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ORIGINAL ARTICLES

Magnetic resonance-guided focused ultrasound surgery (MRgFUS). Four ablation treatments of a single canine hepatocellular adenoma

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Abstract

Background. Canine hepatocellular adenomas are benign, well-differentiated, primary hepatic tumors. Surgical resection is technically demanding and is considered a major procedure with relatively high morbidity rates. Magnetic resonance-guided focused ultrasound surgery (MRgFUS) uses focused ultrasonic energy to non-invasively create a heat-coagulated lesion deep within the body. This effect can be achieved in a controlled, accurate manner. The aim of this study was to evaluate the safety, accuracy and efficacy of non-invasive focal ablation of tissue volumes of a canine benign liver tumour by consecutive MRgFUS sonications. *Materials and methods*. Four MRgFUS procedures were performed in a 10-year-old, male, mixed large breed dog (45 kg) under general anaesthesia. The exact location and volume of the ablated areas were planned on the MR images. Real-time MR imaging and temperature mapping enabled the immediate evaluation of the effect of each sonication. Different areas were chosen within the tumour. These volumes of tumoral tissue were ablated by multiple sonications. To allow accurate targeting and quality imaging, sonications were performed during 20–30 s of apnoea. Between the sonications the dog was normally ventilated. The dog was operated 21 days after the fourth ablative procedure. The tumour was resected and histopathologically examined. *Results*. The MRgFUS created necrosis with contiguous areas of complete tissue destruction within the liver tumour, in full accordance with the planning. A focal thermal injury to the cartilage of the right lower ribs was noted after the fourth treatment. This lesion became infected and was treated surgically. Ten months after the last treatment the dog is well and healthy. *Conclusions*. Focused ultrasound ablation of liver tumoral tissue with MR guidance under general anaesthesia and controlled apnoea is a safe and accurate treatment modality. Its main advantage is that it is a completely non-invasive image-guided treatment. The ablation of significant volumes of a highly vascular liver tumoral tissue was achieved. Such tissue can be ablated in a very accurate manner, exactly according to the pretreatment planning on the MR images. The MR imaging characteristics, including real-time temperature mapping, enable real-time control of every step of the ablation process. Mechanical ventilation with intermittent apnoea periods overcomes the problem of the respiratory movements of the liver. Care must be taken to avoid the passage of the ultrasound beam through energy-absorbing calcified tissue.

Key Words: *Hepatocellular adenoma, magnetic resonance-guided focused ultrasound surgery, treatment planning*

Introduction

Canine hepatocellular adenomas are benign, well-differentiated, primary hepatic tumours, most often diagnosed as an incidental finding. These tumours occur with a higher frequency than the malignant counterpart, and usually occur in dogs over 10 years of age. Grossly, adenomas appear well circumscribed and demarcated. They are usually single, may be quite large (up to 20 cm) and often exhibit a pedunculated attachment. Adenomas consist of a friable, highly vascular parenchyma, and rupture with subsequent haemoperitoneum may be the clinical presentation. Grossly and histologically, these tumours may be difficult to distinguish from nodular hyperplasia or

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even normal liver tissue. Histologically, encapsulation and compression of adjacent hepatic parenchyma are characteristic features. Complete surgical resection is curative but by the time of diagnosis high tumour burden may make this unachievable. The prognosis for respectable hepatocellular adenomas is good, and survival times of up to 2 years have been reported [1,2].

Liver tumours are among the most common tumours in human beings. Surgical removal is very often the only chance for cure, but only a small percentage is operable. Major liver surgery is technically a demanding and complicated procedure with high morbidity rates [3]. In the last few decades, liver surgery has changed dramatically, to a well understood, accurate, anatomical procedure with acceptable low rates of complications [4]. Minimally invasive ablative technologies such as ethanol injection, microwave, laser ablation, radiofrequency and cryoablation are being used primarily for non-resectable liver tumours, or as adjuvant palliative procedures. These technologies suffer the lack of real-time control of their efficacy [5–11]. The ablation of primary liver tumours by a non-real-time control, ultrasound-guided focused ultrasound has been reported recently [12]. The integration of focused ultrasound and magnetic resonance imaging resulted in a new prominent method of non-invasive surgery. By using this integrated delivery system, the surgeon can correctly localize tumours, optimally deliver acoustic energy ('sonicate'), monitor energy deposition in real time, and accurately control the deposited thermal dose within the entire volume of the tumour. This novel technology represents a potential useful treatment modality in liver surgery [13], and also in other surgical fields [13,14]. However, to deliver safe and effective treatment to the liver with magnetic resonance-guided focused ultrasound surgery (MRgFUS), the clinician has to overcome the problem of respiratory movement of the liver during energy delivery. Otherwise, the energy might not be delivered to the planned focused region, the energy might become unfocused, and the magnetic resonance (MR) system may be unable to provide quality thermal imaging.

