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Full Length Research Paper

Extracorporeal ultrasound-guided high intensity focused ultrasound therapy: Present limitations

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Extracorporeal ultrasound-guided high intensity focused ultrasound (USgFU) ablates solid lesions non-invasively. Limitations manifested in preclinical and clinical trials are discussed in brief. The ablation efficiency (necrosis rate) is low. Tissue responses are monitored in real time during USgFU treatment, based upon the appearance of hyperecho within the insonated volume. However, hyperecho does not necessarily indicate tissue necrosis, with a low specificity and negative predictive value. A preoperative treatment plan cannot predict the ablation outcome satisfactorily. A reflection interface in the travel path of therapeutic ultrasound obstructs the propagation, refocuses beams and shifts the focus or burns adjacent tissues. A diagnostic transducer is located in the center of a therapeutic one in a USgFU device; hence there is a blind field of the diagnostic transducer; tissues within this area cannot be constantly observed during HIFU insonation. The motion of an organ may shift a target lesion leading to untoward tissue damages. The drastic variance between tissue types/individuals is the greatest challenge for the standardization of USgFU treatment. The quantitatively clinical data of limitations are still unavailable, and USgFU therapy is with a low level of evidence from the perspective of evidence based medicine. Some potential solutions are introduced briefly.

Key words: High intensity focused ultrasound, ultrasound imaging, ablation efficiency, real-time monitoring, treatment plan.

INTRODUCTION

Extracorporeal high intensity focused ultrasound (HIFU) non-invasively destructs a preselected volume within the body without harming overlying tissues via heat and cavitation, which has been applied for the treatment of a solid lesion. HIFU treatment is guided by ultrasound (USgFU) or magnetic resonance imaging (MRgFU) (ter Haar, 2007).

HIFU therapy falls into two types--one for radical cure and the other for palliation. In a radical treatment, the whole lesion, including definitely surrounding tissues when needed, is completely destructed. In palliative HIFU treatment, segments of a tumor are ablated to shrink the size thus alleviating the clinical symptoms and improving the quality of life; partial ablation is frequently applied for an advanced cancer and for some benign diseases (such as uterine fibroids) (Yu et al., 2008a).

USgFU has been used to treat diseases of liver, kidney, breast, pancreas, uterus, prostate, bone and soft tissues; the safety and efficacy have been demonstrated in clinical trials (Kim et al., 2008). Several devices have received approval and some are in clinical trials (Table 1). The limitations of USgFU, demonstrated in preclinical and clinical trials, are discussed briefly in this paper.

ABLATION EFFICIENCY

Quantifying the ablation efficiency

The necrosis rate, the volume of necrotized tissues per 1-s HIFU exposure (mm^3/s), is an index of ablation

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Table 1. List of ultrasound-guided HIFU devices.

Device	Manufacturer	Status
2000	Shenzhen Xifukang Med. Treatment Technol. Co.	Approved in China
2001	Shanghai Jiaoda Shiye Co.	Approved in China
CZ901	Mianyang Sonic Electronic	Approved in China
FEP-BY	Beijing Yuande Biomed. Eng. Co.	Approved in China
JC	Chongqing Haifu Technol. Co.	Approved in China
NIT-9000	Shanghai A&S Sci. Technol. Development Co.	Approved in China
RDS	Beijing Ren De Sheng Technol. Ltd.	Approved in China
HY2900	Wuxi Haiying Electronic Med. System Co.	Clinical trial
UTT	Storz Medical AG	Clinical trial

efficiency (Yu et al., 2004). The energy necrosis rate was applied in recent papers, which was the volume of ablated tissues per 1-Joule ultrasonic energy (mm^3/J) (Smart et al., 2006). The energy necrosis rate can be deduced from the necrosis rate since the energy is determined by the power and insonation *time [energy (J) = power (W) × insonation time (s), power (W) = intensity (W/cm^2) × size of the focus (cm^2)].* The energy necrosis rate is limited by, (i) the tissue ablation which is dependent on a temperature of >56℃ in a few seconds (not the total energy exerted), and (ii) the intensity attenuates exponentially with increasing depth in tissues (that is, intensity and energy vary drastically). The inhomogeneous texture of tissues complicates the behavior of ultrasound *in vivo*. That ultrasound should be rapidly delivered into the target tissues indicates that the intensity is the leading physical determinant for HIFU ablation. These cannot be outlined with the energy necrosis rate. The necrosis rate is therefore a better indicator. The intensity and focal depth in tissues should be set equal when comparing the ablation efficiencies between tissue types/individuals.

