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Ultrasound Monitoring of Temperature Change during Interstitial Laser Thermotherapy of Liver: An In Vitro Study

Background/objective: In thermal tissue ablation, it is very important to control the increase in the temperature for having an efficient ablation therapy. We conducted this study to determine the efficacy of measuring pixel shift of ultrasound B-mode images as a function of change in tissue temperature.

Materials and Methods: By fixing some microthermocouples in liver tissues, temperature at different points was monitored invasively *in vitro* during laser-induced thermotherapy. According to our results, optimum power and exposure time were determined for ultrasound temperature monitoring. Simultaneously, noninvasive temperature monitoring was performed with ultrasound B-mode images. These images were saved on computer from 25°C to 95°C with 10 °C steps. The speed of sound changes with each 10°C temperature change that produce virtual shifts in the scatter positions. Using an image processing method, the pixel shift due to 10 °C temperature change was extracted by motion detection.

Results: The cubic regression function between the mean pixel shifts on ultrasound B-mode images caused by the change in speed of sound, which in turn was a function of the mean change in temperature, was evaluated. When temperature increased, pixel shift occurs in ultrasound images. The maximum pixel shift was observed between 60 to 70 °C (temperature changes (ΔT) of 35-45 °C). After 70°C, the local pixel shift due to change in the speed of sound in liver tissue had an irregular decreasing. Pearson correlation coefficient between invasive and non-invasive measurements for 10°C temperature changes was 0.93 and the non-linear function was suitable for monitoring of temperature.

Conclusion: Monitoring of changes in temperature based on pixel shifts observed in ultrasound B-mode images in interstitial laser thermotherapy of liver seems a good modality.

Keywords: hyperthermia, induced, thermotherapy, temperature monitoring, ultrasound B-mode images

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Received April 23, 2006;
Accepted after revision December 16, 2006.

Winter 2007;4:95-101

Introduction

Primary liver neoplasms and metastatic diseases to the liver represent a significant source of morbidity and mortality worldwide. Hepatocellular carcinoma is one of the most common solid organ malignancies, with an annual incidence of at least 1 million new patients. Virtually, every cancer can metastasize to the liver.[1-4] The use of laser as a source of heat to destroy liver tumors was first reported by Bown in 1983.[5,6] Laser-induced thermotherapy (LITT) consists of the percutaneous or intraoperative insertion of laser fibers directly into the liver tumor followed by heating for 20–60 min with low powers (2–4 W).[2] The maximum achievable lesion diameter with bare-tip fibers is two cm.[5] It is very important to control the temperature increase for having efficient tumor treatment plan, because at low temperatures there would be no irreversible thermal lesion and at high temperatures, tissue carbonization, charring, and smoking occur which can damage normal tissues.[7] There are invasive (with use of thermocouple or thermister) and non-invasive imaging techniques like magnetic

resonance (MR) imaging, computed tomography (CT) and ultrasound (US) techniques for monitoring tissue temperature.[5,8,9] The LITT procedure generally carries out under US guidance because it provides real time visualization of probe placement, and is portable, costs little and can target and guide ablation therapy for most intracavitary and endoluminal applications.[1,3]

Although conventional US does not provide clear delineation of the treated regions by LITT, information in the raw US signals may prove useful. Several US methods have been proposed to estimate temperature changes in tissue. These methods are related different temperature-induced changes in the tissue, including changes in the frequency-dependent attenuation, backscattered power, speed of sound, thermal expansion, or a combination of the latter two effects. Different algorithms have been used for estimation of temperature changes. Several techniques are based on tracking the echo shift in the time domain and differentiating the time shift estimates along the axial direction to obtain a temperature profile. Although promising, none of the US methods mentioned above are used to measure temperature changes larger than a few degrees.[1]

The variation in speed of sound with temperature introduces apparent or virtual shifts in the scatter positions and time shift into the received echo signals. It can cause changes and pixel shift on B-mode images. In this paper these changes were measured during LITT of excised sheep liver tissue for every 10°C temperature increase from 25–95°C.

