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REVIEW ARTICLE

Focused ultrasound: tumour ablation and its potential to enhance immunological therapy to cancer

[1]GIOVANNI MAURI, [2]LUCA NICOSIA, MD, [3]ZHEN XU, [2]SALVATORE DI PIETRO, [4]LORENZO MONFARDINI, [1]GUIDO BONOMO, [1]GIANLUCA MARIA VARANO, [5,6,7]FRANCESCO PRADA, [1]PAOLO DELLA VIGNA and [1]FRANCO ORSI

[1]Deparmtent of interventional radiology, European istitute of oncology, Milan, Italy
[2]Postgraduate School of Radiology, Università degli Studi di Milano, Milan, Italy
[3]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA
[4]Department of Radiology and diagnotic imaging, Poliambulazna di Brescia, Brescia, Italy
[5]Department of Neurosurgery, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[6]Department of Neurological surgery, University of Virginia Health Sciences Center, Charlottesville, VA, USA
[7]Focused Ultrasound Foundation, Charlottesville, VA, USA

Address correspondence to: Dr Luca Nicosia
E-mail: *lucanicosia88@gmail.com*

ABSTRACT

Various kinds of image-guided techniques have been successfully applied in the last years for the treatment of tumours, as alternative to surgical resection. High intensity focused ultrasound (HIFU) is a novel, totally non-invasive, image-guided technique that allows for achieving tissue destruction with the application of focused ultrasound at high intensity. This technique has been successfully applied for the treatment of a large variety of diseases, including oncological and non-oncological diseases. One of the most fascinating aspects of image-guided ablations, and particularly of HIFU, is the reported possibility of determining a sort of stimulation of the immune system, with an unexpected "systemic" response to treatments designed to be "local". In the present article the mechanisms of action of HIFU are described, and the main clinical applications of this technique are reported, with a particular focus on the immune-stimulation process that might originate from tumour ablations.

INTRODUCTION

Image-guided ablations are nowadays applied for the treatment of a large variety of malignant and benign disease, being often included in international guidelines as an effective alternative to standard surgical treatments.[1–3] The advantages of percutaneous ablation *vs* surgery include reduction in hospitalization length and patient's morbidity and allows to treat patients not eligible for surgery. Also, thanks to the improvement of image guidance techniques, image-guided ablations are nowadays indispensable in clinical practice, and interventional oncology is widely recognized as the fourth pillar of oncology.[4,5]

Some different techniques have been applied in the last years for percutaneous treatment of tumours located in different body regions. Radiofrequency ablation has been the first technique widely accepted for the treatment of hepatic and renal tumours, while other techniques, such as cryoablation, laser ablation and microwave ablation are gaining increasing interest in different scenarios due to their peculiar characteristics.[6–8] Among the different options for image-guided tumour ablation, high intensity focused ultrasound (HIFU) achieved a particular interest in the last years, being the only totally non-invasive technique, as with HIFU not even a small incision for device insertion is needed, and actually is used in several clinical application including treatment of benign and malignant tumours[3,9–11] functional neurosurgery for back pain,[12] for essential tremor[13] or Parkinson's disease.[14]

Biological properties of ultrasound were first discovered in 1927 and studied (explored) in subsequent years.[15] For a long time, however, these effects have not been used in clinical applications: indeed the first clinical use in literature was published in 1994 for prostate cancer,[16] followed by larger series in recent years in which the utility of HIFU in various disease has been reported.[17–21]

One of the most fascinating aspects of image-guided ablations that has been recently investigated is their ability to achieve a sort of stimulation of the immune system, with an unexpected "systemic" produced by a "local" approach.[22–24] Sparse evidence of an immunomodulated effect has been reported, and a better identification of the mechanism underlying the systemic effect generated by a local ablative treatment represents one of the most intriguing challenges for investigators at the present time.

In the present article the mechanisms of action of HIFU are described, and the main clinical applications of this technique are reported, with a particular focus on the evidence regarding the immune response to local ablative treatments, and in particular HIFU.