Preclinical findings

Ablation efficiencies vary between tissue types, and have not been systemically determined *in vivo*. In our studies, the necrosis rates were 6.97 and 12.02 mm^3/s in rabbit (14300 W/cm^2 at 1.0 MHz) and 4.17 and 14.46 mm^3/s in goat (22593 W/cm^2 at 1.0 MHz), for kidney and liver, respectively (Yu et al., 2004, 2006a, 2006b, 2008b).

A direct means to improve the ablation efficiency is to increase the intensity and/or to prolong insonation time. However, Seket et al. (2007) manifested that these two methods did not solve the problem satisfactorily. The cutoff of blood flow (ligating both the hepatic artery and portal vein) decreased heat diffusion thereby extending the size of necrotized tissues in the rat liver. Increments were -27.27-16.67%, 2.38-37.50% and 20.45-45.00% at 3, 6 and 12 s-insonation (106-266 W/cm^2 at 1.7 MHz), respectively (Chen et al., 1991). This technique, therefore, has a poor clinical relevancy. Using a drug is an alternative.

A synergist for USgFU should not affect the precision of treatment and not spare viable tissues within the insonated volume. Other criteria include, (i) low toxicity, (ii) a high efficiency constant of increasing the necrosis rate, (iii) assisting the ablation of a deeper volume, (iv)a high affinity to a specific tissue type, and (v) ease of administration. If the agent also benefits the detection of a lesion and the assessment of tissue responses in real time, additional advantages are provided.

Iodized oil leads to a higher and faster temperature rise and is used to enhance HIFU (Cheng et al., 1997). In the goat liver, the required energy for ablating 1 mm^3 tissues (1.0 MHz, 5500 W/cm^2) was decreased when administrating iodized oil *via* a hepatic artery before insonation (11.2±3.5 vs. 28.3±6.4 J; with efficiency indexes of 0.09 vs. 0.04 mm^3/J) (Xiong et al., 2003).

Microbubbles improve the necrosis rate. In rabbit, administrating microbubbles during HIFU increased the necrosis rate 3.75 times in liver, and increments were 4.53 for left and 3.15 for right kidneys (Yu et al., 2004, 2006a). When applying a clinical HIFU regime, the necrosis rate in goat was increased with the intravenous injection of microbubbles (14.46±4.20 vs. 33.53±12.44 mm^3/s for liver and 4.17±1.33 vs. 9.32±2.27 mm^3/s for kidney) (Yu et al., 2006b, 2008b). There were no residual intact tissues within the insonated volume. In rat liver cancers, Levovist led to a larger volume ablated (275.3±120.0 vs. 60.1±23.6 mm^3, corresponding to necrosis rates of 9.18 vs. 2.00 mm^3/s) (Hanajiri et al., 2006). SonoVue increased the volume of necrotized tissues when subjecting rabbit VX_2 liver tumors to HIFU (Luo et al., 2009). A lesion is hyperechoic, isoechoic or hypoechoic and the vasculature is rich, equal or poor, compared with the surrounding tissues. Bubbles distribute into a hypervascular lesion spontaneously favoring HIFU treatment. The use of microbubbles for an isovascular or a hypovascular tumor should be performed carefully. The dynamics of microbubbles within a lesion is constantly monitored with ultrasound images, and therapeutic ultrasound is released in the phase of relative

enrichment (Yu et al., 2006a). Bubbles can be a reflection interface preventing post-focal tissue lesions (Zderic et al., 2008). The level of microbubbles in a lesion should be within a due range bacause an over-high concentration may hamper the travel of therapeutic ultrasound beams.