This study aimed to evaluate the safety and accuracy of MRgFUS for the focal ablation of tumoral tissue within the liver, in a totally non-invasive manner, using general anaesthesia with intermittent short periods of apnoea.

Materials and methods

A 10-year-old, male, mixed large breed dog (45 kg) had been diagnosed at the Koret School of Veterinary Medicine Hospital to have a huge, asymptomatic, irresectable hepatocellular adenoma (Figure 1). Four separate MRgFUS procedures were performed during a period of 8 weeks, under general anaesthesia. The induction and maintenance were achieved by: i.v. fentanil 0.002 mg/kg/h, i.v. propofol 2 mg/kg/h and i.v. atracurium 0.5 mg/kg/h. The dog was intubated and kept under controlled, positive pressure, mechanical ventilation using an operating room portable ventilator (Ivent 201 v. 1.4, VersaMed Inc., Pearl River, NY 10965, USA), delivering a respiratory rate of 14/min, FiO_2 of 0.4, and PEEP of 7 cmH_2O. The ablation of each area within the tumour was created by the combined ablative focused thermal effect of several sonications. Sonications were performed with the MRgFUS system, using a phased array transducer of 208 elements (ExAblate 2000, InSightec, Tirat Hacarmel, Israel) and MR, Signa Twinspeed 1.5T (GEHC, USA).

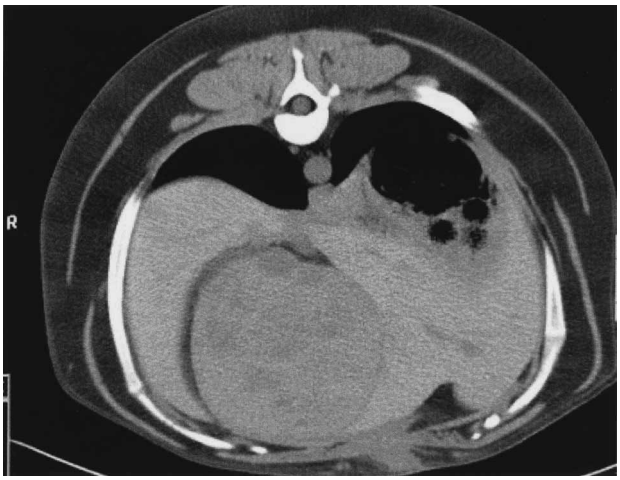

Figure 1. An axial CT image of the huge hepatocellular adenoma.

Areas within the huge tumour were defined as targets for ablation by the MRgFUS. These were outlined on the planning screen of a single coronal view of the MR image. In all the four treatments of this tumour, the treated volume was planned to create only one layer of adjacent sonications. The ablation planning software (ExAblate 2000, Version 4.1 InSightec) calculated the type and number of sonications required to completely destroy the defined region within the tumour. During each sonication, the energy of an ultrasound beam was focused at a small bean-shaped volume of tissue and was directed into the target for 5–12 s, heating the tissue to induce thermal coagulation. Each sonication was controlled in real time by the MR scanning and thermometry for anatomical accuracy and thermal efficiency. Once sonication was completed at one point, the transducer was automatically moved to the next treatment point and the process was repeated until the entire target tissue had been ablated. These MR images, taken during sonication, provided a diagnostic quality image of the target tissue and a quantitative, real-time temperature map overlay to confirm the therapeutic effect of the treatment.