Materials and Methods

LITT was performed *in vitro* on 11 slices of freshly-excised sheep liver tissues measured 50×60×60 mm.[3] The specimen was encased in a Plexiglas chamber with measured 50×60×50 mm³. An aluminum plate was placed in chamber's floor as a reference in US images. The tissue was completely fixed in the chamber with a polystyrene drawer door. Liver tissue was covered by gelatin so that it would provide a regular surface for placing the transducer. US imaging to guide the laser's fiber and thermocouples placement and to monitor the temperature in tissue was non-invasively performed using a real time scanner (LOGIC 500 GE, GE Inc, Germany). The scanner was operated with a 6–9 MHz linear array transducer.

The tissue temperature was invasively monitored by K-type wiry thermocouples (TP-01, Lutron Electronic Enterprise Co, Taiwan) that were inserted into the tissue through holes drilled along the length of the chamber at the height of 25 mm. Thermocouple's data were recorded every second in a file by a digital thermometer (Multiligger Thermometer CHY502A, Taiwan). Thermometers were connected to computer by RS-232C serial port. For calibration of thermocouples and thermometer, thermocouples were inserted into 100°C boiling water and 0°C cold water.

An Nd:Yag laser model Hercules 5060 (Heraeus Surgical, Inc. Germany, P<60W) with 1064 nanometer continues wavelength was used for *in vitro* ablation. The bare-tip optical fiber, 600 μm in diameter (Heraeus Lasersonic Inc, Germany) was used for delivery of laser's energy to the tissue. The fiber was inserted into the liver by a hole drilled in the width of the chamber at the height of 25 mm. US imaging was performed in a direction perpendicular to fiber. The laser fiber was inserted into the tissue by a 22G needle. To find the optimum power for noninvasive temperature monitoring by ultrasound B-mode images, powers commonly delivered in LITT, i.e., 2, 2.4, 3 and 3.4 W, in addition to 1 and 1.5 W were examined. The optimum power for this research was assumed as a power by which enough temperature change could be attained so that we can study the resultant change in the speed of sound in ultrasound B-mode images. Under ultrasound guide, a thermocouple was inserted 2.5 mm far from the laser fiber tip. The recorded temperatures for each second during the exposure time (300±10 s) and during the down time (200±30 s) were saved in a computer. The procedure was repeated three times for each power. According to our results, the optimum power was determined for ultrasound temperature monitoring.

To choose the optimum exposure time with optimum power, according to available reference paper and common exposure time (10-15 min), liver tissue was heated for 400, 700 and 1000 s.[10] Its temperature data was saved on computer by thermocouple at a distance 2.5 mm in front of the laser tip. After evaluation of these data, the optimum time exposure was determined.

For invasive temperature monitoring at different points of liver tissue during LITT, thermocouples were inserted at distances 2.5, 5.0, 7.0, 10.0 and 15.0 mm in front of the laser fiber and 1.0, 3.0 and 5.0 (±1.0) mm in the back of the laser fiber, under US guide.[10] LITT was performed with the optimum power and exposure time. Simultaneously, noninvasive temperature monitoring was performed with ultrasound B-mode images. These images were saved on a computer by a video blaster, for each 10°C temperature increasing from 25 to 95 °C. According to all of invasive temperature measurements, two points—2.5 mm in front and 1 mm in back of the laser fiber—were chosen for monitoring and measurement of pixel shifts in ultrasound images. Because these points had the maximum temperature changes from 25 to near 100°C. US images were saved at 25°C and used as reference and were compared with ultrasound images at 35 to 95°C with temperature steps of 10°C. The pixel shifts that occur through every 10°C temperature increase were then measured by motion detection technique.

