepatic metastases [73, 79]. At present surgical resection of hepatic metastases is the well accepted method for curative treatment for this kind of cancer, if extrahepatic spread is excluded. But only 20 % of patients are candidates for resection according to clinical conditions like presence of lesions in both hepatic lobes or extrahepatic tumor spread or a poor clinical status [16, 18, 27, 29, 43, 51, 53, 56, 62, 63, 68]. Surgery is associated with a mortality rate of approximately 5% and actual studies show, that two-third of patients develop recurrences in the remaining liver part [21, 23, 26, 28, 70, 71]. So the development of alternative treatment methods is required, which are discribed in the chapters above.

Ultimate goal of the MR-guided LITT is defined by one hundred percent of local tumor control. There is no effect to the surrounding tissue and the MRI online thermometry allows an exact guidance of the interventional procedure. MRI provides unparalleled topographic accuracy due to its excellent soft tissue contrast and high spatial resolution. Therefore the early detection of local complications like bleeding and hemorrhage and treatment effects like coagulative necrosis is possible. Dynamic contrast-enhanced MR-images represent the superior parameter for the evaluation of the treated lesions especially for the short-and long term evaluation [12, 17, 30, 49, 57, 64, 74].

In the literature Stangl followed up 1099 consecutive patients with colorectal liver metastases [68]. 566 of whom (51,1 %) received no treatment for their hepatic metastases; 340 (31%) underwent hepatic resection; 123 (11,2 %) received regional chemotherapy; and 70 (6,4 %) received systemic chemotherapy. Thirty-four patients died within 30 days as a result either of postoperative complications or advanced disease; 48 were excluded, because they developed a second primary cancer. After hepatic resection, 60 % of all patients survived five years (median survival 30 month). In patients who underwent regional or systemic chemotherapy, the median survival was 12,7 and 11,1 month, respectively. In the untreated group, 31,3 % of the patients were alive at one year, 7,9 % at two years, 2,6 % at three years and 0,9 % at four years. Considering these data our results are comparable to those of surgery.

Lack of perioperative mortality, low rate of side effects combined with an outpatient management are responsible for high patient tolerance.

Patients with irresectable liver tumors need a multi-modal therapy concept in palliative intention, while preserving a good quality of life. LITT alone or combined with systemic or locoregional chemotherapy, transarterial chemoembolisation and surgical resection does improve local tumor control and the tumor-free survival in patients with several primary tumors.

Conclusions

The percutaneous MR-guided interstitial laser induced thermotherapy (LITT) of malignant liver tumours is a reliable treatment concept for destroying tumours palliatively and is also potentially curative. Here the treatment concept must be differentiated according to the underlying histology: for hepatocellular carcinoma a local ablative procedure instead of or in combination with the local alcohol installation (PEI) or the transarterial chemoembolisation (TACE) can be used. According to the latest studies local procedures such as radio-frequency ablation and laser therapy (LITT) permit reliable local tumour control in the case of HCC.

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 extrahepatic manifestations can be justified clinically. Magnet resonance tomography proves to be an indispensable tool for monitoring and controlling percutaneous LITT. MRT is used both for monitoring and controlling complete tumour removal and also for the follow-up process and is proven to be the optimum examination procedure in assessing very small tumour manifestations.