The tumour areas chosen as targets for ablation varied in volume and were located in different aspects

of the tumour. These predefined areas within the tumour were each ablated by multiple sonications. The ablative focus of each sonication is jellybean-shaped and its dimensions can be controlled. In each treatment session we applied foci of different measurements: 0.32–0.64 cm in diameter and 2.2–3.4 cm in length. There was a 25% overlap between adjacent sonications. Each sonication was performed during apnoea. Apnoea periods always started at the end of inspirium and ranged from 22 to 30 s. Between phases of apnoea, controlled mechanical ventilation (CMV) periods of 90 s were applied. The dog was monitored continuously to evaluate its haemodynamic status and blood oxygen saturation. Arterial blood levels of gases, pH, electrolytes and blood counts were taken periodically during the procedure. At the end of the ablative procedures, MR scans including axial, sagittal, and coronal views with i.v. contrast agent 2.5 ml/kg (Dotarem, Guerbet, 95943 Roissy CdG cedex, France) were performed to evaluate the location, shape and volume of the ablated, non-perfused areas. We used sonications of different lengths – from 6.8 s to 16.2 s, along with different levels of power (207–284 W). The characteristics of the sonications in each treatment are summarized in Table I. An experienced veterinarian performed careful daily clinical follow-up after each procedure. Complete blood counts, electrolytes and liver function tests were performed daily. Follow-up by MRI was performed at the beginning of each treatment. Three weeks after the fourth treatment, the dog was operated by an experienced human liver surgeon. The entire peritoneal cavity, the liver and adjacent organs were inspected. The tumour was resected and pathologically examined.

Results

The procedure

The length of each sonication including the apnoea and the inter-apnoea ventilation period was almost 2 min. The total length of the anaesthesia was in the range of 125–215 min. No motion artifacts during apnoea interfered with the image quality. The liver returned to the same location between sonications. During sonications the liver was practically motionless, and the thermal imaging was adequate. The range of temperatures achieved in the ablated foci of each sonication was 60–82°C. A description of the characteristics of sonications given in each treatment is provided in Table I. The dog remained haemodynamically stable during and after all four treatment sessions. The dog was fully recovered from each treatment within 1 h after the termination of anaesthesia, and resumed eating and normal behaviour.

Complications

There was one post treatment complication event, which became evident after the fourth treatment. The ultrasound beam in its proximal pass zone created a localized thermal injury to the right costal margin in the mid-clavicular line. This area of thermal injury became infected and fistulated to the skin. The lesion was surgically treated and healed completely.

Blood tests

All blood tests taken during the procedures and the follow-up, including blood counts, electrolytes, creatinine, amylase, liver function tests and coagulation profile, were normal, except a moderate (up to four times the normal levels), transient elevation of liver transaminases (AST, ALT and GGT), observed during the first 3 days after the procedures. Alkaline phosphatase was also transiently elevated up to three times the normal limits, during 1 week after the procedures. Bilirubin remained within normal limits. Creatine phosphokinase (CPK) was transiently elevated up to two to four times the normal limits after each session.

Post treatment imaging

Immediate post treatment contrast-enhanced images showed areas of non-perfused tissue, which matched the thermal dose areas created during the procedures. According to the thermal dose mapping, each sonication created an elliptic focus of high temperature, 22–34 mm in length and 3.2–6.4 mm in diameter, fully compatible with their expected size. The non-perfused tissue in the post treatment contrast-enhanced imaging perfectly matched the pretreatment imaging plus the new ablated area of the same session. The changes in the volume of the tumour during the experiment and the volume of the non-perfused areas before and after treatments are shown in Table II. The volume of the tumour itself grew significantly during that period. The geometric pattern of the dose mapping which was created during each treatment perfectly overlapped the new non-perfused area (Figures 2 and 3). The anatomical arrangements of the necrotic areas that were observed in the specimen were in full accordance with the post treatment contrast imaging done immediately after the fourth procedure.

Pathology

The tumour was completely resected 21 days after the fourth treatment and 118 days after the first treatment. The resected tumor was histopathologically examined and revealed a well-differentiated hepatocellular adenoma, with tumour growth in large cellular aggregates and sheets and interspersed bun-

Table I. Characteristics of sonications in each treatment.