All the observations and procedures were performed by the same investigator under same standard conditions. Statistical analyses were performed with SPSS 11.5 (SPSS/PC Inc, Chicago, IL). The invasive temperature profile at different distances in front and back of the optical fiber were reported. The maximum temperature in every distance was measured after 700 s exposure. With image processing, pixel shift due to 10°C temperature changes were extracted and a non-linear regression analysis with the higher correlation coefficient between the independent variable of temperature changes and the dependent variable of pixel shift due to speed of sound changes was performed.

Results

Figure 1 shows the temperature increase trend during the heating process and down for powers of 1.0, 1.5, 2.0, 2.4, 3.0 and 3.4 W at 2.5 mm far from the laser fiber tip. Only with a power of 4 W and after 90 s, tissue temperature at 2.5 mm far from the laser tip reached to the maximum value which our thermometers could be measured.

Figure 1 shows that that there was moderate temperature increase for powers of 1 and 1.5 W. For 2 and 3 W, temperature was quickly increased until 200 s. With a power of 3.4 W, temperature was increased very quickly. A linear regression analysis was performed using the time as independent variable and temperature as dependent variable. The correlation coefficients of linear model for temperature increase trend during heating for each power are shown in Table1.

According to Figure 1, the temperature increase trend for the power of 1 W was moderate with a correlation coefficient of 0.98 (Table 1), this power is optimum. If temperature increases moderately it will be possible to monitor and save the ultrasound images for each 10°C temperature rise. In addition, the maximum temperature attainable with this power was 100°C which was optimum because in high temperatures, tissue carbonization would be occurred and there would be too much bubble formation which would decrease the quality of US images and would made some difficulties for measurements.

Figure 2 (a) and (b) show the temperature increase trend with the maximum temperatures and energy induced to tissue for 400, 700 and 1000 s exposure and power of 1 W at 2.5 mm in front of the laser fiber tip. Linear regression analysis was performed with energy delivered as the independent variable and

Table 1. Time and energy of reaching to saturation temperature and maximum temperature of liver tissue after 300 s exposure of LITT and Pearson correlation coefficient as a result of heating with exposure powers recorded at 2.5 mm far from the tip of laser fiber.

Power (W)	Time of saturation temperature (s)	Energy (J)	Saturation temperature (°C)	Maximum temperature (°C)	Correlation coefficient (r)
1.0	300	300	100.0	100.0	0.98
1.5	294	441	107.4	107.5	0.98
2.0	215	422	277.2	276.9	0.87
2.4	212	509	358.2	365.4	0.87
3.0	224	672	407.9	412.5	0.90
3.4	299	1017	713.2	717.0	0.91

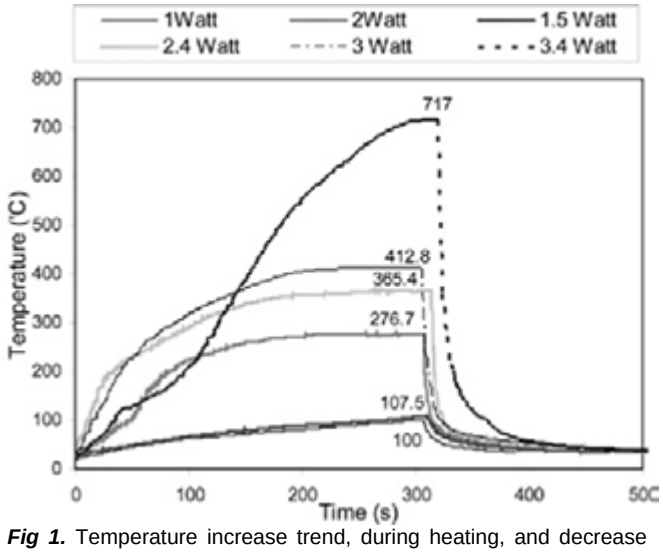

Fig 1. Temperature increase trend, during heating, and decrease trend, during down, for various powers in distance 2.5mm from laser fiber tip. Maximum temperature for each power is shown in Figure.

temperature as the dependent variable (Figure 2b).

