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REVIEW

Ultrasound monitoring of temperature and coagulation change during tumor treatment with microwave ablation

Chunlan YANG, Shuicai WU (✉), Yanping BAI, Hongjian GAO

College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, China

Abstract Microwave ablation therapy has become an important method for tumor treatment in recent years. The temperature and the coagulation region need real-time noninvasive monitoring to ensure the safety and effectiveness during the treatment. The authors reviewed the ultrasonic monitoring methods for tumor microwave ablation therapy both at home and abroad. In addition, the authors also prospected this technique in the future.

Keywords microwave ablation, temperature, coagulation, ultrasound monitor

1 Introduction

As we know, traditional cancer treatments include surgery, radiotherapy, chemotherapy, and immunological therapy. In recent years, hyperthermia has become an attractive method for tumor treatment (Liang, 2006). The microwave ablation treatment uses the microwave antenna as the heating source, which is inserted into the tumor guided by the ultrasound. Since the local temperature rises so quickly that it is high enough over the coagulation point within the heating region, the microwave inactivation can be realized.

In order to ensure the effectiveness and safety of hyperthermia, noninvasive temperature estimation, and real-time monitoring of the treatment region are necessary. Noninvasive ultrasonic monitoring methods use the ultrasonic tissue characterization to detect the change of the tissue. This technique can estimate the temperature of the treatment region noninvasively. It can also measure the position and size of the tissue coagulated. Thus, the procedures of tumor inactivation can be evaluated real time. Doctors can adjust the operation plan timely to ensure the stability and safety during the hyperthermia treatment.

This paper will introduce the research on temperature estimation and coagulation monitoring respectively both at home and abroad in the following parts. Finally, the technique in the future is prospected.

2 The status of ultrasonic temperature estimation research

With increased clinical applications, the uncertainty of the temperature within the treatment region has become an obstacle to the improvement of the therapeutic efficacy. In addition, monitoring the changes of the treatment region is a key problem to the safety and effectiveness during the microwave ablation. Currently, most of the clinical temperature monitorings use the needle thermometer that is invasive to the patient. However, the measurement cannot acquire the spatial distribution of the temperature within the region. On the other hand, imaging methods are used to evaluate whether the residual tumor is false positive or false negative. In addition, puncture biopsies cannot measure the degree or the extent of the focal necrosis, and thus, it cannot become a common examination method.

Important temperature estimation methods in clinics mainly include those based on magnetic resonance and those based on ultrasound (Wu et al., 2002; Mi et al., 2003; Guiot et al., 2004; Parmar and Kolios, 2004; Amini et al., 2005; Arthur et al., 2005a, 2005b; Miller et al., 2005; Maleke and Konofagou, 2006; Pousek et al., 2006; Qian et al., 2006; Ren et al., 2006; Wu et al., 2006; Zhang et al., 2006; Anand et al., 2007; Zhong et al., 2007). However, for the methods based on magnetic resonance, the cost is

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E-mail: wushuicai@bjut.edu.cn

too high, and it cannot be real time. thus, it is unfit in the microwave hyperthermia. Naturally, the ultrasonic methods have become the focus both at home and abroad.

Ultrasonic temperature estimation methods are based on the correlation between the ultrasonic characteristics and the temperature of the tissue. Generally, there are five kinds of methods as follows: (1) temperature estimation based on the echo time shift and deformation caused by the acoustic velocity change and the thermal expansion (Miller et al., 2005; Maleke and Konofagou, 2006; Anand et al., 2007); (2) temperature estimation based on the tissue ultrasonic attenuation parameters (Parmar and Kolios, 2004); (3) temperature estimation based on the frequency shift and the changes of the spectral parameters caused by the change of tissue scattering space (Amini et al., 2005; Qian et al., 2006; Zhong et al., 2007); (4) temperature estimation based on intensity of backscattered echo and the energy (Arthur et al., 2005a); and (5) temperature estimation based on the video features of B-mode image (Guiot et al., 2004; Pousek et al., 2006; Zhang et al., 2006).