Number of sonications	Average* power (W)	Average* duration (s)	Average* energy (J)	Planned depth (mm)	Average* temperature of sonicated volume (°C)	Average* tissue volume ablated per sonication (ml)
Treatment no. 1						
35	210.1	16.2	3425.3	65.0	66.0	0.7
Treatment no.2						
5	207.2	6.8	1330.2	55.0	62.7	0.3
13	251.6	9.1	1982.0	68.0	60.0	0.2
9	284.2	8.2	2335.9	47.0	80.0	0.9
Treatment no.3						
50	264.4	9.3	2450.6	58.0	69.7	0.8
Treatment no. 4						
39	220.4	8.9	1991.6	47	82.6	0.6

*Average data are per sonication.

dles of fibrous tissue, some with entrapped haemosiderin-laden macrophages. Large zones of necrosis were found within the tumour (Figure 4). Intracellular details were lost – typical of coagulation necrosis (Figure 5). Complete destruction of the tumoral tissue appeared adjacent to major blood vessels of the tumour, which were included in the treatment area, indicating that the entire tumoral tissue surrounding these vessels had been completely ablated.

Discussion

Focused ultrasound thermal ablation has been known for many years [15]. The lack of real-time imaging control and tissue thermometry has made this technology very inaccurate. The actual location of the beam focus could be roughly predicted. Real-time verification of the result in terms of tissue temperature and perfusion could not be achieved. A new combined technology of focused ultrasound with MRI was presented by Jolesz and Hynynen [14,16,17]. Several clinical reports were published regarding the ablation of breast tumours and uterine fibroids [17–19]. In the past, liver tissue and liver tumours have been treated with FUS, both in animal studies and clinical trials. These trials proved the ability of FUS to create irreversible sharply demarcated homogeneous coagulative necrosis. FUS in all these studies was performed with partial imaging guidance of diagnostic US or with no imaging at all, without temperature monitoring, and no real-time control or feedback regarding the deposited thermal dose [20–25]. Wu et al. recently published their experience of ablating primary liver tumors with ultrasound-guided high intensity focused ultrasound (HIFU) [12]. The added value of MRI guidance to the process of focused ultrasound ablation deserves an elaboration. At the beginning of every MRI-guided FUS treatment, it is usual practice to verify the accuracy of the system by applying an experimental diminished power sonication. Very often the thermometry of the MRI guidance shows deviation of the foci from their predicted location, then an adjustment of the system to the specific parameters of that treatment is performed. The non-MR-guided HIFU is less accurate, and the efficacy of the treatment only becomes evident during the clinical follow-up. For many patients, the authors [12] used several sessions of transcatheter arterial chemoembolization, including 10–20 ml of iodinized oil, 2–4 weeks before HIFU treatment in order to decrease tumour blood flow and increase the energy deposition in the target region. Fourteen patients who had partial treatment in the first session, as was proved in the follow-up imaging studies, had some ribs resected to enable an 'acoustic window' for further HIFU treatment. In some patients, the intraprocedural ultrasound showed increased grey-scale changes in the treated area. These changes became less evident and sometimes disappeared within a few minutes. Obviously these changes are not used as an integral part of the treatment process. Follow-up imaging (Doppler ultrasound, CT or MRI studies) was performed 3–6 months after the procedure; these studies could assess the combined late effect of the different treatment modalities that were used on these patients. Actually there was no real-time temperature mapping, nor imaging feedback that could be used during the treatment in order to change the treatment parameters and achieve more accurate results. MRgFUS, on the other hand, allows online monitoring of the energy deposition and temperature changes of the induced lesion creation [16,26]. The deposited dose is defined as the tissue volume that has been exposed to critical ablative temperature during the sonications (Table I). The critical thermal dose in terms of tissue temperature and length of exposure was described by Sapareto and Dewey in 1984 [26]. They arbitrarily chose a reference temperature of 43°C to convert all thermal exposures to equivalent length of time, to determine its prognostic ability. The

Table II. Volumes of viable and non-perfused tumoral tissue.

Treatment no.	Days from first treatment	Total volume of tumour (ml)	Non-perfused volume before treatment (ml)	Non-perfused volume after treatment (ml)	Viable tumoral tissue (ml)
1	0	735	0	54	681
2	21	937	54	214	723
3	69	949	291	322	627
4	118	1093	199	234	859

