

REVIEW

ABSCOPAL EFFECTS INDUCED BY LOCALIZED INTERVENTIONS IN ONCOLOGICAL PATIENTS

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ABSTRACT

Abscopal, or out-of-fields effects were reported among a number of oncological patients, who were treated with radiation therapy in combination with immune checkpoints inhibitors. The radiations induce a localized immunogenic cell death within the malignant tissues of the irradiated area. Necro-apoptotic cancer cells, in turn, stimulate tumor-specific immune responses in oncological patients, who were previously treated with immune checkpoints inhibitors. Consequently, the host immune system is able to target

malignant cells that are present in various parts of the organism. Similar findings were observed in cancer immunotherapy clinical trials that combined immune checkpoints inhibitors with oncolytic viruses, immunomodulatory agents and chemotherapeutics, whereas some clinical trials are underway to combine immune checkpoints with focused ultrasound techniques. Clinical studies are currently in progress to increase the frequency and the efficacy of abscopal effects among oncological patients.

KEY WORDS

Abscopal effects; radiation therapy; cancer immunotherapy; CTLA4; PD1; PDL1; PDL2; immunomodulators; immunogenic cell death; oncolytic viruses; oncolytic peptides.

IMPACT STATEMENT

This article covers the most recent findings in the field of oncology. Immune checkpoints inhibitors have been utilized in clinical trials in combination with therapeutic agents that induce traumatic cell death in malignant tissues, which, in turn, may result in system immune responses against the tumor.

INTRODUCTION

Radiation therapy is an important technique for the treatment of malignancies (1, 2). Roughly 60% of oncological patients receive radiation therapy, often in combination with chemotherapy and/or surgery (1-6). Radiations can be administered into patients either as external-beam radiation therapy (EBRT), or internal radiotherapy (1, 7, 8). EBRT utilizes collimated γ -rays, X-rays and particle therapy (1, 7, 8). The latter comprises protons, carbon ions (9), electrons (10, 11) and 10B-based neutron capture therapy (12-15). Internal radiotherapy consists of two kinds of methodologies, such as brachytherapy and systemic radiation therapy (7). Brachytherapy utilizes radioactive material incorporated inside a small capsule, which can be either implanted within the tumor mass (interstitial brachytherapy), or into a cavity that is adjacent to the tumor (intracavity brachytherapy) (7).

All types of ionizing radiations induce genetic and molecular alterations in the cells, which result in substantial antiproliferative and cytotoxic outcomes, leading to malignant cell death (16, 17). Naturally, ionizing radiations may also affect normal tissues, generating, therefore, a variety of unwanted adverse effects in patients (16, 17).

The in-field irradiation consists of a radiotherapy beams that is directed against malignant tissues in a specific area of the body (18). Over the decades, the energy and intensity of the incident radiation were remarkably enhanced, while the delivered dose was sharply restricted to the target, in order to reduce the detrimental side effects in healthy tissues and organs. To this end, more selective techniques have been developed, such as stereotactic ablative radiotherapy (SABR) and stereotactic radiosurgery (SRS) that are regulated with high precision either by computed tomography (CT)-, or magnetic resonance imaging (MRI)-based imaging systems (19-21), which allow for a more selective detection and destruction of small tumor masses, such as oligometastases and early-stage malignancies (19, 22-28).

Interestingly, the radiation beam may also affect tissues and/or cells that are external to the irradiated target (18, 21). These phenomena were termed out-of-field, or abscopal effects (29). Studies in the 1950s reported a variety of radiation-derived effects in tissues that were far away from the irradiated site (29). The out-of-field effects induced a wide variety of biological artifacts, such as chromosomal aberrations, genetic instability, abnormal gene expression,

radiation-induced malignant transformation in normal cells, either increased resistance or sensitivity to radiations, various types of cell death and, intriguingly, regression of non-irradiated tumor masses (21, 30, 31). The latter finding attracted suddenly the interest of the oncologists. However, the spontaneous out-of-field tumor remissions were very rare among oncological patients and were referred to as abscopal effects (3, 21, 32, 33).