However, there are still some unsolved problems in these researches. First, for the method based on the time shift of ultrasound echo signal, the specific ultrasonic velocity of the tissue and the thermal expansion coefficient must be acquired beforehand. In addition, it is very difficult to measure the time shift precisely because of the tissue complexity and the movement caused by the breath. Furthermore, thermal lens effect influences the region beside the coagulation. Therefore, the movement compensation and the thermal lens effect must be considered in clinical measurement. Second, in the measurement of ultrasonic attenuation coefficient, the methods based on ultrasound transmission and those based on reflection are recommended. Since the ultrasonic transmission-based method is limited to the posture that leads to the difficulty of *in vivo* measurement, methods based on ultrasonic reflection are relatively widely used. However, the precision of ultrasonic attenuation coefficient is poor and needs to be improved. Third, because the temperature coefficient of nonlinear ultrasonic parameter is more sensitive than that of ultrasonic velocity, B/A parameter may improve the resolution of the temperature. However, the detection of B/A is difficult in clinic. Fourth, theoretically, the frequency of the ultrasonic scattered signal changes with the temperature because the biological tissue has discrete semiregularly distributed point structure. Temperature information of the tissue can be acquired according to the frequency shift. However, the regularity of the scattered particle is poor; thus, the frequency shift cannot be satisfactorily precise. There are some researches using modern spectrum estimation technique such as spectral analysis of autoregressive and nonlinear spectral analysis to improve the precision. Fifth, for the method based on ultrasound scattering energy, the ultrasonic velocity and the thermal expansion coefficient need not be known beforehand. However, the spatial resolution is poor, and the precision is relative low. Last, under the common hyperthermal temperature (42°C–45°C), the average intensity of B-mode ultrasonic image has a high correlation with temperature (above 0.96) during the heating procedure. Some texture features of the image also have a high correlation with temperature.

In summary, these ultrasonic temperature estimation researches are still at experimental stage. How to extract the ultrasonic tissue characteristics exactly and improve the precision of the measurement are the crucial problems in clinical applications.

3 Monitoring of the coagulation change based on ultrasonic tissue characterization

Under high temperature especially when the tissue has coagulated, it is difficult to measure the correlation between the ultrasound characteristics and temperature. In this case, ultrasonic tissue characterization can be used to monitor the change in the coagulated region.

The focus is displayed by gray-level imaging ultrasonic instrument dynamically. In addition, localization and puncturing are also guided by this instrument during tumor treatment with microwave ablation. For these reasons, the sonogram is expected to monitor the dense echo signal covering the tumor in clinic during the whole treatment. Ultrasonic tissue characterization is a research hotspot both at home and abroad. It has been applied both in noninvasive ultrasonic monitoring and in hyperthermia therapy.

Ultrasonic tissue characterization (UTC) is a technique to measure the relationship between ultrasonic characteristics and the tissue. The ultrasonic parameters of an organism can reflect the state of the structure and the tissue. How to extract the effect features is the key to recognize different structures and the pathological changes. Ultrasonic tissue characterization can also be used to detect small pathological changes in the tumor in addition to observe its size, movement, and the neighboring structure. Therefore, this technique is of important clinical value (Huang et al., 2007; Lai et al., 2007; Mehdi et al., 2007; Saijo et al., 2007).

The research on ultrasonic tissue characterization includes the methods based on ultrasonic velocity, ultrasonic attenuation, ultrasonic scattering, echo intensity, tissue rigidity, ultrasonic microscope, ultrasound with pathology, the application of UTC in therapeutics, and tissue contrast echocardiography, empirical judgment, histological dynamic analysis, *etc*. (Wang, 2001; Li and Wang, 2002; Liu et al., 2007). In these methods, the echo-intensity-based method and the ultrasonic integrated backscatter method are most prospective and valuable.