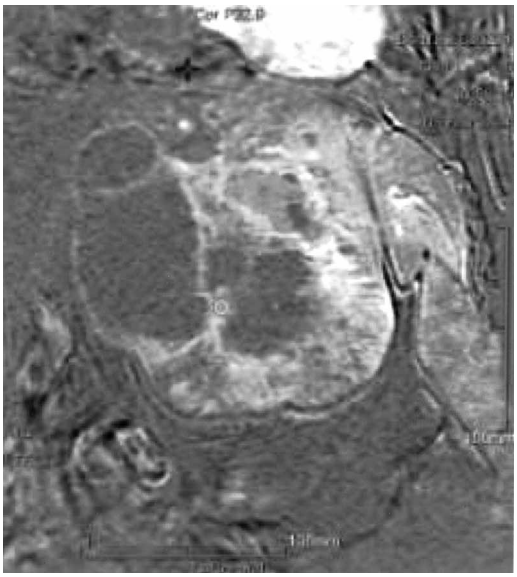

Figure 2. Third liver treatment. Blue coloration shows post treatment accumulated dose mapping.

temperature mapping by MRI enabled us to evaluate the average tissue volume that was ablated per sonication. We prefer to describe this ability as a 'closed circle' ablation, with real-time feedback and control over the expected results. The ablative thermal energy in FUS is deposited during a few seconds only (6–16 s). This relatively rapid and steep gradient of tissue temperature in comparison to other thermal ablation modalities is less dependent on the specific blood perfusion parameters. Sonication, as performed by the MRgFUS technique, achieves ablation of a predetermined area of tissue with a precision of <1 mm [13]. Our present study shows that a relatively large number of consecutive sonications may be performed safely. We have thermally ablated relatively small volumes of the tumour, while at the same time the tumour grew further and expanded in volume (Table II). In the future, to achieve the complete ablation of such huge tumours, the pace of treatment should be increased. By overlapping the sonication areas, by treating multiple layers with overlap along the long axis of the sonication, taking into account their spindle shape and the thin margin of incompletely ablated tissue, larger volumes of tumoral tissue may be ablated. In all four sessions of treatment, we used only one (coronal) layer of sonications. There was no vertical overlap between sonication foci, along the long axis of the focus. The spherical nature of liver tumours and the definite need in the future for complete tumoral ablation, will dictate the combined ablation of a few such overlapping layers, each layer consisting of several horizontally overlapping single sonications. In this study we achieved complete tissue destruction within each treated volume, using 26.5% of horizontal overlap (Figures 4 and 5). The optimal horizontal and vertical overlap percentage, both between adjacent sonica-

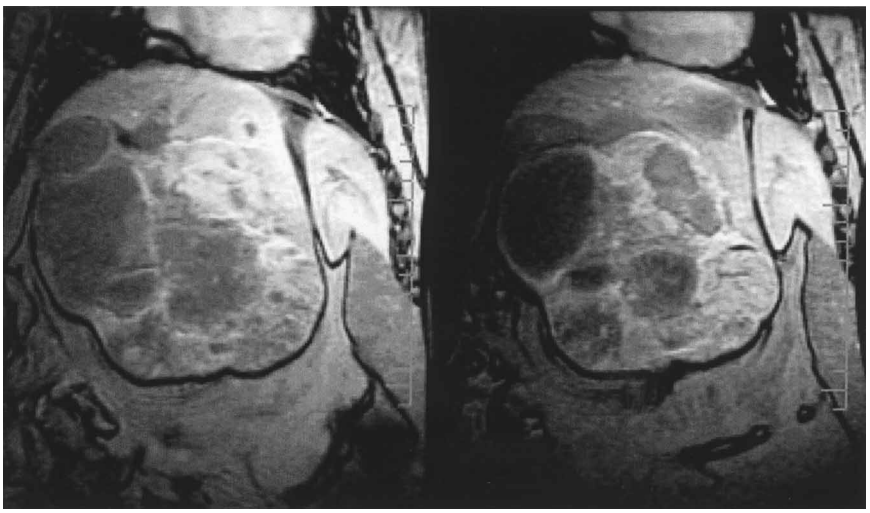

Figure 3. Before and after the third liver treatment; T1-weighted contrast-enhanced images. The blue area that appears in Figure 2 is viable on the pretreatment contrast images (left) and non-perfused on the post treatment images (right).