References

1. Adson MA, Heerden van J, Adson MH, Wagner JS, Ilstrup DM (1984) Resection of Hepatic Metastases From Colorectal Cancer. Arch Surg 119:647-651.
2. Amin Z, Bown SG, Lees WR (1993) Local treatment of colorectal liver metastases: a comparison of interstitial laser photocoagulation (ILP) and percutaneous alcohol injection (PAI). Clin-Radiol 48(3):166-71.
3. Anzai Y, Desalles AA, Black KL, Sinha S, Farahani K, Behnke EA, Castro DJ, Lufkin RB (1993) Interventional MR imaging. Radiographics 13(4):897-904.
4. Bozzetti F, Doci R, Bignami P, Morabito A, Gennari L (1987) Patterns of Failure following Surgical Resection of Colorectal Cancer Liver Metastases. Ann Surg 205(3):264-269.
5. Brewer WH, Austin RS, Capps GW, Neifeld JP (1998) Intraoperative Monitoring and Postoperative Imaging of Hepatic Cryosurgery. Seminars in Surgical Oncology 14:129-155.
6. Butler J, Attiyeh FF, Daly JM (1986) Hepatic resection for metastases of the colon and rectum. Surg-Gynecol-Obstet 162(2):109-13.
7. Cady B, Stone MD, McDermott WV, Jenkins RL, Bothe A, Lavin PT, Lovett EJ, Steele G (1992) Technical and Biological Factors in Disease-Free Survival After Hepatic Resection for Colorectal Cancer Metastases. Arch Surg 127:561-569.
8. Charnley RM, Doran J, Morris DL (1989) Cryotherapy for liver metastases: a new approach (comment in: Br J Surg 1990; 77: 354). Br J Surg 76:1040.
9. Cline HE, Hynynen K, Hardy CJ, Watkins RD, Schenck JF, Jolesz FA (1994) MR temperature mapping of focused ultrasound surgery. Magn-Reson-Med 31(6):628-36.
10. Cline HE, Hynynen K, Watkins RD, Adams WJ, Schenck JF, Ettinger RH, Freund WR, Vetro JP, Jolesz FA (1995) Focused US system for MR imaging-guided tumor ablation. Radiology 194(3):731-7.
11. Cline HE, Schenck JF, Hynynen K, Watkins RD, Souza SP, Jolesz FA (1992) MR-guided focused ultrasound surgery. J-Comput-Assist-Tomogr 16(6):956-65.
12. Cline HE, Schenck JF, Watkins RD, Hynynen K, Jolesz FA (1993) Magnetic resonance-guided thermal surgery. Magn-Reson-Med 30(1):98-106.

13. Doci R, Gennari L, Bignami P, Montalto F, Bozzetti F (1991) One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostics determinants. Br. J. Surg. 78:797-801.

14. Ekberg H, Tranberg K-G, Andersson R, Hägerstrand I, Ranstam J, Bengmark S (1986) Determinants of survival in liver resection for colorectal secondaries. Br. J. Surg. 73:727-731.

15. Feifel G, Schüdder G, Pistorius G (1999) Kryochirurgie - Renaissance oder echter Fortschritt ? Der Chirurg 70:154-159.

16. Fortner JG, Silva JS, Golbey RG, Cox EB, MaClean BJ (1984) Multivariate Analysis of a Personal Series of 247 Consecutive Patients with Liver Metastases from Colorectal Cancer. Ann Surg 199:306-315.

17. Fried MP, Morrison PR, Hushek SG, Kernahan GA, Jolesz FA (1996) Dynamic T1-weighted magnetic resonance imaging of interstitial laser photocoagulation in the liver: observations on in vivo temperature sensitivity. Lasers Surg Med 18(4):410-9.

18. Gayowski TJ, Iwatsuki S, Madariaga JR (1994) Experience in hepatic resection for metastatic colorectal cancer: Analysis of clinical and pathological risk factors. Surgery 116:703-10.

19. Gewiese B, Beuthan J, Fobbe F, Stiller D, Muller G, Bose Landgraf J, Wolf KJ, Deimling M (1994) Magnetic resonance imaging-controlled laser-induced interstitial thermotherapy. Invest-Radiol 29(3):345-51.

20. Goldberg SN, Gazelle GS, Solbiati L, Livraghi T, Tanabe K, Hahn PF, Mueller PR (1998) Ablation of liver tumors using percutaneous RF therapy. AJR 170:1023-1029.

21. Griffith KD, Sugarbaker PH, Chang AE (1990) Repeat hepatic resections for colorectal metastases. surgery 107:101-4.

22. Harned RKn, Chezmar JL, Nelson RC (1994) Recurrent tumor after resection of hepatic metastases from colorectal carcinoma: location and time of discovery as determined by CT. AJR-Am-J-Roentgenol 163(1):93-7.

