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● *Review Article*

HIGH-INTENSITY FOCUSED ULTRASOUND– AND RADIATION THERAPY–INDUCED IMMUNO-MODULATION: COMPARISON AND POTENTIAL OPPORTUNITIES

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Abstract—In recent years, high-intensity focused ultrasound (HIFU) has emerged as a new and promising non-invasive and non-ionizing ablative technique for the treatment of localized solid tumors. Extensive pre-clinical and clinical studies have evidenced that, in addition to direct destruction of the primary tumor, HIFU-thermoablation may elicit long-term systemic host anti-tumor immunity. In particular, an important consequence of HIFU treatment includes the release of tumor-associated antigens (TAAs), the secretion of immuno-suppressing factors by cancer cells and the induction of cytotoxic T lymphocyte (CTL) activity. Radiation therapy (RT) is the main treatment modality used for many types of tumors and about 50% of all cancer patients receive RT, often used in combination with surgery and chemotherapy. It is well known that RT can modulate anti-tumor immune responses, modifying micro-environment and stimulating inflammatory factors that can greatly affect cell invasion, bystander effects, radiation tissue complications (such as fibrosis), genomic instability and thus, intrinsic cellular radio-sensitivity. To date, various combined therapeutic strategies (such as immuno-therapy) have been performed in order to enhance RT success in treating locally advanced and recurrent tumors. Recent works suggested the combined use of HIFU and RT treatments to increase the tumor cell radio-sensitivity, in order to synergize the effects reaching the maximum results with minimal doses of ionizing radiation (IR). Here, we highlight the opposite immuno-modulation roles of RT and HIFU, providing scientific reasons to test, by experimental approaches, the use of HIFU immune-stimulatory capacity to improve tumor radio-sensitivity, to reduce the RT induced inflammatory response and to decrease the dose-correlated side effects in normal tissues. (E-mail: giusi.forte@ibfm.cnr.it) **© 2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **High-intensity focused ultrasound, Thermal ablation, Anti-tumor immunity, Tumor vaccine, Radiation therapy, Cancer, Immuno-therapy.**

INTRODUCTION

In recent years, high-intensity focused ultrasound (HIFU) has emerged as a new and promising non-invasive and non-ionizing ablative technique for the treatment of localized solid tumors, including breast cancer (BC), prostate cancer, hepatocellular and pancreatic carcinoma, uterine fibroids and bone malignancies (Chaussy et al. 2005; Kennedy 2005; Wu 2006). As reported by Wu (2013), "the main advantage of HIFU is that it is less invasive than a surgical procedure, resulting in an associated reduction in mortality, morbidity, hospital stay, cost and improved quality of life for cancer patients."

Magnetic resonance–guided focused ultrasound surgery technology, which combines a HIFU beam and magnetic resonance imaging system, has the potential to locally achieve complete tumor cell destruction through thermal ablation, with great precision and minimal

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damage to adjacent tissues. By focusing a high-energy ultrasound beam to a well-defined target region, a local coagulative necrosis occurs due to the thermal dose released as the acoustic energy propagates through the focal tumor volume (Bastianpillai et al. 2015; ter Haar 1995; Wu et al. 2007a; Yang et al. 1992; Zhou 2011).

Over the last 10 y, a growing number of clinical trials have examined HIFU treatment of both benign and malignant tumours of the liver, breast, pancreas, bone, connective tissue, thyroid, parathyroid, kidney and brain. For some of these emerging indications, HIFU is poised to become a serious alternative or adjunct to current standard treatments—including surgery, radiation, gene therapy, immuno-therapy and chemotherapy (Maloney and Hwang, 2015).

Even if the best known method of HIFU is thermal ablation, interest in non-thermal, mechanical destruction is increasing; the advantages of mechanical ablation are that thermal protein denaturation remains limited and less damage is created to the surrounding tissue by thermal diffusion (Hoogenboom et al. 2015).