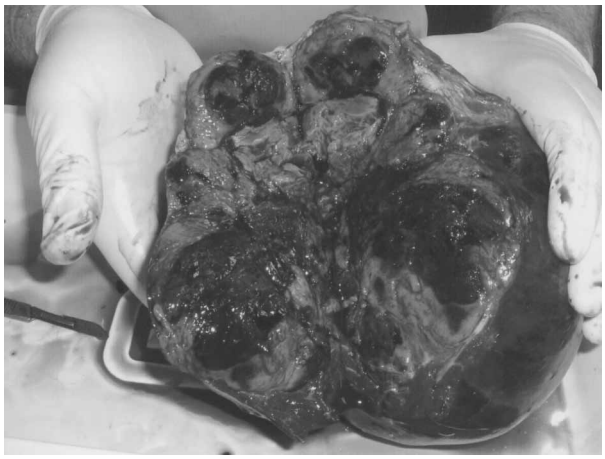

Figure 4. A macroscopic view of the resected hepatocellular adenoma, cut along its long axis, demonstrating the thermally ablated necrotic areas within the tumour.

tions and between coronal layers, is yet to be explored in further experiments.

To properly achieve a continuity of ablated foci of sonications, the tissue being treated should be immobile. Mechanical ventilation with intermittent apnoea periods overcame this problem of the respiratory movement of the liver during sonication. The training of awake patients to hold their breath during sonications in FUS liver tumours has been described [24]. These treatments were performed under partial US guidance only. There was no imaging during the sonication itself. MR thermometry is motion sensitive and in our study the MRgFUS requires general anaesthesia with intermittent apnoea ventilation. Future developments in technology may enable MRgFUS without general anaesthesia. This may help to shorten the length of treatment, and hence enable the ablation of larger tumours, like this hepatocellular adenoma. Effort should be directed at trying to substantially shorten the treatment. As observed in previous studies, an intermediate zone of incomplete tissue destruction is present around the margins of the necrotic foci. The presence of these margins of incomplete destruction must be taken into account when planning the MRgFUS treatment of a malignant lesion, by including wider margins of healthy tissue within the ablated area.

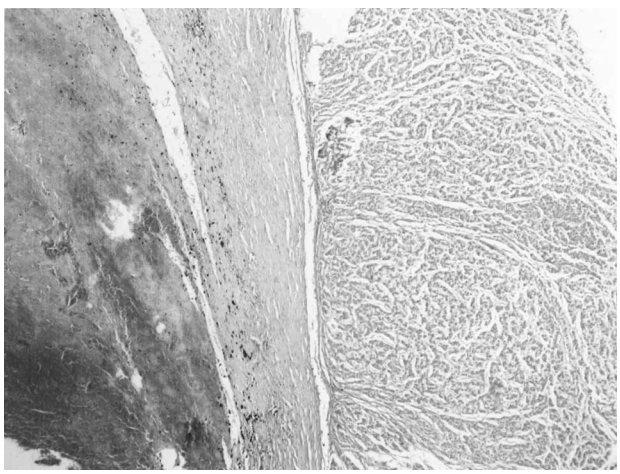

Figure 5. Sharp histological demarcation of the necrotic tissue (on the left), ablated in the first session.

When applying MRgFUS to tumoral tissue, it should be expected that liver tumours may present different tissue parameters like neovascularity and parenchymal heterogeneity, which could influence the MRgFUS efficacy and impose different sonication parameters. Special attention must be paid to preventing the ultrasound beam from aiming at bony or calcified tissue, because of the very high rate of energy absorbance in such tissue. The complication of fistulating osteomyelitis of the right lower costal margin could have been prevented or at least diagnosed earlier if the higher levels of CPK after the treatment had been interpreted correctly.

Nevertheless, the present study indicates that MRgFUS under general anaesthesia may become a valuable, safe and accurate addendum to the armamentarium of therapeutic techniques for the ablation of liver lesions. Being a non-invasive procedure, it has a definitive advantage over all other invasive and minimally invasive techniques. Further studies are needed to validate the safety and efficacy of this technology in the treatment of benign and malignant liver tumours.