23. Herfarth C, Heuschen UA, Lamade W, Lehnert T, Otto G (1995) Rezidiv-Resektionen an der Leber bei primären und sekundären Lebermalignomen. Chirurg 66:949-958.

24. Hill CR (1994) Optimum acoustic frequency for focused ultrasound surgery. Ultrasound-Med-Biol. 20(3):271-7.

25. Hohenberger P, Schlag P, Schwarz V, Herfarth C (1988) Leberresektion bei Patienten mit Metastasen colorektaler Carcinome. Ergebnisse und prognostische Faktoren. Chirurg 59:410-417.

26. Holm A, Bradley E, Aldrete JS (1989) Hepatic Resection of Metastases from Colorectal Carcinoma. Morbidity, Mortality and Pattern of Recurrence. Ann Surg 209(4):428-434.

27. Hughes KS, Simon R, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG, Maclean BJ, Foster JH, Daly JM, Fitzherbert D, Sugarbaker PH, al. e (1988) Resection of the liver for colorectal carcinoma metastases: A multi-institutional study of indications for resections. surgery 103(3):278-288.

28. Hughes KS, Simon R, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG, Maclean BJ, Foster JH, Daly JM, Fitzherbert D, Sugarbaker PH, Iwatsuki S, Starzl T, Ramming PH, Longmire WP, O'Toole K, Petrelli NJ, Herrera L, Cady B, McDermott W, Nims T, Enker WE, Coppa GF, Blumgart LH, Bradpiece H, Urist M, Aldrete JS, Schlag P, Hohenberger P, Steele G, Hodgson WJ, Hardy TG, Harbora D, McPherson A, Lim C, Dillon D, Happ R, Ripepi P, Villella E, Rossi RL, Remine SG, Oster M, Connolly DP, Abrams J, AlJurf A, Hobbs KEF, Li MKW, Howard T, Lee E (1986) Resection of the liver for colorectal carcinoma metastases: A multi-institutional study of pattern of recurrence. Surgery 100(2):278-284.

29. Iwatsuki S, Shaw BW, Starzl TE (1983) Experience with 150 Liver Resections. Ann Surg 197(3):247-253.

30. Jolesz FA, Bleier AR, Jakab P, Ruenzel PW, Huttl K, Jako GJ (1988) MR imaging of laser-tissue interactions. Radiology 168(1):249-53.

31. Jolesz FA, Blumenfeld SM (1994) Interventional use of magnetic resonance imaging. Magn-Reson-Q 10(2):85-96.

32. Kahn T, Bettag M, Ulrich F, Schwarzmaier HJ, Schober R, Furst G, Modder U (1994) MRI-guided laser-induced interstitial thermotherapy of cerebral neoplasms. J-Comput-Assist-Tomogr 18(4):519-32.

33. Lee FT, Mahavi DM, Chosy SG, Onik GM, Wong WS, Littrup PJ, Scanlan KA (1997) Hepatic Cryosurgery with Intraoperative US Guidance. Radiology 202:624-632.

34. Lee TH, Anzai Y, Lufkin RB (1993) Magnetic resonance imaging-guided needle biopsy of head and neck lesions. West-J-Med 159(1):69.

35. Lencioni R, Goletti O, Armillotta N, Paolicchi A, Moretti M, Cioni D, Donati F, Cicorelli A, Ricci S, Carrai M, Conte PF, Cavina E, Bartolozzi C (1998) Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. Eur. Radiol. 8:1205-1211.

36. Lewin JS, Connell CF, Duerk JL, Chung Y, Clampitt ME, Spisak J, Gazelle GS, Haaga JR (1998) Interactive MRI-Guided Radiofrequency Interstitial Thermal Ablation of Abdominal Tumors: Clinical Trial for Evaluation of Safaty and Feasibility. JMRI 8:40-47.

37. Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, Pompili M, Brunello F, Lazzaroni S, Torzilli G, et al. (1995) Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 197(1):101-8.

38. Livraghi T, Goldberg N, Lazzaroni S, Meloni B, Solbiati L, Gazelle GS (1999) Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology 210:655-661.

39. Livraghi T, Goldberg S, . N., Monti F, Bizzini A, Lazzaroni S, Meloni F, Pellicano S, Solbiati L, Gazelle GS (1997) Saline-enhanced Radio-Frequency Tissue Ablation in the Treatment of Liver Metastases. Radiology 202:205-210.

40. Livraghi T, Lazzaroni S, Meloni F, Torzilli G, Vettori C (1995) Intralesional ethanol in the treatment of unresectable liver cancer. World-J-Surg 19(6):801-6.

41. Lopez RL, Pan SH, Lois JF, McMonicle ME, Hoffmann AL, Sher LS, Lugo D, Makowa L (1997) Transarterial chemoembolization is a safe treatment for unresectable hepatic malignancies. Am Surg 63:923-926.

42. Lorentzen T (1996) A cooled needle electrode for radiofrequency tissue ablation: thermodynamic aspects of improved performance compared with conventional needle design. Acad-Radiol 3(7):556-63.

43. Lorenz M, Rossion I (1995) Adjuvante und palliative regionale Therapie von Lebermetastasen kolorektaler Tumoren. Dtsch. med. Wschr. 120:690-697.

44. Lorenz M, Staib-Sebler E, Rossion I, Koch B, Gog C, Encke A (1995) Ergebnisse der Resektion und adjuvanten Therapie von Lebermetastasen kolorektaler Primärtumoren -eine Literaturübersicht. Zentralbl. Chir. 120:769-779.

45. Lufkin RB, Robinson JD, Castro DJ, Jabour BA, Duckwiler G, Layfield LJ, Hanafee WN (1990) Interventional magnetic resonance imaging in the head and neck. Top-Magn-Reson-Imaging 2(4):76-80.

46. Martin M, Tarara D, Wu YM, Ukah F, Fabrega A, Corwin C, Lange E, Mitros F (1996) Intrahepatic arterial chemoembolization for hepatocellular carcinoma and metastatic neuroendocrine tumors in the era of liver transplantation. Am Surg 62:724-732.

47. Masters A (1990) Cryotherapy for liver metastases [letter; comment]. Br-J-Surg 77(3):354.

48. Masters A, Steger AC, Lees WR, Walmsley KM, Bown SG (1992) Interstitial laser hyperthermia: a new approach for treating liver metastases. Br-J-Cancer 66(3):518-22.

49. Matsumoto R, Oshio K, Jolesz FA (1992) Monitoring of laser and freezing-induced ablation in the liver with T1-weighted MR imaging. J-Magn-Reson-Imaging 2(5):555-62.

50. McDannold N, Hynynen K, Wolf D, Wolf G, Jolesz F (1998) MRI Evaluation of Thermal Ablation of Tumors with Focused Ultrasound. JMRI 8:91-100.

51. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D (1996) 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 77(7):1254-62.

52. Nordlinger B, Vaillant J-C. Repeat resections for recurrent colorectal liver metastases. Boston: Kluwer Academic Publishers, p. 57-61, 1994.

53. Ohlsson B, Stenraum U, Tranberg KG (1998) Resection of colorectal liver metastases: 25 year experience. World J Surg 22:268.

54. Onik GM, Atkinson D, Zemel R, Weaver ML (1993) Cryosurgery of Liver Cancer. Seminars in Surgical Oncology 9:309-317.

55. Ravikumar TS, Kane R, Cady B, Jenkins R, Clouse M, Steele G (1991) A 5-Year Study of Cryosurgery in the Treatment of Liver Tumors. Arch Surg 126:1520-1524.

56. Ringe B, Bechstein WO, Raab R, Meyer H-J, Pichlmayr R (1990) Leberresektion bei 175 Patienten mit colorektalen Metastasen. Chirurg 61:272-279.