Echo-intensity-based method primarily depends on the analysis of B-ultrasonogram using computer. The DFY-type ultrasonogram quantitative analysis and diagnosis instrument in China can measure the maximum, minimum, and average of the gray value in the image. The resolution of the image can reach 660×440 pixels, 256 GS, 85 dB. The apparatus can also protract stereo three-dimensional images. In the three-dimensional reference frame, X axis, Y axis, and gray-level G axis are the three axes. Two-dimensional image lies in the X-Y plane. Three-dimensional image has moderate perspective to enhance the third dimension. The intensity of the echo and the morphology of the tissue can be acquired according to the change of the kurtosis in the image. The kurtosis becomes high and dense for the tissue whose echo intensity is strong. On the contrary, the kurtosis becomes low and sparse. Thus, this is a texture analysis method, which is visual and intuition based, to know about the distribution of the gray level. The low level and the decrease of the kurtosis mean that the gray-level distribution curve is relatively wide. In other words, the gray values of the pixels within the measuring region are almost similar. It has been reported that UTC could measure the gray value of the ultrasonogram for chronic hepatitis patients. Based on the comparison of its pathohistology fibrosis classification by liver puncture, it is significant that the gray value can be regarded as liver fibrosis criteria in clinic (Li et al., 2005). It has also been demonstrated that the texture features of the ultrasonic image such as second-order moment, contrast, entropy, and inverse difference moment can describe the liver ultrasonic image. These features are very useful for the quantitative analysis of B-mode ultrasonic image (Xu et al., 2006; Wu et al., 2007).

King et al. (2003) analyzed the correlation between the intensity of the image and the temperature by acoustic camera imaging. During the experiment, the tissue was put in the middle of the camera with an ultrasonic sensor which has 10 M frequency. The reversible intensity change of the image within the treated region was observed clearly. The coagulation implies that before heating, during heating, and after heating states were different. The precision of the edge detection needs to be improved, and a lot of work needs to be done *in vivo* and in clinical application. Pousek et al. (2003) have extracted the image features such as average gray value, gradient, and other structural parameters and applied them to the ultrasonic monitoring during microwave hyperthermia *in vivo* successfully. The temperature distribution within the tumor can be computed. However, the real-time temperature estimation still has not been realized. Moreover, the disturbance caused by the high-frequency field of temperature measuring system and heating system, and movement artifacts are still difficult problems that need to be solved. In addition, Guiot et al. (2004) found that microbubbles contrast agent could strengthen the ultrasound backscatter reflect plane and improve the sensitivity of the temperature measured by the ultrasonic image. Therefore, it can be regarded as the intermedia of the noninvasive temperature monitoring. This research should establish the perfect concentration of the contrast agent and repetition time precisely. *In vivo* experiments are also necessary. Kennedy et al. (2004) compared the size of the coagulation region before and after the treatment by the tissue perfusion rate using contrast agents. The size of the treatment region can be corrected according to the observation results.

In the research of ultrasonic dispersion, the integrated backscatter (IBS)-based method is a new technique that quantitatively analyzes the acoustic density. The scattering will happen when the acoustic impedance difference of the media is larger than 0.1% during the ultrasound transmission if the diameter of the interface is much shorter than the wavelength. For example, the cell, microvessels, and collagen fiber will produce the scattering. Especially, the scattering facing the transducer whose angle between the scattering and the incidence is 180° is called backscattering. The integral of the power spectra for the radio signal within the scattering region is called the integrated backscatter of this region. This technique can help achieve the recognition and evaluation of the pathological changes in the tissue by analyzing the backscatter signal from the microstructures. Thus, the histopathological features can be detected.

There are many factors influencing the intensity of the ultrasonic backscatter. They primarily include the concentration of the scatterer, size, shape, mode of arrangement, the difference of the acoustic impedance, elasticity of the scatterer, and the ultrasound frequency. In theory, if one or more factors change to a certain degree due to pathological change of the tissue, the value of ultrasonic integrated backscatter will also change (Balen et al., 1994).

The traditional two-dimensional ultrasound imaging technique is based on the reflected wave, while the backscatter imaging is based on the backscatter radio signal of the scatterer. Under the frequency of current clinical ultrasonic diagnosis, most wave length is between 0.07–0.75 mm. Thus, the diameter of the scatterer structure or the medium is very short. IBS technique can detect, process, and analyze the ultrasonic integrated backscatter of the tissue. Moreover, the radio signal is not demodulated or log compressed. It can reflect the tissue characteristics by detecting changes in the microstructure quantitatively and precisely. Many researches used ultrasonic integrated backscatter technique to investigate the liver tissue. The results show that IBS value of the normal liver tissue will increase with age and decrease from near field to far field (Cao et al., 2003; Xie et al., 2004). IBS value increases with the degree of hepatic fibrosis of the patients and has significant differences compared with the value of healthy people (Zang et al., 2002; Ye et al., 2003).