Microbubbles assist HIFU ablation *via* enhancing heat and cavitation (Kaneko et al., 2006; Yu et al., 2006b). In a HIFU treatment, coagulative necrosis is first induced in the deepest plane, and then the shallower slices are ablated gradually; this is realized *via* a programmed array of single shot/scan. Inter-plane and -slice intervals must be set carefully in order to cover the whole lesion. Intervals can be increased in microbubble-assisted HIFU, thus decreasing the number of insonation required for ablating a volume (Yu et al., 2006b, 2008b). Microbubbles have been clinically used for contrast ultrasonography. Recent trials have shown that microbubbles assisted the assessment of tissue responses in real time improving the accuracy, sensitivity and positive predictive value (Yu and Xu, 2008c). These suggest that microbubble is an idea sensitizer for USgFU therapy.

Delayed necrosis occurred in tissues just outside the reaction zone (the demarcation between ablated and unaffected tissues in HIFU), when subjecting the goat liver to HIFU (Yu et al., 2006b). This may be mediated by free radicals due to cavitation, because reactive species can exacerbate hyperthermia-induced tissue lesions. Temperature within a definite extent outside the focus is >41℃, (that is, the “free radical-sensitive area” of HIFU field); tissues within this area are susceptible to the combination of heat and free radicals (Zhang et al., 2010). Delayed necrosis can be applied to realize a radical surgery indirectly, when a tumor cannot be directly covered.

Clinical findings

In vivo efficiency indexes for most human tissues are unavailable yet, and differ in literatures. For uterine fibroids, a coefficient of 0.03 cm^3/J was reported by Smart et al. (2006), and the value was 0.00088-0.00039 cm^3/J in the study of Funaki et al. (2007). The ablation efficiency, therefore, should be standardized. The necrosis rate varies between tissue types, and is high in tissues with a high absorption coefficient. An organ with high perfusion rate usually has a lower necrosis rate as blood flow transfers heat.

In uterine leiomyomas, a pretreatment with a gonadotropin-releasing hormone agonist (GnRHa) improved the ablation efficiency to 0.06 cm^3/J, while that in group control was 0.03 cm^3/J (Smart et al., 2006). A GnRHa leads to the shrinkage and devascularization of a tumor, thereby decreasing the treatment depth and heat loss. A drug which specifically contract uterine muscles/vessels may be used to enhance HIFU against leiomyomas.

Transcatheter arterial chemoembolization (TACE) was performed before ablating liver cancers. The combined treatment resulted in smaller tumor sizes at 1, 3, 6 and 12 months, compared with TACE alone (Wu et al., 2005). The dispersion of iodized oil into tissues increases the absorption coefficient and the cutoff of blood supply decreases heat loss, thereby enhancing HIFU. However, the ablation efficiency was not quantified. That how many folds the necrosis rate was increased by iodized oil remained unclear? TACE is not a standard regime, in which anticancer drugs and their dose vary between individuals. The combination of TACE and HIFU, therefore, is with a low level of evidence from the perspective of evidence-based medicine.

MONITORING TISSUE RESPONSES IN REAL TIME

Hyperecho

Monitoring tissue responses in real time is an advantage of USgFU, indicating that a treatment plan can be modified in due course (ter Haar, 2007). The appearance of a hyperechoic area within the target volume is considered as an indicator of tissue necrosis, which is used to monitor HIFU treatment (Wu et al., 2005). However, hyperecho does not necessarily mean tissue necrosis and the systemically clinical data are unavailable yet (Rivens et al., 2007; Yu et al., 2008c). Computerized tomography (CT) and MRI are the gold standard to follow up thermal ablation. Intraoperative ultrasonography should be compared with postoperative CT/MRI, thus determining the predictive value of hyperecho.