57. Roberts HRS, Paley M, Sams VR, Wilkinson ID, Lees WR, Hall-Graggs MA, Bown SG (1997) Magnetic Resonance Imaging control of laser destruction of hepatic metastases: correlation with post-operative helical CT. Min Invas Ther & Allied Technol 6:53-64.

58. Rossi S, Di Stasi M, Buscarini E, Quaretti P, Garbagnati F, Squassante L, Paties C, Silverman DE, Buscarini L (1996) Percutaneous RF Interstitial Thermal Ablation in the Treatment of Hepatic Cancer. AJR 167:759-768.

59. Sanz-Altamira PM, Spence LD, Hubermann LS, Posner MR, Steele Gj, Perry LJ, Stuart KE (1997) Selective chemoembolization in the management of hepatic metastases in refractory colorectal carcinoma: a phase II trial. Dis Colon Rectum 40:770-775.

60. Sarantou T, Bilchik A, Ramming KP (1998) Complications of Hepatic Cryosurgery. Seminars in Surgical Oncology 14:156-162.

61. Scheele J, Altendorf-Hofmann A, Stangl R, Schmidt K (1996) Surgical Resection of Colorectal Liver Metastases: Gold Standard for Solitary and Completely Resectable Lesions. Swiss Surg Suppl. 4:4-17.

62. Scheele J, Stangl R, Altendorf Hofmann A, Gall FP (1991) Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery 110(1):13-29.

63. Schlag P, Hohenberger P, Herfarth C (1990) Resection of Liver Metastases in colorectal cancer- competitive analysis of treatment results in synchronous versus metachronous metastases. European Journal of Surgical Oncology 16:360-365.

64. Schwarzmaier HJ, Kahn T (1995) Magnetic resonance imaging of microwave induced tissue heating. Magn-Reson-Med 33(5):729-31.

65. Shiina S, Tagawa K, Unama T, Fujino H, Uta Y, Niwa Y, Hata Y, Komatsu Y, Shiraton Y, Terano A, Sugimoto T (1990) Percutaneous Ethanol Injection Therapy of Hepatocellular Carcinoma: Analysis of 77 Patients. AJR 155:1221-1226.

66. Sironi S, De Cobelli F, Livraghi T, Villa G, Zanello A, Taccagni G, DelMaschio A (1994) Small hepatocellular carcinoma treated with percutaneous ethanol injection: unenhanced and gadolinium-enhanced MR imaging follow-up. Radiology 192(2):407-12.

67. Solbiati L, Goldberg SN, Ierace T, Livraghi T, Meloni F, Dellanoce M, Sironi S, Gazelle SG (1997) Hepatic metastases: Percoutaneous Radio-Frequency Ablation with Cooled-Tip Electrodes. Radiology 205(2):367-373.

68. Stangl R, Altendorf Hofmann A, Charnley RM, Scheele J (1994) Factors influencing the natural history of colorectal liver metastases. Lancet 343(8910):1405-10.

69. Steele G, Jr. (1994) Cryoablation in hepatic surgery. Semin-Liver-Dis 14(2):120-5.

70. Steele G, Osteen RT, Wilson RE, Brooks DC, Mayer RJ, Zamcheck N, Ravikumar TS (1984) Patterns of failure after surgical cure of large liver tumors. American Journal of Surgery 147:554-559.

71. Sugihara K, Hojo K, Moriya Y, Yamasaki S, Kosuge T, Takayama T (1993) Pattern of recurrence after hepatic resection for colorectal metastases. Br-J-Surg 80(8):1032-5.

72. van Hillegersberg R (1997) Fundamentals of Laser Surgery. Eur J Surg 163:3-12.

73. Viadana E, Bross IDJ, Pickren JW (1978) The metastatic spread of cancers of the digestive system in man. Oncology 35:114-126.