Arthur et al. (2003, 2005b) found that ultrasonic backscatter energy of the tissue changed with temperature monotonously for the scatterer that had certain wavelength. The research result of temperature measuring function based on cross correlation by radio ultrasonic backscatter signal acquired from the same sensor shows that backscattered energy (CBE) will increase with temperature for lipid, whereas it will decrease for liquid. The CBE of bovine liver changed 4 dB monotonously within the temperature 37°C–50°C. The spatial resolution can reach 1 cm^3 after the tissue movement compensation by Hilbert transformation and average filtering. The biggest merit of this temperature estimation method based on ultrasonic scatter energy is its insensitivity to tissue anisotropy. Moreover, the temperature function of tissue acoustic velocity need not be acquired beforehand. Once the scatterer is defined, two-dimensional and three-dimensional temperature fields can be constructed real-time based on the signal processing algorithm. Automated definition and scatter tracking have not been realized currently. The temperature dependency of different tissue CBE should be measured accurately. In addition, realization of *in vivo* application also needs more efforts. The efficiency and the precision of the tissue movement tracking also need to be improved.

In the research of tissue rigidity detection based on ultrasonic characterization, Konofagou et al. (2002) estimated the spatial thermal field by the bimodality ultrasonic phase array and expected to construct an economical closed-loop system completely based on ultrasound. The new method (USAE) for detecting the tissue acoustic and mechanic characteristics was used, and the results show that the amplitude of USAE increased with temperature. The time and space resolution could reach 1 s and 5 mm, respectively. Yao et al. (2001) also used this ultrasonic phase array in both clinical treatment and monitoring. They improved the injury contrast of the image to 6–15 dB using new reconstruction algorithm. Real-time visualization has been realized in thermal damage.

Bharat et al. (2005) have demonstrated that the tissue rigidity will strengthen monotonously with the increase of the temperature and duration time of the ablation commonly. The reason why the change of the rigidity under 80°C is irregular in experiments is probably the influence of the blood perfusion. Seo et al. (2005) used tissue texture variation of the elastic image to estimate the thermal damage of canine renal tissue in *in vitro* experiment. The elastic image describes the elastic characteristics of the tissue, which are related to the local tissue strain and have no direct relation to the imaging parameters. The basic principle of the elastic imaging is acquiring the strain distribution of the tissue from the radio information before and after the compression under certain external force.

The echo stress is generated by the acoustic velocity change and the deformation caused by the thermal expansion from the ultrasonic backscatter signal. Miller et al. (2005) and Souchon et al. (2005) described the degree of thermal damage by analyzing the echo stress image. The high fat organ is the most distinct part whose reflection is strong. The thermal damage of the heated tissue becomes clear in the echo stress image with its coagulation expansion. The damaged tissue compressed the other neighboring tissue for its tension. The noise can be reduced by changing the angle between the imaging beam and the treatment beam. The error of the temperature estimation is lower than 2°C. However, the damaged position needs to be predicted, and the change of acoustic velocity caused by the temperature needs to be acquired in order to reconstruct the temperature.

4 Conclusion and discussion

From these researches mentioned, we can see that some achievement has been made in detecting the changes of tissue ultrasonic characteristics during the heating process. However, there are still some difficulties in clinical treatment. Noninvasive real-time monitoring of the coagulation and precise temperature estimation are both difficult and urgent work. This project will use ultrasonic tissue characterization as the basic technique of microwave tissue hyperthermia therapy. Novel approaches are needed to overcome the limitations of traditional treatment through theoretical analysis and experimental research. It is believed that more effective ultrasonic monitoring methods that are real time and noninvasive should be able to provide strong technical support for the microwave tissue hyperthermia therapy.

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