The relationship between hyperecho and tissue necrosis was investigated in rabbit. The accuracy, sensitivity and specificity were 48.72, 49.25 and 45.45% for liver and 55.83, 76.06 and 26.53% for kidney, respectively; the positive predictive values were 84.62% for liver and 60.00% for kidney and the negative predictive values were poor, when using hyperecho to forecast tissue necrosis. The use of microbubbles during HIFU improved the sensitivity in liver and the positive predictive value in kidney, but the negative predictive values were still low (Yu and Xu, 2008c). Thus, hyperecho can only be applied to monitor tissue responses in some tissue types. The major concern is a high rate of false negative; the misdiagnosis may lead to over-insonation resulting in unwanted tissue damages.

The diagnostic transducer is located in the center of the therapeutic transducer in all present USgFU devices. There is a region which lies in the travel path of therapeutic beams but is out of the scope of diagnostic ultrasound, namely, the blind field of diagnostic transducer (Figure 1). Tissues within this area cannot be monitored in real time during insonation, thereby being at a high risk of being damaged by therapeutic ultrasound. Adverse events, such as skin burn, frequently occur in

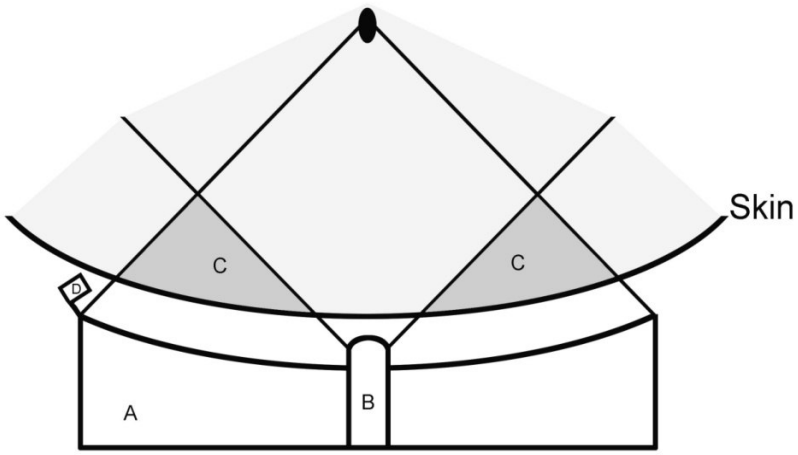

Figure 1 Illustration of the blind field of diagnostic transducer in a USgFU device. The blind field is within the near field of therapeutic ultrasound beams. A camera is used to view skins constantly throughout HIFU treatment, but other tissues within the blind field cannot be monitored yet. *A*, therapeutic transducer; *B*, diagnostic transducer; *C*, blind area; *D*, camera.

tissues within the blind field. A camera is applied to view skins constantly throughout HIFU treatment in some devices, but other tissues within the blind field cannot be observed yet.

Future development

Ultrasonic elastography senses the tissue stiffness, and is used to assess tissue responses after HIFU exposure. In human prostate cancers, elastograms underestimated the necrosis volume with a correlation of 0.62 (Curiel et al., 2005). Vibration elastography was recently applied to detect a HIFU lesion. External vibration is introduced into the target tissues thus detecting the elasticity. In porcine livers, the lesion boundary was clear in elastograms, but not visualized in grayscale images in 42.9% cases. The sizes of a HIFU lesion calibrated with elastograms accorded with the actual values (R^2 were 0.9543, 0.8555 and 0.9079 for area, long axis and short axis) (Zhang et al., 2008). Elastograms can be combined with grayscale ultrasound images to monitor HIFU ablation in real time.

Monitoring temperature in the insonated tissues can be applied to monitor tissue responses. It entails using ultrasonic images to map the temperature rise within the target volume. A direct approach is to utilize the grayscale level, but a linear correlation only exist within a range of 30-43℃ (Guiot et al., 2004). Recently, ultrasound backscatters have been used to track shifts in time and frequency due to temperature-depended changes in the sound speed and tissue thermal expansion, thereby calculating the temperature rise; linear, nonlinear or spectral analysis has been proposed. *In vitro* findings manifested that two- and three-dimensional temperature images can be displayed in real time (Amini et al., 2005; Liu et al., 2010). This technique is at an early stage, as the complex texture of tissues decreases the sensitivity and reliability *in vivo*.