A considerable increase in radiation therapy-related abscopal effects among oncological patients was reported in the last years, in clinical trials that utilized immune checkpoints inhibitors either in combination with radiation therapy (**figure 1**) (3, 21, 32-34), or with oncolytic viruses (34). Several cancer immunotherapy clinical trials were conducted in the last decade (34-41), which used monoclonal antibodies for the inhibition of immune checkpoint systems, such as the cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death protein 1 (PD1), programmed cell death 1 ligand 1 (PDL1) and PDL2 (34, 42-47). Oncological patients were enrolled in the cancer immunotherapy clinical trials for the treatment of hematological malignancies and for a wide range of solid tumors (34-54). The clinical outcomes were rather promising among a considerable proportion of participants (34-54). Over the last five years, most cancer immunotherapy clinical trials administered immune checkpoints inhibitors in combination with other treatments, such as immunomodulators (54-58), chemotherapeutic agents (57), radiation therapy (58) and oncolytic viruses (34). In summary, immune checkpoint inhibitors predispose the host immune system of the patient to tackle the cancer cells, whereas a localized therapeutic intervention enhances the efficiency of the immune response in eliminating tumor deposits, which may result in a systemic response against the malignancy.

This review describes the strategies that have been adopted in cancer immunotherapy clinical trials to optimize abscopal effects in oncological patients.

IMMUNOGENIC CELL DEATH AND ABSCOPAL EFFECTS

As anticipated, in radiobiology the out-of-field effects include a wide range of possible interactions

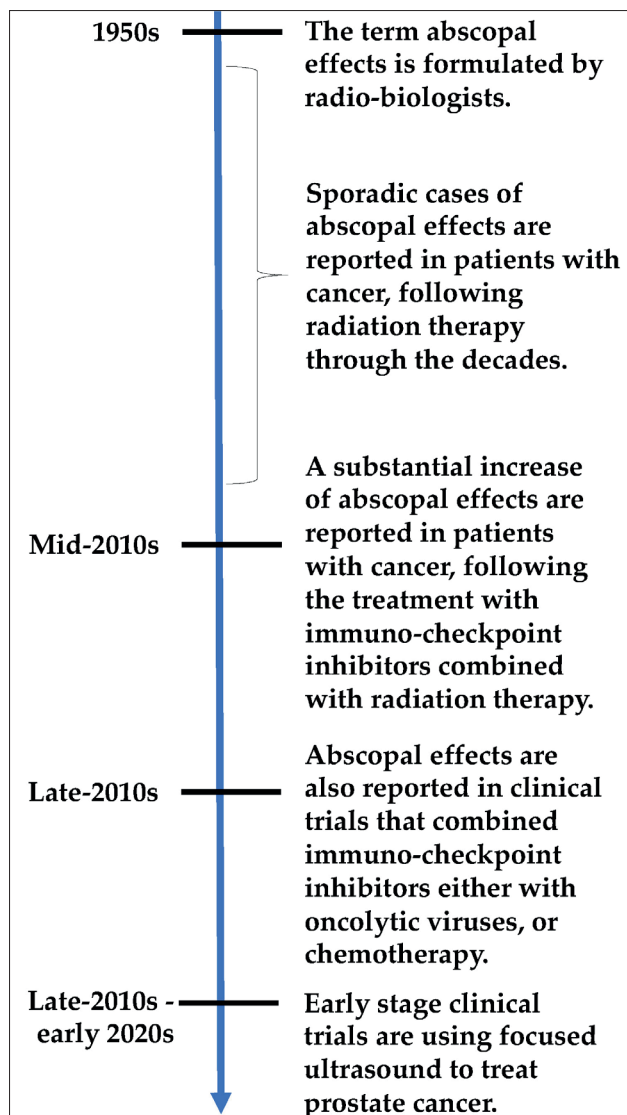


Figure 1. Timeline of abscopal effects reported in cancer therapy and in clinical trials.

on organs and on healthy and/or malignant tissues, such as genetic and/or epigenetic modifications that may induce secondary malignancies, either enhanced resistance or susceptibility to the radiations, necrotic and/or apoptotic cell death and other types of events that may be responsible to tissue and/or organ damage (21, 30-32). Oncologists, however, are mainly interested in characterizing the possibility that a localized intervention may ultimately stimulate a systemic reaction of the organism against cancerous tissues (3, 21, 32, 33). The localized therapeutic intervention may be based on radiation therapy, chemotherapeutics, oncolytic viruses, lysing peptides and so on. Of course, a particular emphasis has been placed on radiation therapy over the last years, because of the significant increase of reported abscopal effects in oncological patients, who

were treated with immune checkpoints inhibitors in combination with radiation therapy.