After 400 s of heating, tissue temperature reached to 65.0 ºC; after 700 s, it reached 74.2 °C; after 1000 s, it reached 77.0°C (Figure 2a). An energy level of 400 J could increase the tissue temperature up to 65.0°C that caused tissue necrosis; 700 J increased the temperature up to 74.2°C and 1000 J increased it to 77.0°C (Figure 2b). Therefore, when the energy delivered ranged from 700 to 1000 s, there was only less than 3°C temperature increase, hence, we selected 700 s exposure.

The means of the temperature profiles recorded during 11 separate *in vitro* experiments after an exposure of 700 s with power of 1 W and a cutoff value of 200 s LITT are shown in Figure 3. At this stage, five thermocouples are placed at different distances (2.5, 5.0, 7.0, 10.0 and 15.0 mm) in front of the fiber tip and three thermocouples (1.0, 3.0 and 5.0 mm) in back of the fiber tip. The maximum temperatures in each place are also shown.

According to all temperature measurements, two points—2.5mm in front and 1.0 mm at back of the laser fiber—were chosen for monitoring and measurement of pixel shifts in US images. Regression functions applied and Pearson correlation coefficients are presented in Table 2.

The cubic function had the maximum correlation coefficient between the local pixel shift and the temperature changes; when temperature increased, pixel shift occurred in US images.

The mean pixel shifts observed on US B-mode images caused by change in the speed of sound *vs* the mean of temperature change and a cubic regression curve fitted to the data are shown in Figure 4. The correlation coefficient in this model is more than that observed for other models (Table 2). The maximum pixel shift was observed between 60 to 70°C (temperature changes [ΔT] of 35–45°C). After 70°C, the local pixel shift due to the change in the speed of sound in liver tissue had an irregular decreasing trend.

According to these profiles and considering the maximum temperatures measured at each point, tissue necrosis occurred at distances of less than 7 mm in front and in less than 3 mm at the back of the optic fiber. At distances less than 1 mm, temperature reached near 100°C which can cause carbonization.

Discussion

In spite of many *in vitro* research in which water bath were used to heat whole tissue, in this study, the temperature of liver tissue have been increased locally.[11-15] In this method, the control and monitoring of tissue temperature with imaging methods is easier because every point of tissue has the same temperature, thus, the change in speed of sound and ultrasonic attenuation coefficient remain the same in liver tissue. This method, however, could not be used *in*

Table 2. Linear and non-linear regression functions for temperature changes (ΔT: °C) and pixel shift of images (ΔX: mm) and their correlation coefficient. A P value <0.01 was considered significant.

Regression Functions	Function	Coefficient of Determination (R^2)
Linear	$\Delta X= 0.067+0.003\Delta T$	0.47
Logarithmic	$\Delta X= -0.206+0.111\ln\Delta T$	0.68
Inverse	$\Delta X= 0.28 - \frac{2.748}{\Delta T}$	0.83
Quadratic	$\Delta X= -0.098+0.014\Delta T$	0.78
Cubic	$\Delta X= -0.262+0.033\Delta T-0.001\Delta T^2+ 4.56\times10^{-6}\Delta T^3$	0.873