PREOPERATIVE TREATMENT PLAN

Theoretically, preoperative data can be used to formulate a treatment plan, and then the tumor is ablated programmatically. Assessing tissue responses in real time makes it possible to modify a treatment plan in due course during USgFU. The clinical outcome of the first HIFU treatment can be used to optimize the subsequent treatment plans, when applying the mode of fractionated insonation (Figure 2). Oncologists hope to understand the acoustic property of tissues *via* trial shots (insonation under lower intensities), thereby forming an individualized guideline. A challenge is to extrapolate tissue responses under therapeutic intensities, because HIFU works in the range of nonlinear acoustics.

Responses to ultrasound vary between tissue types and between individuals. A tumor is with a mixed pattern comprising many components, and each has distinct acoustic property. The energy required for ablating an aliquot differs from that for another one. The insonation manner must be modified constantly throughput a HIFU treatment according to tissue responses. A Preoperative treatment plan has poor practicability; this is consistent with the findings in goat--volumes of ablated tissues varied drastically between animals when applying the same insonation template, either in liver or kidney (Figure 3) (Yu et al., 2006b, 2008b).The difference in exposure duration required for necrotizing predetermined tissues indicates that the insonation time cannot be reckoned in a preoperative plan. Variances between individuals

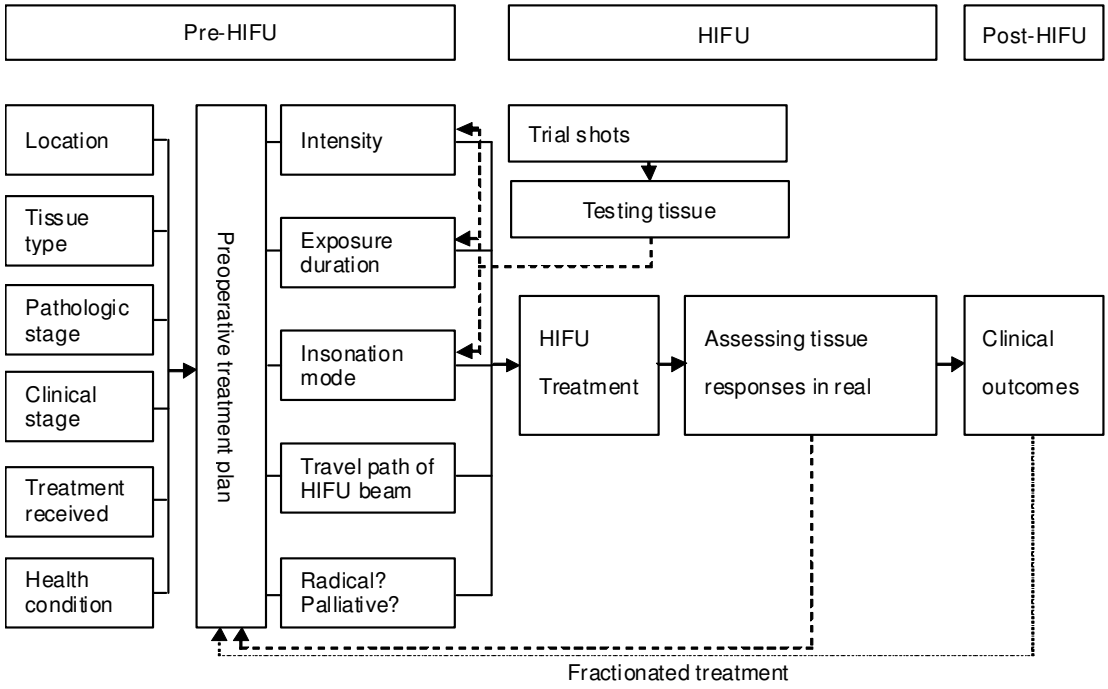

Figure 2. Scheme of a treatment plan in USgFU therapy. Understanding the panorama of a tumor formulates a preoperative treatment plan. The acoustic property of tissues is tested with trial shots, by which are tissue responses under therapeutic intensities extrapolated to modify the insonation mode. The plan is modified instantly according to tissue responses during HIFU exposure. The clinical outcomes of the first HIFU treatment is used to optimize the subsequent treatment plans, when applying the fractionated mode.