Radiation therapy technology has been significantly improved over the decades, in order to increase the specificity of the in-field effect on the area of the tumor (19, 32, 59, 60, 61). The radiation portals of old instruments were wider and often affected healthy tissues and/or organs contiguous to the area of the irradiated tumor (61-63). A more specific in-field application for the tumor of recent instruments minimizes the collateral damages of the radiations to the healthy tissues and organs of the patients (19, 32, 59, 60, 61). The hematopoietic system has been particularly exposed to the detrimental effects of less specific radiation portals of old instruments, with consequent immunosuppression of the subject (61-63). In addition to the radiation portal size, other out-of-field effects may be related to scattered radiations inside the body (64-66), leaky radiations from the source of the instrument that produces the beam (30, 67) and bystander effects that are induced in response to the radiations (21, 30, 33, 60, 68). The impact of the radiation on the surface of the target may deflect a portion of the beam, which, in turn, diffuses inside the body and affects other organs and tissues (64-66), whereas various bystander effects may derive from factors that are secreted or released by irradiated malignant cells and/or surrounding normal cells tissues or cells (21, 30, 33, 60, 68). The secreted factors, in turn, may interact with the tissues of distant organs (21, 30, 33, 60, 68).

The major focus of oncologists consists of improving the efficiency of clinical protocols leading to abscopal effects, which derive from an intervention in a restricted area of the body that ultimately results in a systemic response against the tumor (3, 21, 32, 33). The characterization of abscopal effects in oncological patients has demonstrated an involvement of the immune system (3, 21, 32-34). In fact, abscopal effects are more frequent when the immune checkpoint inhibitors are combined with radiation therapy for the treatment of the oncological patients (3, 21, 32-34, 69). A common adverse effect of radiations in cancer therapy is related to the immune suppression of the subjects. However, many clinical trials showed that localized interventions may eventually trigger systemic immune responses against the tumor in a significant number of patients (18, 21, 30-34). The highly collimated radiation that targets the in-field area of the tumor induces necrotic and/or apoptotic cell death (**figure 2**), along with epigenetic mutations that induce phenotypic alterations

of cancer cells, which may increase the expression levels of a variety of molecules on the surface of malignant cells, such as tumor-associated antigens, cell death receptors and adhesion molecules (34, 70, 71). Taken together, the phenotypic alterations of malignant cells and the necro-apoptotic cell death produce a sort of immunogenic hub, which may act as an *in situ* vaccine against cancer cells (**figure 2**) (18). Naturally, the use of immune checkpoint inhibitors increases the efficiency of the radiation-induced *in situ* vaccine, which may lead to a systemic immune response against the malignancy (18, 21, 30-34). Overall, radiation therapy is utilized to induce genetic and molecular injuries in tumor cells, which may lead to proliferative arrest (72), activation of caspases resulting in apoptosis (73, 74) and different kinds of programmed necrotic cell death, or necroptosis (75-77). Intracellular and extracellular factors take place in the regulation of the traumatic cell death that leads to necroptosis (**table I**). The so-called necroptotic pathway is associated with two intracellular axis: (I) the mixed lineage kinase domain-like (MLKL)-protein and the receptor-interacting protein

kinase 3 (RIPK3) (73-75); (II) the poly(ADP-ribose) polymerase 1 (PARP1) and the apoptosis-inducing factor mitochondrion-associated 1 (AIFM1) (78, 79). The PARP1 and AIFM1-related necroptotic cell death is also known as *parthanatos*, which is a Greek mythology-derived term for messenger of death (78, 79). The tumor suppressor protein p53 is another important player in mediating the elimination of the cells that cannot complete the mitotic program, due to radiation-induced mitotic catastrophe (80-82). Danger associated molecular pattern molecules (DAMPs) can also take a role in modulating radiation therapy-mediated host immune responses (**table I**) (83, 84). DAMPs are discharged by injured and/or dying cells and comprise chromatin, fragments of double-stranded DNA, RNA molecules and high-mobility group protein 1 (HMGB-1) (83, 84). The released DAMPs are then recognized by the toll-like receptors (TLRs), following a mechanism that is analogous to the pathogen-associated molecular pattern molecules (83). The interaction between DAMPs and TLRs leads to immunogenic cell death that requires the activation of mac-