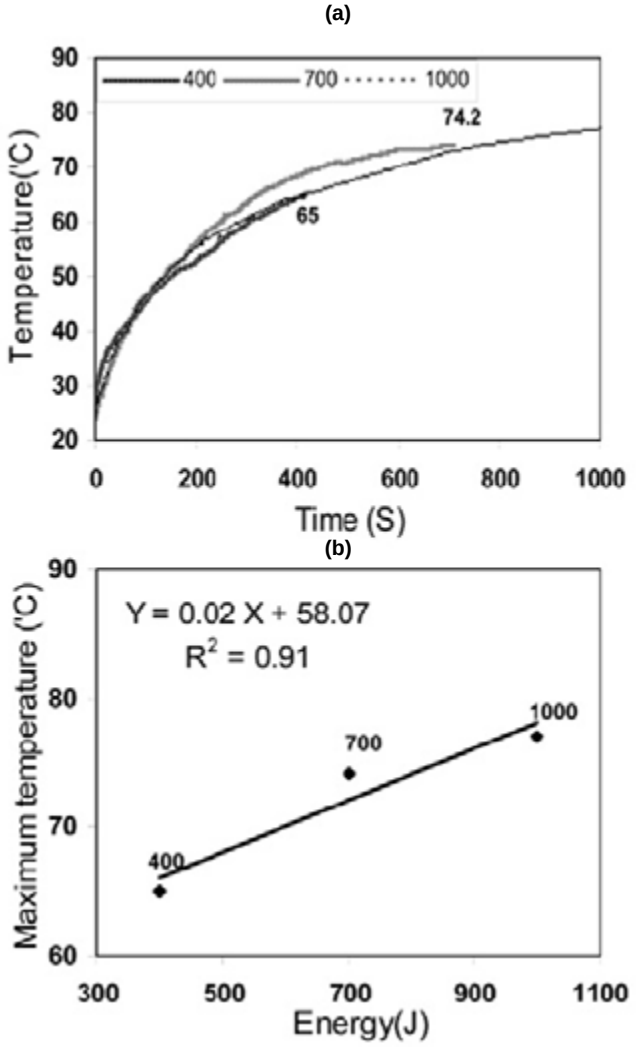

Fig 2. (a) The temperature increase trend and maximum temperatures for 400, 700 and 1000 seconds exposure with a power of 1 W recorded 2.5 mm in front of the laser fiber tip. (b) The liver tissue maximum temperature *vs* energy. Linear regression function and coefficient of determination (R^2) are shown.

vivo, because it is impossible to rise the temperature of whole liver tissue *in vivo*.

In a few studies examinations of changes in US properties of liver tissue by local radiation were qualitatively reported using temperature mapping based on time shift in RF signals and log envelope slope attenuation.[1,16]

In this paper, liver tissue was heated locally by laser bare-tip fiber and tried to do stages of this procedure like *in vivo* LITT. This method could use in clinical study. There is limitation for monitoring of local thermotherapy with US because changes in US properties just create in a small part of tissue.

In most of the published papers, investigators examined changes of US properties in less than 40 ºC. In just a few studies, changes in US properties were evaluated in temperatures up to 80 ºC.[11-13,16,17] There is just one report by Varghese et al. on monitoring of temperature changes up to 100 ºC.[1]

In the present paper, we examined the temperature range from 25°C (room temperature) to 95°C because in temperature higher than 100°C bubble formation increased and quality of US B-mode images changed very much. On the other hand, at high temperatures, carbonization occurs too, hence, US absorption is increased which in turn could change the quality of US B-mode images. Of course, physicians believe that the ideal temperature is that no carbonization occurred.

In most articles, RF signals were used for monitoring temperature.[1,16] In this study, however, the pixel shifts that occurred due to the increase in tissue temperature were evaluated by US B-mode images; B-mode images are the most commonly used ultrasound modality and are readily available. In this study, the pixel shifts caused by variation in the speed of sound due to temperature were examined. Because the speed of sound is our basic factor to study the image changes there was no difference to evaluate the pixel shifts either in front or in the back of the laser fiber—just temperature was important for us.

Figure 4 shows that increasing of temperature from 25 to 35°C did not cause any observable pixel shifts. After that, by every 10°C temperature rise, the pixel shifts had an ascending trend.

The maximum pixel shifts was observed in a temperature rise from 65 to 75ºC; after that stage, as temperature increased the pixel shifts were decreased in an irregular way.