cannot be eliminated with the use of iodized oil, microbubble or GnRHa (Smart et al., 2006; Yu et al., 2006b, 2008b). A preoperative treatment plan should, therefore, concentrate on the decrease of adverse events; the insonation manner is instantly optimized during HIFU treatment according to tissue responses.

TRACING THE TARGET LESION

Present status

The motion of an organ due to respiration and/or adjacent organs decreases the precision of HIFU. The target lesion therefore should be traced throughout HIFU treatment. A USgFU device emits therapeutic and diagnostic ultrasound sequentially and intermittently. Target tissues cannot be viewed in ultrasonic images in the phase of therapeutic ultrasound; this may lead to a shift of the focus producing untoward lesions.

Extending the volume of desired tissues appropriately is a method to compensate the shift of a lesion, but a slight shift will result in severe adverse events when the lesion lies near a vital structure. Controlled respiration was employed to overcome the motion of a liver cancer when locating near the diaphragm, (that is, suspending respiration while releasing therapeutic ultrasound beams); by such a means, was the cancer ablated completely without harming the diaphragm (Zhu et al., 2001).

A reflection interface in the travel path of ultrasound obstructs the propagation and refocuses HIFU beams. These occur when shooting a liver/kidney tumor as ribs are with high impedance, thus wasting ultrasonic energy, distorting/shifting the focus and burning adjacent tissues (Tanter et al., 2007). Ribs are removed before HIFU insonation to create an acoustic window in the present regime, which deviates from the essence of HIFU as a noninvasive surgery (Zhu et al., 2009).

Developing techniques

Gate-control has been used to correct the shift of focus in radiotherapy. An external/internal marker is tracked with a sensor and therapeutic beams are suspended whenever the target is outside a preset area (Tanter et al., 2007). This technique can serve HIFU therapy tracing a target lesion.

Approaches for overcoming ribs include the delivery of ultrasound *via* intercostal spaces and a rib-shape transducer combined with gate control. Time-reversal with a transducer array provides a means. A hydrophone is placed into the liver to emit waves. Signals are recorded by the array, and then elements launch