74. Vogl TJ, Mack MG, Straub R, Müller P, Eichler K, Engelmann K, Felix R (1998) MR-guided laser-induced thermotherapy of malignant liver lesions: technique and results. Onkologie 21:412-419.

75. Vogl TJ, Mack MG, Straub R, Roggan A, Felix R (1997) Magnetic Resonance Imaging - guided abdominal interventional radiology: laser-induced thermotherapy of liver metastses. Endoscopy 29:577-583.

76. Vogl TJ, Muller PK, Hammerstingl R, Weinhold N, Mack MG, Philipp C, Deimling M, Beuthan J, Pegios W, Riess H, et al. (1995) Malignant liver tumors treated with MR imaging-guided laser-induced thermotherapy: technique and prospective results. Radiology 196(1):257-65.

77. Vogl T. J., M. G. Mack, R. Straub, A. Roggan, R. Felix. Percutaneous MRI-guided laser-induced thermotherapy for hepatic metastases for colorectal cancer. The Lancet 1997; 350: 29

78. Vykhodtseva NI, Hynynen K, Damianou C (1994) Puls duration and peak intensity during focused ultrasound surgery: theroretical and experimental effects in rabbit brain in vivo. Ultrasound-Med-Biol. 20(9):987-1000.

79. Weaver ML, Ashton JG, Zemel R (1998) Treatment of Colorectal Liver Metastases by Cryotherapy. Semin. Surg. Oncol. 14:163-170.

80. Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, Fenoglio Preiser CM, Napier J, Horne CH, Lopez MJ, et al. (1986) Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. J-Pathol 150(3):195-203.

81. Wingo PA, Tong T, Bolden S (1995) Cancer Statistics, 1995. CA Cancer J Clin 45(1):8-30.

82. Yeh KA, Fortunato L, Hoffmann JP, Eisenberg BL (1997) Cryosurgical Ablation of Hepatic Metastases from Colorectal Carcinomas. The American Surgeon 63(1):63-67.

83. Zhou X-D, Tang Z-Y, Yu Y-Q, Weng J-M, Ma Z-C, Zhang B-H, Zheng Y-X (1993) The role of cryosurgery in the treatment of hepatic cancer: a report of 113 cases. J. Cancer Res Clin Oncol 120:100-102.

Figures

Fig.. 1 a

The mean survival time in the total population of patients with liver metastases is 48.0 months (95% confidence interval: 44.4 – 52.8 months).