Physical basis of tissue destruction by HIFU

HIFU is based on the possibility to deliver high intensity energy into a very small focal spot inside the body, by precisely focusing an ultrasound beam on a specific target (often deeply located in the body). High-intensity ultrasound (in general greater than 5 W cm^{-2}) can produce coagulation necrosis in biological tissue and this is the phenomenon mainly exploited in HIFU ablation technique. In contrast, low-intensity ultrasound (0.125–3 W cm^{-2}) leads to non-destructive heating and can be used for other clinical applications (*e.g.* treatment of back pain).[25]

The biological effects of HIFU can be explained considering two principal mechanisms: thermal damage and mechanical damage.

The thermal effect of HIFU can be explained by absorption of the acoustic energy and its conversion to heat at the targeted point. The heat increases the temperature rapidly to 60°C or higher, producing local coagulative necrosis.[26] Similar to other thermal ablations, increase in temperature above 60°C causes protein denaturation and coagulation necrosis. As thermal effects of ultrasound absorption are linearly proportional to the sonic intensity, they can be predictable.[27]

Even though thermal damage is the most considered effect of HIFU, non-thermal mechanical destruction might have an even more relevant role in HIFU ablation, particularly regarding the immunomodulated effect.[28] Mechanical ablation rather than thermal ablation seems to provide less damage to the surrounding tissue, as the mechanical effect is not impacted by heat perfusion via blood flow, and the treated area is more precisely demarcated as it coincides with the ultrasound focal region.[29] One of the most important differences in mechanical ablation as opposed to thermal ablation is the absence of protein coagulation necrosis.

Tissue exposure to repeated short duration pulses with low duty cycles of HIFU let to achieve mechanical disruption and to fractionate tissue in a controlled manner.[30]

The main mechanisms associated with mechanical tissue destruction in HIFU ablation are represented by acoustic cavitation.

Acoustic cavitation

Acoustic cavitation is based on the interaction between ultrasound waves and bubbles of gas. In HIFU ablation, sinusoidal frequencies in the range of 0.5–5 MHz with high acoustic intensity are generally used. In the tissue, at high acoustic pressure level, the peak positive (compression) part of the sinusoidal wave travels faster than the peak negative (rarefraction) part of the wave due to the non-linear ultrasound wave propagation, which creates a shockwave as the ultrasound wave penetrates the tissue. Cavitation occurs as the result of this non-linear effect for which microbubbles (that are different from the boiling bubbles formed in thermal effects) can be formed if the negative pressure is sufficiently intense. Briefly, cavitation phenomenon occurs when ultrasound wave intensity exceeds a specific threshold, as the negative pressure is sufficiently high to overcome the surface tension of the gas nuclei available in the tissue. These bubbles are subjected to non-linear oscillations caused by the ultrasound with consequent asymmetrical collapse and disintegration associated with cell death and tissue damage. To obtain cavitation in biological tissues the presence of gaseous nuclei, which is typical of mammalian tissues[31] is needed. Two main types of acoustic cavitation can be described: stable cavitation and inertial cavitation. Stable cavitation develops when a bubble oscillates repeatedly in an ultrasonic field, intercepting and radiating energy to the surrounding tissues. This causes microstreaming of fluid around the bubble and destruction of surrounding tissues. When the ultrasound pressure is high, the radius of the bubbles expands significantly larger than twice of the initial radius followed by energetic collapse, causing localized high acoustic pressure of several thousand atmospheres.[32]

In literature cavitation has been sometimes related to vascular damage and disruption, which can cause local and potentially systemic effect in tumour treatment, even if the main mechanisms underlying the interaction of these agents with HIFU remain unknown.[33,34]

Some studies showed that when acoustic cavitation is combined with radiation or chemotherapy, enhanced therapeutic effects are observed.[35]

For example, when treating *in vivo* 45 cases of bladder cancer in mice, Tran et al[36] showed additive antitumour and antivascular effects when ultrasound microbubbles were combined with radiation, thus opening up a wide spectrum of possibilities for future treatment of human cancer.