According to Mass-Moreno and Damianou study (1996), the time shift occurred by changes in the speed of sound through a rise in temperature. Worthington et al. (2001 and 2002) note that in pig's liver and human's prostate, the maximum speed of sound are at 50°C and 55°C.[1,11,12] In another study (1998), Sun and Ying supposed that the relationship between the speed of sound and temperature in the simulated tissue was governed by the following equation:

$$C(T)= 0.000126\ T^3 - 0.046645\ T^2 + 4.807092\ T + 1453.43,$$

where C represents "speed of sound"and T desig-

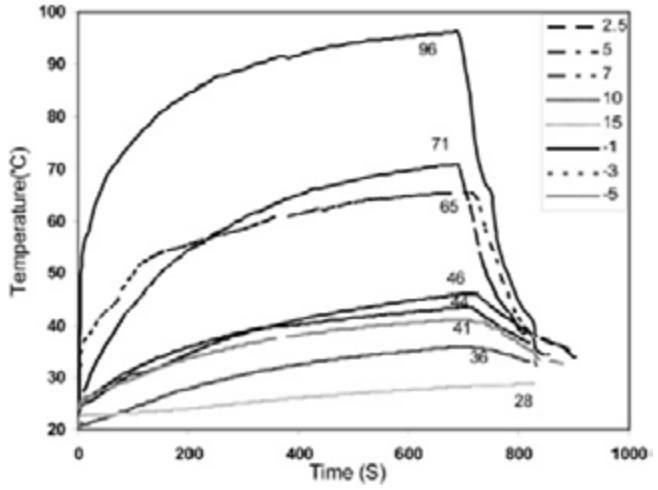

Fig 3. Temperature profiles at thermocouple positions 2.5, 5.0, 7.0, 10.0 and 15.0 mm in front of the fiber and 1.0, 3.0 and 5.0 mm at back of the fiber. The maximum temperature is also shown.

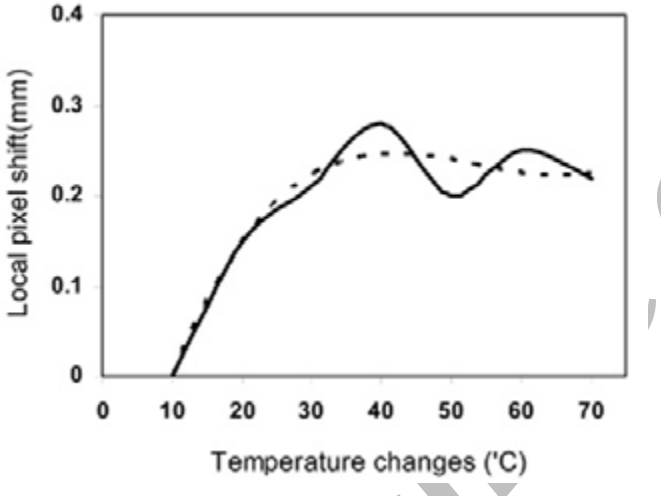

Fig 4. The pixel shift of ultrasound B-mode images as a function of temperature changes (solid line) for every 10°C temperature increase, and estimated cubic regression function curve between mean pixel shifts on ultrasound B-mode images due to speed of sound changes as a function of mean temperature changes (dashed line).

nates "temperature".[18] This relation was adopted from a C *vs* T relation in water. According to this equation, they showed that for temperatures more than 52 °C, a certain speed of sound corresponds to two different temperatures. They also showed that at T=73.3°C, sound has its maximum speed.[18]

In this research, according to Figure 4, for temperatures more than 45°C, a certain pixel shift corresponds to two different temperatures. In addition, at T=65°C, the observed pixel shift in US images is maximum.

At higher temperatures, physical shift in position of scatter is introduced by thermal expansion of medium that affects on B-mode images. On the other hand, bubble formation, vaporization and carbonization affect the quality of images at temperatures near and more than 100 ºC. Therefore, at such temperatures, measurement of pixel shift with this method is difficult. This could be one of the limitations of this method. Actually, the aim of hyperthermia and thermal therapy is to create necrosis and not carbonization, hence, this imaging and monitoring method could help physicians.