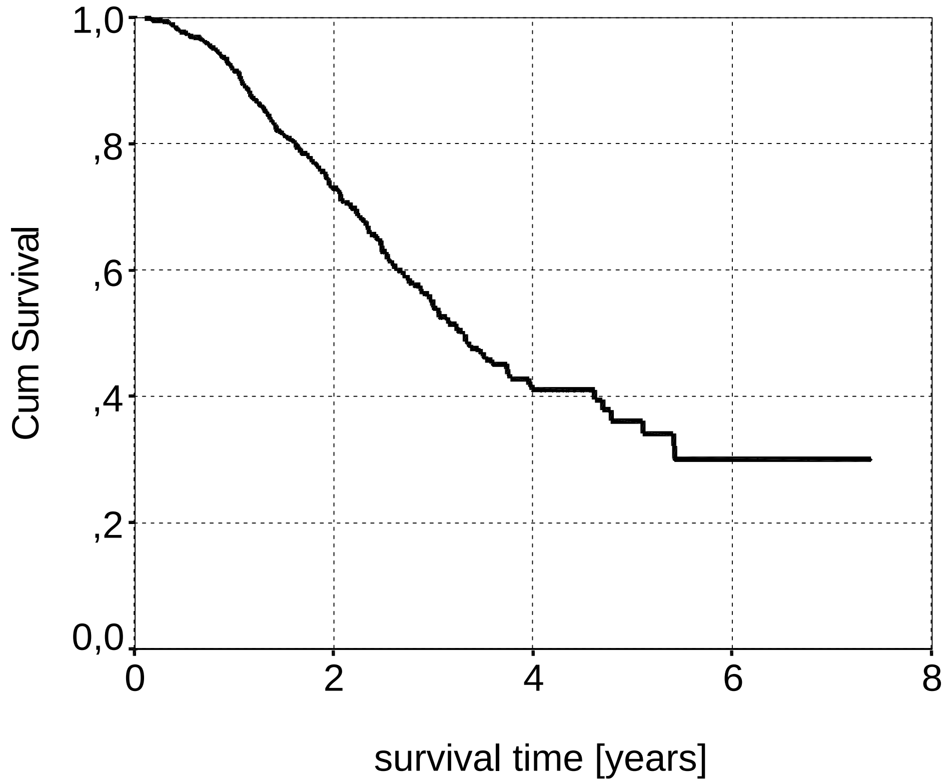

Fig.. 1b

For patients with liver metastases from a colorectal carcinoma the mean survival time is 41.8 months (95% confidence interval 37.3 – 46.4 months).

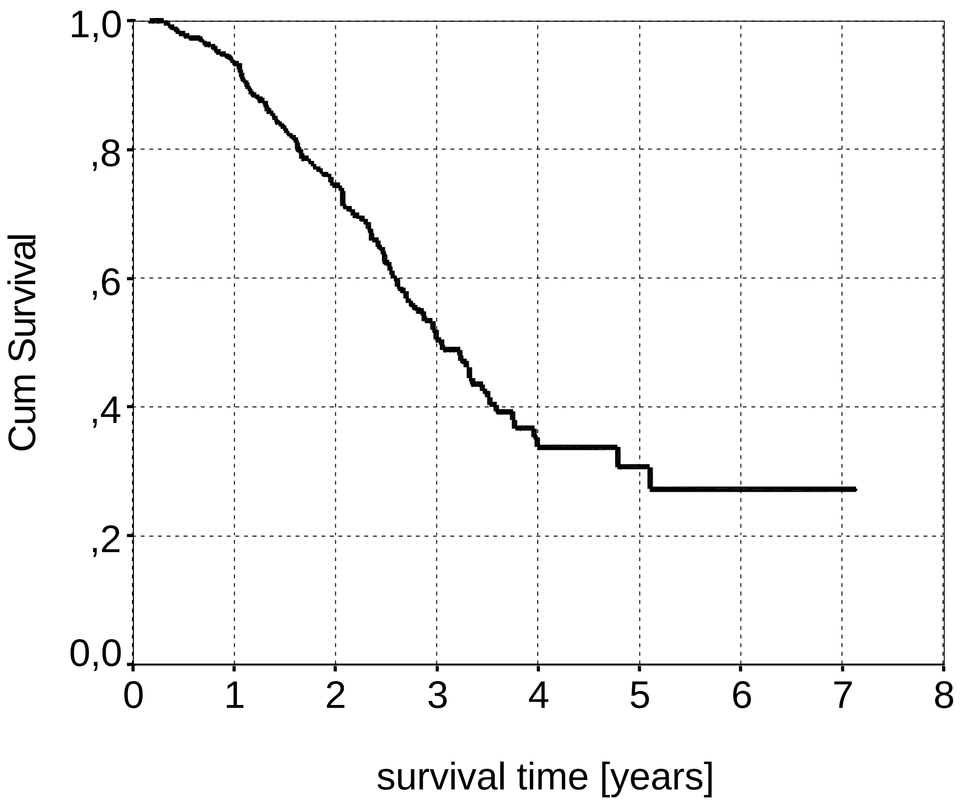

Fig.. 3a

35-year old female patient with liver metastasis from a colorectal carcinoma (initial tumour stage pT3, N1, M1). The T1-weighted thermosensitive gradient echo sequence in axial tomographic orientation shows the metastasis in liver segment 8 before starting the laser