Compared to conventional cancer therapy modalities, such as RT and chemotherapy, HIFU can be administered repetitively without increasing the risk of systemic toxicity (Kennedy 2005), therefore, multiple HIFU sessions can be performed if local recurrence occurs.

Although these HIFU advantages have been demonstrated in extensive animal studies and clinical trials, several significant drawbacks still exist because, to date, HIFU treatment is well suited only for localized early-stage tumors and as secondary therapy used after the failure of radiation or chemotherapy treatment (Chen et al. 1998; Gelet et al. 2001, 2004).

Extensive pre-clinical and clinical studies have revealed increasing evidence that, in addition to direct destruction of the primary tumor, HIFU-thermoablation may elicit long-term systemic host anti-tumor immunity (Rosberger et al. 1994; Hu et al. 2005, 2007; Hundt et al. 2007; Kramer et al. 2004; Wang and Sun 2002; Wu et al. 2004a; Zhou et al. 2008). A stronger HIFU-enhanced anti-tumor immune response can help to remove residual cancer cells at the primary treatment site, thus decreasing or suppressing local recurrence and distant metastasis occurrence in cancer patients with original dysfunction of anti-tumor immunity.

Tumor cells develop various strategies to fully escape immune surveillance. Most tumor cells down-regulate the expression of tumor antigens and do not express major histo-compatibility complex (MHC) molecules, in order to hinder the recognition of the neoplastic cells by T lymphocytes. In this way, they cause T cell anergy or deletion and dendritic cell (DC) dysfunction (Formenti and Demaria 2009; Pinzon-Charry et al. 2005; Zeng et al. 2013). In addition, tumor cells can inactivate effector T lymphocytes through the secretion of immuno-suppressive cytokines or induction of apoptosis.

It has long been recognized that the immune system plays a pivotal role in tumours. On the one hand, immunologic factors can suppress tumour development by killing cancer cells or inhibiting their growth. On the other hand, immune cells are able to induce an immuno-suppressive micro-environment that contributes to promote tumour progression (Di Maggio et al. 2015).

A pivotal role of anti-tumor immunity is the selective recognition and disruption of tumor cells by the host immune system. To achieve this effect, tumor cells should express tumor-associated antigens (TAAs) able to induce a tumor specific immune response. However, the presence of impaired immune functions is one of the main factors involved in cancer development and progression. Basically, cancer cells escape the immuno-surveillance by secreting cytokines with immuno-suppressive potential and by reducing the TAA presentation (Lindau et al. 2013). Furthermore, in most tumor patients, lymphocyte-mediated immunity fails to control the primary lesion outgrowth and cannot prevent local recurrence and metastasis that are usually cause of many cancer therapies' failure. Instead, tumor growth control and spontaneous regression have been observed after thermal ablation of primary lesion in some cancer patients (Ablin et al. 1973; Cammarata and Forte 2014; Gravante et al. 2009; Sanchez-Ortiz et al. 2003; Soanes et al. 1970; Zhou 2011), suggesting that, during the necrotic tissue resorption process, the immune system is stimulated by the ablated mass to activate and enhance a stronger specific long-term immune response against tumor (Bayjoo et al. 1991; Miya et al. 1987; Muller et al. 1985). In recent y, several reports have described that HIFU, as thermoablative technique, has the capacity to induce boost host anti-tumor immunity successfully, although clinical evidences have also revealed that local recurrence and metastasis can unfortunately also occur after HIFU treatment. Therefore, an active immunologic stimulation using immuno-adjuvants could be useful in order to enhance the effectiveness of HIFU-triggered anti-tumor immunity.

On the other hand, RT is the main standard therapeutic modality for many types of localized solid tumors, used in both curative and palliative cancer treatment, as about 50% of all cancer patients receive RT, often used in combination with surgery and chemotherapy (Bernier et al. 2004).

Recent data suggest that RT can modulate the anti-tumor immune responses, modifying the tumor and its micro-environment, triggering an inflammatory process