Moreover, cavitation mechanism can indirectly cause the formation of a lithotripsy shockwaves that seems to present broad potential for non-thermal biologic effect in treating tumour, even if limited experiences reports that lithotripsy associated with cavitation phaenomenon may increase the development of distance metastasis.[37,38]

Histotripsy

Another important effect that might be achieved with HIFU is the so-called "histotripsy": mechanical fractionation and emulsification of tissue into liquid-appearing acellular homogeneate produced by high pressure ultrasound pulses. There are two types of histotripsy: cavitation cloud histotripsy and boiling histotripsy. In CH, microsecond-length (<20 µs) ultrasound pulses at very high pressure (>15 MPa) and low duty cycle (<5%) are used to generate a dense cloud of cavitation microbubbles.[39]

The pulsing method in CH is different than in acoustic cavitation method commonly reported, where the acoustic pressures are about two times lower and the pulses are about 1000 times longer. In CH, the energetic expansion and collapse of the cavitation bubbles formed by microsecond pulses produce high strain and stress to fractionate the target tissue into liquid appearing acellular debris.[40, 41] In BH, millisecond-long (1–20 ms) bursts of high amplitude HIFU shock waves (p +> 60 MPa) are used to cause boiling at the focal spot[42] to form large boiling bubbles (up to millimetre).[43] The millimetre-sized boiling or vapour bubbles fractionate the target tissue into liquid-appearing acellular fragments.[42, 43] The physical mechanism of fragmentation is due to the rapid heating within milliseconds produced by the high amplitude shock fronts formed via the non-linear propagation effects and its further interaction with previously formed gas bubbles that cause mechanical fractionation of tissue.

Furthermore, cavitation bubbles in CH and boiling bubbles in BH are hyperechogenic, and tissue fractionation and emulsification are hypoechonic, so the histotripsy treatment process and result can be easily monitored in real time using ultrasound imaging. The damage induced is purely mechanical and contained no visible signs of thermal denaturation.

Emulsified lesions with no evident thermal damage can be induced using different parameters of the pulsing scheme and the lesion created by CH and BH is very homogeneous, with no visible cellular components.[44–47] Thus histotripsy is more predictable and repeatable over the conventional thermal method.

In the *in vivo* large animal model, CH has been used to create lesions in the liver kidney,[48] prostate[49, 50] and heart.[51, 52] Lesions were generated with very sharp margins (<1 mm), and the large vessels in the treated region were structurally intact while the surrounding tissue was completely fractionated and liquefied into acellular homogenate.The liquefied tissue homogenate is completely absorbed within 1 month, resulting in tissue volume reduction similar to surgery and with minimal fibrous tissue remaining.The number and range of animal studies by BH is less but indicated the similar results.[46]

Clinical applications of HIFU

HIFU has been used in the treatment of a large variety of diseases. The two actual most represented applications are the treatment of uterine fibroids and the palliative treatment of unresectable pancreatic cancer.

HIFU is nowadays widely used in the treatment of uterine fibroids, and may result in reduction of pain and pressure, frequent urination and/or constipation, and excessive menstrual bleeding with less complications in comparison with surgery.[53, 54] In a study by Dobrotwir et al[54] the treatment of 100 females with HIFU was safe and effective with no significant complications reported during the treatments or during the course of the follow-up period. HIFU has also shown promising results in the treatment of adenomyosis with hypothermic destruction of "islands" of aberrant endometrium after precise targeting of adenomyotic tissue.[55]

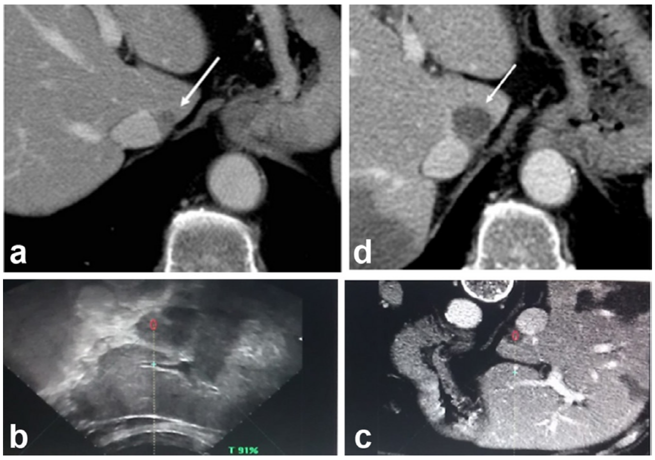
Complications related to the HIFU treatment for fibroid are limited and rarely severe, and include haematuria for bladder heating, skin burnt or pain after the procedure.[56]