Invasive monitoring of temperature at each position of the fiber tip shows that a 2477 J/mm^2 laser delivered with a bare-tip optical fiber with a power of 1 W, could create necrosis in a distances less than 5 mm.

It is, therefore, concluded that local temperature estimates during LITT can be obtained using the pixel shifts in US B-mode images as described in this paper. Noninvasive *in vivo* and real-time monitoring of the ablated biologic tissue temperature is essential, so that the region under treatment can be easily visualized. Because US B-mode images are routinely used to guide the LITT procedure, the same system can be adapted for monitoring of temperature. Of course, it is necessary to improve the image analysis technique to decrease the amount of false data.

References

1. Varghese T, Zagzebski JA, Chen Q, Techavipoo U. Ultrasound monitoring of temperature change during radiofrequency ablation: preliminary In-vivo Results. Ultrasound Med Biol 2002;28: 321-9.
2. Moroz P, Jones AK, Gray BN. Status of hyperthermia in the treatment of advance liver cancer. J Surg Oncol 2001;77:259-69.
3. Mayoclinic Staf. Coloncancer. http:// www.mayoclinic.com/health/colon-cancer/CO99999 2006 jun.
4. Geoghegan JG, Scheele J. Treatment of colorectal liver metastases. Br J Surg 1999;86:158-69.
5. Nikfarjam M, Christophi C. Interstitial laser thermotherapy for liver tumors. Br J Surg 2003;90:1033-47.
6. Muralidharan V and Christophi C. Interstitial laser thermotherapy in the treatment of colorectal liver metastases. J Surg Oncol 2001;76:73-81.
7. Solbiati L. New applications of ultrasonography: interventional ultrasound. Euro J Radiol 1998;28:200-6.
8. Ishikawa T, Zeniya M, Hokari A, Kawabe T, Suziki K, Fujise K et al. An experimental study on Nd-YAG laser induced thermotherapy it possible application of the laser irradiation for therapy of hepatocellular carcinoma. Hepato Res 2002;23:25-30.
9. Volg T J, Eichler K, Straub R, Engelmann K, Zangos S, Woitaschek D et al. Laser-induce thermotherapy of malignant liver tumors: general principle, equipment, procedure-side effects, complications and results. Euro J Ultrasound 2001;13:117-27.

10. Gorjiara T, Mokhtari-Dizaji M, Ganaeati H. Evaluation of temperature growth and thermal lesion dimensions in liver laser interstitial thermotherapy. Iran J Med Phys 2004;5:75-82.
11. Worthington A E and Sherar M D. Changes in ultrasound properties of porcine kidney tissue during heating. Ultrasound Med Biol 2001;5:673-82.
12. Worthington AE, Trachtenberg J, Sherar MD. Ultrasound properties of human prostate tissue during heating. Ultrasound Med Biol 2002;10:1311-18.
13. Clarke RL, Bush NL, Ter Haar GR. The changes in acoustic attenuation due to in vitro heating. Ultrasound Med Biol 2002;29:127-35.
14. Guiot C, Cavalli R, Gaglioti P, Danelon D, Musacchio C, Trotta M et al. Temperature monitoring using ultrasound contrast agents: in vitro investigation on thermal stability. Ultrasonics 2004;42:927-30.
15. Gertner MR, Worthington AE, Wilson BC and Sherar MD. Ultrasound imaging of thermal therapy in in vitro liver. Ultrasound Med Biol 1998;24:1023-32.
16. Bevan PD, Sherar MD. B-scan ultrasound imaging of thermal coagulation in bovine liver: log envelope slope attenuation mapping. Ultrasound Med Biol 2000;3:379-87.
17. Bamber JC, Hill CR. Ultrasonic attenuation and propagation speed in mammalian tissue as a function of temperature. Ultrasound Med Biol 1979;5:149-57.
18. Sun Z, Ying H. A multi-gate time of flight technique for estimation of temperature distribution in heated tissue: theory and computer simulation. Ultrasonics 1999;37:107-22.