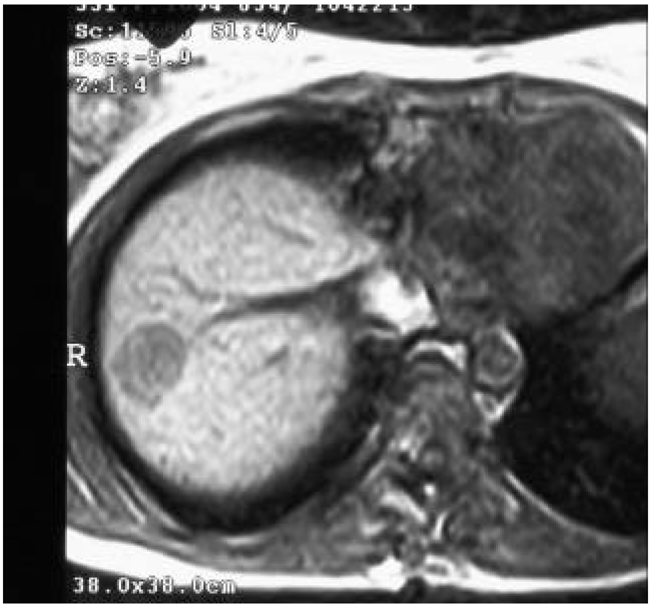

Fig.. 3b

T1-weighted thermosensitive gradient echo sequence in axial tomographic orientation in the 1st minute. Clear drop in the signal intensity in the heated area.

Fig.. 3c

T1-weighted thermosensitive gradient echo sequence in sagittal tomographic orientation in the 3rd minute. Clear drop in the signal intensity in the heated area.

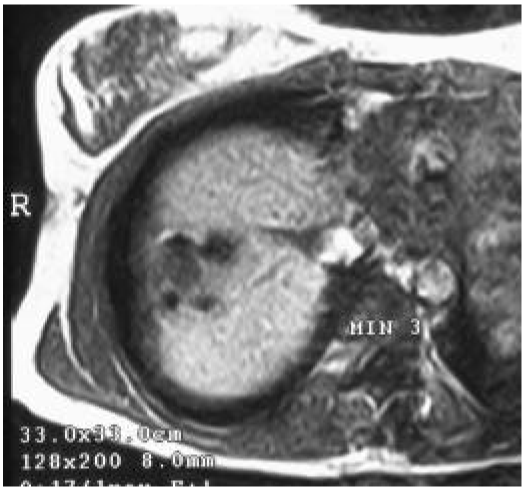

Fig.. 3d

T1-weighted thermosensitive gradient echo sequence in sagittal tomographic orientation in the 7th minute. Clear drop in the signal intensity in the heated area.

Fig.. 3e

T1-weighted thermosensitive gradient echo sequence in sagittal tomographic orientation in the 16th minute. Clear drop in the signal intensity in the heated area.

Fig.. 3f

T1-weighted thermosensitive gradient echo sequence in sagittal tomographic orientation in the 20th minute. Clear drop in the signal intensity in the heated area.

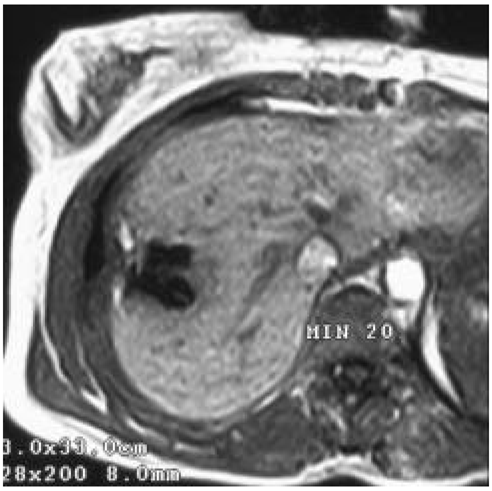

Fig.. 3g

T1-weighted spin echo sequence in axial tomographic orientation after the administration of gadolinium-DTPA (0.1 ml per kg body weight). Sharp demarcation of the LITT-induced necrosis with a safety margin surrounding the lesion.