In the treatment of advanced stage pancreatic cancer, HIFU showed promising results in pain relief and in increasing median survival.[57–60] Li et al[59] performed a study on 120 patients with pancreatic cancer refractory to gemcitabine. Among these patients 61 were treated with combination of HIFU and S-1, and 59 with only S-1. Authors found a significantly longer median overall survival (10.3 *vs* 6.6 months, p < 001) and median progression free survival (5.1 *vs* 2.3 months) in the group of patients treated with HIFU in combination with S-1. Also, pain remission rate was significantly higher in patients treated with HIFU (57 *vs* 20%, p < 001) than in patients treated with S-1 alone. Li et al[61] performed in 2016 a systematic review of the literature on HIFU treatment of pancreatic cancer. Even though affected by a low quality of the included studies, in this systematic review clinical benefit rate of HIFU plus radiation and chemotherapy was significantly higher than in patients treated with radiation therapy ($p < 0.05$), or various regimen of chemotherapy ($p < 0.05$) alone.

HIFU is currently used in the liver for the treatment of both unresectable advanced HCC (Hepatocellular Carcinoma) and liver metastases with good results and tolerance even in patients with advanced Child-Pugh stage and cirrhosis.[62] Cheung et al[62] analysed a group of 100 cirrhotic patients treated with HIFU ablation, including also Child-Pugh C patients, trying to identify predictive factors for HIFU intolerance. Authors found 13% of complications, mainly represented by skin burn of various grade. Age was the only predictive factor for complications at univariate analysis. They concluded that HIFU might represent a well-tolerated new alternative treatment even for Child-Pugh B or C patients. Moreover, HIFU has been found to be both safe and effective also in treating tumours adjacent to major vessels. One case of a patient with colorectal liver metastasis close to the inferior vena cava treated with HIFU is shown in Figure 1. However, application of HIFU to the liver might be difficult due to obstacles to ultrasound-directed therapy, such as ribs, interposed lung parenchyma and respiratory motion of the liver itself.[63] Some rare complications are reported in literature such as rib fractures, pneumothorax, pleural effusion, biliary obstruction and fistula formation.[64] Some recent studies demonstrate the possibility to use HIFU with transarterial chemoembolization in the treatment of HCC with very promising results.[65]

Utility of HIFU in treating breast cancer has been proved in a few studies, in particular for early stage disease. HIFU could be particularly useful in treating females who do not desire surgery or who are not surgical candidates.[3, 66, 67] The work proposed by Merckel et al[67] reported successful MR-HIFU ablation with a dedicated breast system with histopathologically proven complete tumour necrosis. In a recent systematic review and meta-analysis on minimally invasive treatments of breast tumours, HIFU was reported to have 96% (90–98%) technical success and 49% (26–74%) pooled technique efficacy.

Figure 1. Case of a patient with colorectal liver metastases in a difficult location close to the inferior vena cava successfully treated with HIFU. (a) A contrast-enhanced CT showing a lesion (arrow) located very close to the inferior vena cava. (b) Treatment with HIFU and fusion of real-time ultrasound images. (c) Treatment with HIFU and fusion of real-time CT images. (d) A contrast-enhanced CT showing large area of ablation without residual vital tissue 3 months after the treatment. HIFU, high intensity focused ultrasound.



Also prostate diseases can be treated with HIFU: initially treatment was proposed only for benign prostate hyperplasia, while today increasing attention is focused on the treatment of prostate cancer.[68, 69] Some author reported that low-risk patients (prostate-specific antigen level low than 10 ng ml^{-1}; clinical stage cT1 or cT2a; and absence of Gleason pattern 4 or 5 tumour on biopsy) could be better managed with conservative therapy such as HIFU in order to avoid the complications of surgery (incontinence, impotence, anorectal dysfunction) with very satisfactory results.[70, 71] Blana et al[72] reported the results of long-term follow-up in 163 patients who underwent HIFU treatment for prostate cancer. Within the 4.8 ± 1.2 years of follow-up, no patients died of prostate cancer, 86.4% had a PSA nadir of <1 ng ml^{-1} and 92.7% was found to have negative post-treatment biopsy. The most common complications, associated with HIFU ablation of prostate cancer are represented by urinary tract infections, fistula, and urinary incontinence.[73]