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References

[1] Liptak JM, Dernell WS, Withrow SJ. Liver tumors in cats and dogs. Compend Contin Educ Pract Vet 2004;26:50–6.
[2] Hammer AS, Sikkema DA. Hepatic neoplasia in the dog and cat. Vet Clin North Am Small Anim Pract 1995;25:419–35.
[3] Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. Cancer incidence in five continents, Vol 5. IARC Publication, No. 120. Lyon, International Agency for Research on Cancer, 1992.
[4] Bismuth H, Denneson AR. Segmental liver resection. Adv Surg 1993;26:189–95.
[5] Gewiese B, Beuthan J, Fobbe F, Stiller D, Muller G, Bose-Landgraf J, et al. Magnetic resonance imaging-controlled laser induced interstitial thermotherapy. Invest Radiol 1994;29: 345–51.
[6] Yamanaka N, Okamoto E, Tanaka T, Oriyama T, Fujimoto J, Furukawa K, et al. Laparoscopic microwave coagulonecrotic therapy for hepatocellular carcinoma. Surg Laparosc Endosc 1995;5:444–9.
[7] 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.
[8] McCall JL, Booth MW, Morris DL. Hepatic cryotherapy for metastatic liver tumours. Br J Hosp Med 1995;54:378–81.
[9] Mack MG, Straub R, Eichler K, Engelmann K, Zangos S, Roggan A, et al. Percutaneous MR imaging-guided laser-

induced thermotherapy of hepatic metastases. Abdom Imaging 2001;26:369–74.

[10] Vogl TJ, Straub R, Eichler K, Woitaschek D, Mack MG. Malignant liver tumors treated with MR imaging-guided laser-induced thermotherapy: experience with complications in 899 patients (2,520 lesions). Radiology 2002;225:367–77.

[11] Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 2003;90:1240–3.

[12] Wu F, Wang Z-B, Chen W-Z, Zhu H, Bai J, Zou J-Z, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. Ann Surg Oncol 2004;11:1061–9.

[13] Jolesz FA, Hynynen K, McDannold N, Freundlich D, Kopelman D. Noninvasive thermal ablation of hepatocellular carcinoma by using magnetic resonance imaging-guided focused ultrasound. Gastroenterology 2004;127:S242–7.

[14] Jolesz FA, Hynynen K. Magnetic resonance image-guided focused ultrasound surgery. Cancer J 2002;8(Suppl 1):S100–12.

[15] Lynn JG, Zwemer RL, Chick AJ, Miller AE. A new method for the generation and use of focused ultrasound in experimental biology. J Gen Physiol 1942;26:179–93.

[16] Chung AH, Jolesz FA, Hynynen K. Thermal dosimetry of a focused ultrasound beam in vivo by magnetic resonance imaging. Med Phys 1999;26:2017–26.

[17] Hynynen K, Pomeroy O, Smith DN, Huber PE, McDannold NJ, Kettenbach J, et al. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study. Radiology 2001;219:176–85.

[18] Gianfelice D, Khiat A, Amara M, Belblidia A, Boulanger Y. MR imaging-guided focused US ablation of breast cancer: histopathologic assessment of effectiveness – initial experience. Radiology 2003;227:849–55.

[19] Tempany CM, Stewart EA, McDannold N, Quade BJ, Jolesz FA, Hynynen K. MR imaging-guided focused ultrasound surgery of uterine leiomyomas: a feasibility study. Radiology 2003;226:897–905.

[20] Yang R, Reilly CR, Rescorla FJ, Faught PR, Sanghvi NT, Fry FJ, et al. High-intensity focused ultrasound in the treatment of experimental liver cancer. Arch Surg 1991;126:1002–9.

[21] Prat F, Centarti M, Sibille A, Abou FF, Henry L, Chapelon JY, et al. Extracorporeal high-intensity focused ultrasound for VX2 liver tumors in the rabbit. Hepatology 1995;21:832–6.

[22] Chen L, Ter Haar GR, Robertson D, Bensted JP, Hill CR. Histological study of normal and tumor-bearing liver treated with focused ultrasound. Ultrasound Med Biol 1999;25:847–56.

[23] Vallancien G, Harouni M, Veillon B, Mombet A, Prapotnich D, Bisset JM, et al. Focused extracorporeal pyrotherapy: feasibility study in man. J Endourol 1992;6:173–80.

[24] Visioly AG, Rivens IH, Ter Haar GR, Horwich A, Huddart RA, Moskovic E, et al. Preliminary results of a phase I dose escalation clinical trial using focused ultrasound in the treatment of localized tumours. Eur J Ultrasound 1999;9:11–8.

[25] Wu F, Chen WZ, Bai J, Zou JZ, Wang ZL, Zhu H, et al. Pathological changes in human malignant carcinoma treated with high-intensity focused ultrasound. Ultrasound Med Biol 2001;27:1099–106.

[26] Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. Int J Radiat Oncol Biol Phys 1984;10:787–800.