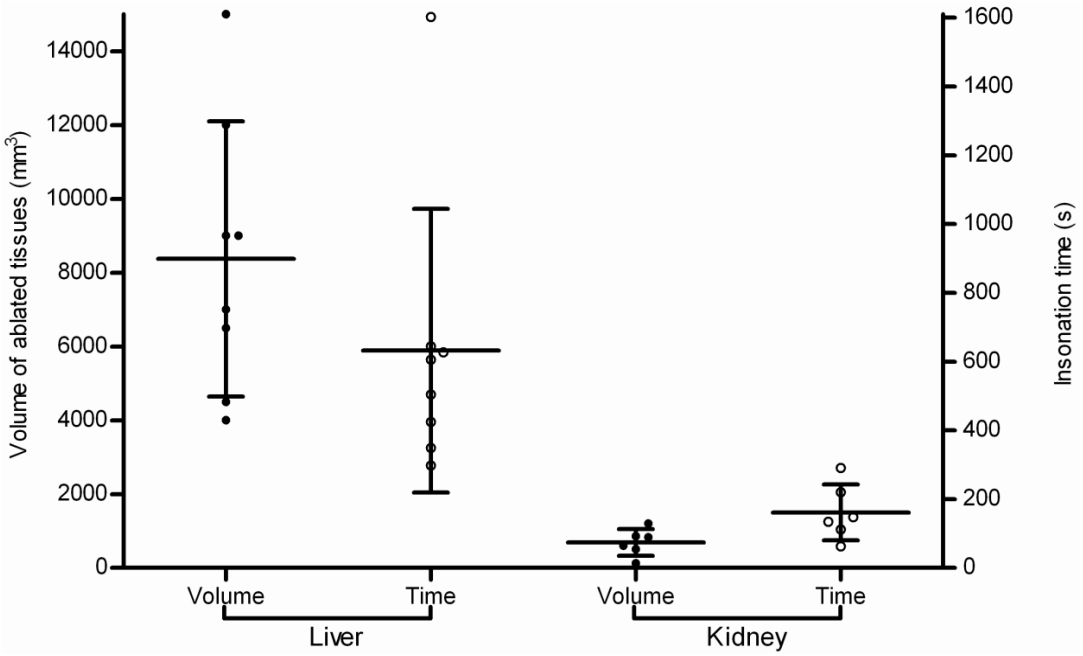

Figure 3. Volumes of ablated tissues and insonation time in the goat liver and kidney, when applying the same preoperative treatment plans. There are drastic variances between individuals. The figure also illustrates the ablation efficiency in kidney is less than that in liver.

therapeutic ultrasound propagating through the same inhomogeneous medium; thus ultrasound focuses at the target (the initial signal source). The temperature rise at the rib was 0.3℃ for time-reversal and 6℃ for conventional focusing, when the temperature rise in the focus was 20℃ (Tanter et al,. 2007).

Three-dimensional tracking is developed to modify the shift of focus. Some elements of a transducer assay work in the mode of pulse-echo, and the shift of a target referring to an element is determined by evaluating two consecutive signals. The motion of a target is caught by setting at least three separate transducers, which is used to control the release of therapeutic ultrasound (Marquet et al., 2006). A dual-mode transducer provides high intensity ultrasound for therapeutic applications and low intensity beams for diagnostic imaging, thus decreasing the shift of focus due to the disharmonism of therapeutic and diagnostic transducers (Owen et al., 2010). Dual-mode can be used to realize time-reversal noninvasively. A short pulse is delivered into the target lesion to generate/rupture cavitation bubbles. The collapse of bubbles produces shock waves, serving as the initial signal source. Shock waves travel through the medium and recorded by the transducer assay. Therapeutic beams are therefore focused at the desired volume efficiently (Gâteau et al., 2010).

COMBINED THERAPY

Radiotherapy enhances HIFU thereby improving the clinical outcomes. The repair capacity is impaired in radiated tissues; thus radiation followed by HIFU may result in burns in tissues lying in the travel path of therapeutic ultrasound and in surrounding tissues, and such traumas are refractory (Ahmed et al., 2009). This must be considered when preparing a treatment plan.

Peri-HIFU chemotherapy is commonly performed. The combination of HIFU and gemcitabine led to a response rate of 43.6% (7.3-47% in chemoradiotherapy) in pancreatic cancers (Zhao et al., 2010). A combined regime does not always improve the therapeutic outcome. The analysis of the interaction between an anticancer drug and insonation in sonochemotherapy showed an antagonism sometimes (He et al., 2011). The anticancer potency of a cytotoxic drug may be decreased by HIFU exposure (Yu et al., 2011). Some drugs, therefore, cannot be applied in HIFU therapy for a specific cancer. How to efficiently administer chemotherapy should be explored.

CONCLUSION

Clinical trials have demonstrated some limitations of USgFU, but systemically quantitative data are unavailable yet. USgFU treatment is with a low level of evidence from the perspective of evidence-based medicine.

Preclinical trials have proposed some means for improving the ablation efficiency, assessing tissue responses, mapping the temperature in real time and tracing the target lesion. These should be perfected and tested in humans.

Drastic variance of responses between tissue types/individuals makes it difficult to formulate a preoperative treatment plan. Objectively assessing tissue responses in real time provides a chance of modifying a treatment plan instantly during HIFU treatment thus improving the clinical outcomes.

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