Of great interest is the application of HIFU for the treatment of intracranial tumours: ultrasound beams generated by multiple transducers, although attenuated, can be in fact directed trans-cranially under MR guidance. Through phase corrections simulated relying on pre-acquired CT the beam's paths are corrected and the focus aimed at the tumour.[74] While there are some pre-clinical studies in this regard[75] there are only very few reports on the use of HIFU for brain tumour ablation in human so far: the first attempt was reported by Ram et al in 2006 using direct HIFU through a craniotomy 7 days prior to treatment in patients with recurrent glioblastoma, resulting in histological evidence of thermocoagulation.[76] In another study published in 2010 by McDannold et al the authors managed for the first time to perform trans-cranial MR-guided HIFU. The aim was ablation of intracranialglioblastomas otherwise not suitable for resection in three patients. Although the authors did not achieve a complete thermal coagulation they demonstrated for the first time the feasibility of this technique.[77] Promising results are also foreseen in the field of blood–brain barrier opening, in order to allow the delivery of therapeutic agents. Many pre-clinical studies demonstrated that the blood–brain barrier can be safely and temporarily opened using HIFU combined with microbubbles, therefore using a low energy, targeted and non-invasive method.[78, 79]

Whatever the organ treated, an important effect of HIFU is represented by an improvement in cancer-related pain. This is of crucial importance, *e.g.* in patient with pancreatic adenocarcinoma, in which cancer-related pain is often very difficult to be controlled even with strong painkillers and morphine. This effect is probably due to the mechanical effect of HIFU, which seems to induce neuromodulation and pain relief through a reversible block of nerve activity maybe for the destruction of some locally active nociceptive nerve fibres in adjunct to a reduction of inflammatory tumour environment.[17, 80]

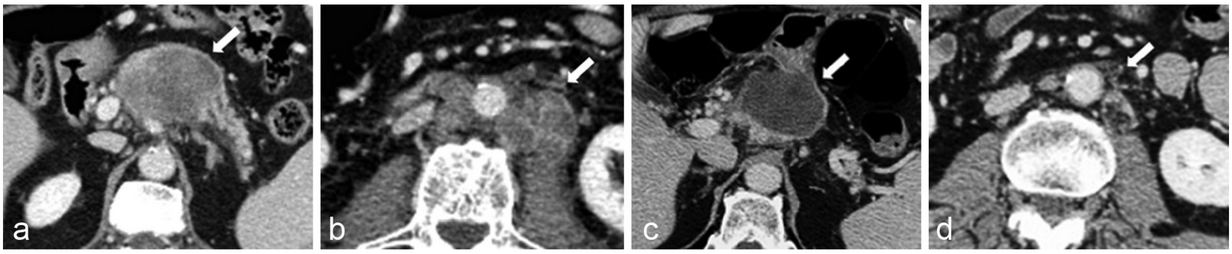
Immunomodulation effect of thermal therapies and HIFU

In the last few years it has been shown that activation of immune system through, *e.g.* adoptive T cell transfer or vaccination can play a role in the treatment of cancer patients.[81] Some cases of systemic response to local ablative therapies have been reported, and the immunostimulating effect of ablative techniques is actually one of the most interesting fields of investigation for researchers.[22–24]

In 2003 Sánchez-Ortiz et al[82] reported the resolution of lung metastasis after ablative treatment of primary renal tumour; similar case of pulmonary and adrenal metastases resolution after ablation of renal cancer was subsequently reported by Kim et al[83] Some authors, investigating the role of immunostimulation of radiofrequency ablation on lung tumours, performed ablation of four lung cancer followed by surgical resection, and documented a local and systemic immune response subsequent to RFA (Radiofrequency Ablation). In this study RFA leads to an activated and highly T-cell-stimulatory phenotype of dendritic cells, which was considered to promote long-term immunity against lung cancer.[84] These preliminary experiences and case reports opened the way for more specific investigations on the systemic effects of local therapies.[85]

Of particular relevance appear to be the immune-response to HIFU treatment. Particularly, the phenomenon of cavitation, not providing thermal destruction and denaturation of the proteins, seems to be a very promising mechanism of immunostimulation.[86] Immunitary response phaenomenon related with HIFU technique, could be explained considering this theory: cancer debris remain *in situ* after HIFU treatment and could be seen as antigens for the immune system. This can act as a sort of *in situ* vaccine able to stimulate systemic immune responses, involving T cells and cytokines, also elsewhere in the body.[87] Tumour antigens present in the depot of damaged or death cells can be captured by phagocytic cells that subsequently migrate toward tumour-draining lymph nodes. Antigens could also passively enter the circulation or lymphatics and be transported

Figure 2. Case of a patient with a pancreatic adenocarcinoma treated with HIFU ablation with abscopal response of distant lymph-node metastases. (a) A contrast-enhanced CT showing a 7 cm mass at the level of pancreatic body (*arrow*). The lesion was considered to be not suitable for surgical resection and was fast growing under chemotherapy. (b) The same CT scan demonstrated the presence of lymph-node metastases in the paraortic space (*arrow*). The patient underwent treatment with USg (Ultrasound guided)-HIFU for pain palliation. (c) A contrast-enhanced CT scan performed 1 year after the procedure demonstrated large avascular area in correspondence of the treated tumour (*arrow*). (d) The same CT scan demonstrated the complete disappearance of the pathological lymph nodes (*arrow*). HIFU, High intensity focused ultrasound.



to lymphnodes where they can be taken up by lymph-node-resident phagocitic. This type of mechanism is essential for tumour-specific immune responses.[81, 88]In general it has been shown that T cells recognizing clonal neoantigens were detected in patients with good clinical outcomes, while poor responders showed enrichment of T cells recognizing only subclonal neoantigens.[81] Wang and Sun report on HIFU treatment of 15 patients with late-stage pancreatic cancer. Changes in natural killer NK cell activity and T lymphocyte and subset were observed in 10 patients after HIFU treatment. The results showed that the average values of NK cell, CD3þ, CD4þ and CD4þ/CD8þ ratios in peripheral blood increased after HIFU.[89] In the study of Wu [108] et al 48 females with biopsy-proven breast cancer (T1–2, N0–2, M0) were randomized to receive modified radical mastectomy or HIFU followed by modified radical mastectomy. In both the primary breast cancer and the axillary lymph nodes, positive expression of DC, macrophages and B lymphocyte were significant higher in the HIFU group than those in the control group.

Immunoresponse to local therapies might be the reason for the so-called "abscopal effect", first described in 1953[90] and widely reported in literature:[81, 91] local treatment of one tissue induces a response in another or similar tissue remote from the treated site. This phenomenon has been explained with antigen presentation (debris of tissue damage from HIFU) to the cytotoxic immune system. Consequence of this activation is the increasing of MHC I on the tumour cell surface, an improving expression of the FAS/CD95 complex, and an increasing production of a cytokine pattern that facilitates migration and function of effector CD8 +T cells.[81, 90] The correlation between abscopal effect and immunological response is a key to explain distant effect after local therapy. The stimulation of immune response after local ablation play an important role on tumour control.[92, 93] The exposure of tumoral antigen, after cellular damage, determines a phenomenon similar to "*in vivo* vaccination" against tumour.[82, 92, 93] Furthermore it is possible the development of antibodies that can influence local tumour eradication, control of distant localization and are responsible for immunologic memory against cancer cells.[92] "Antitumoral-induced immunity" is phenomenon that explain regression of distant metastasis after radiofrequency ablation.[82, 83, 91] One case of a patient treated with HIFU for a pancreatic adenocarcinoma in whom an abscopal effect determined reduction of nodal metastases is presented in Figure 2.

Moreover, in some preliminary studies performed it is shown that cavitation and the damage induced by HIFU in the endothelial cells in the vessel trigger the immune response.[94]

Even though quite widely reported in the literature, the immunomodulated effects of local ablative treatments still have to be fully understood, and further studies on the topic are necessary. Particularly, the role of different kind of ablations needs to be investigated, as at the present moment it is still not clear whether mechanical ablation might be a better way to induce stimulation of the immune system. In this hypothetical scenario, HIFU ablation might represent the ideal ablative technique, being able to achieve mechanical ablation through different mechanisms.

CONCLUSIONS

In conclusion, HIFU appears to be a very promising novel technique for the non-invasive image-guided treatment of cancer. Particularly, thanks to its ability of producing mechanical ablation, HIFU might be the most effective ablative technique in order to achieve an immunostimulation effect against cancer, with consequent possible abscopal effect and induction of a long-term immunity against cancer. This fact opens a new scenario for the application of HIFU in the care of cancer patients, and the basis for future analysis and studies aimed at a better understanding of immunomodulation and immune response related to image-guided local ablative techniques.

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