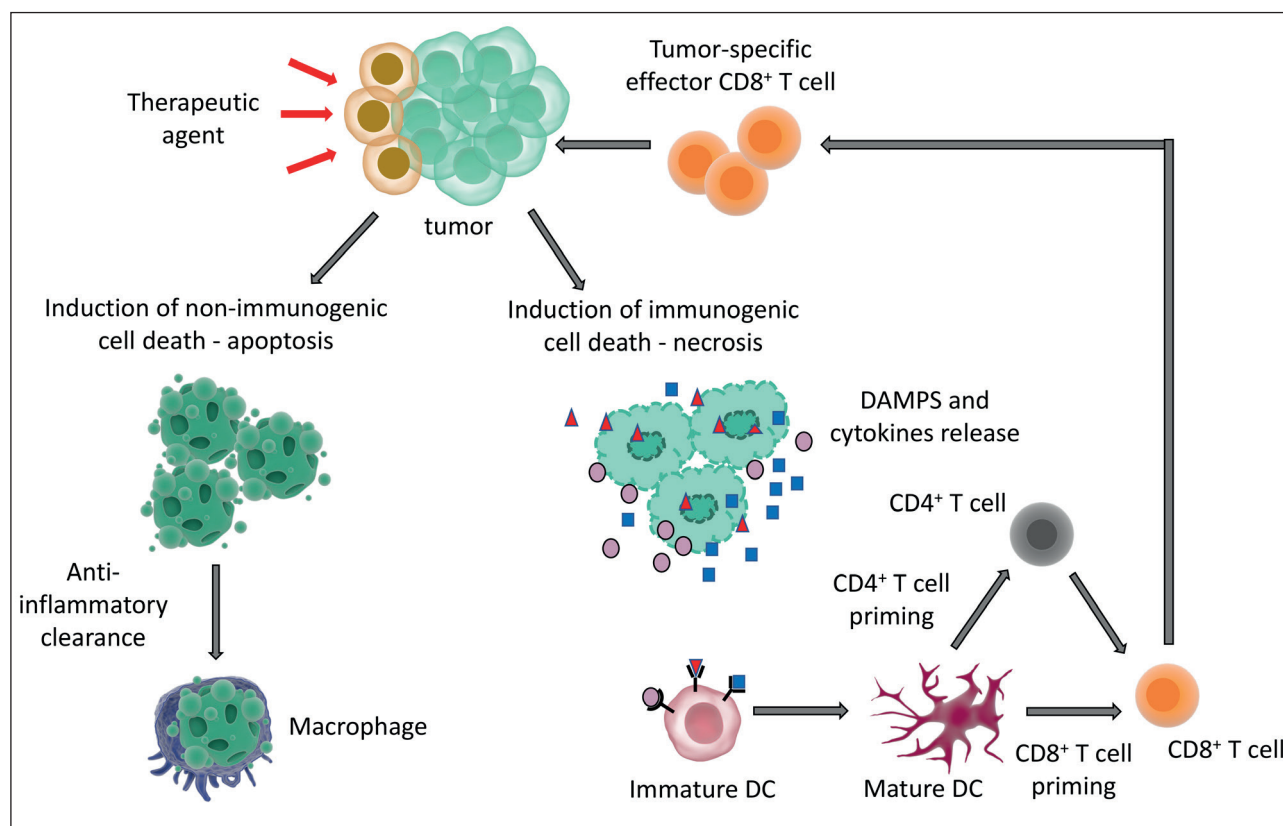


Figure 2. Immunogenic and non-immunogenic cell death. A therapeutic agent destroys part of the malignant cells of the tumor mass. Some cells may undergo apoptosis, which does not elicit inflammatory reactions in the affected tissues, or organs. The cellular debris are subsequently removed by macrophages. Conversely, the necrotic or necro-apoptotic cell death releases cellular debris and other factors, which stimulate inflammatory reactions through DAMPs. The inflammation may ultimately lead to the maturation of dendritic cells, which then program tumor-specific cytotoxic CD8-positive T cells to attack the remaining cancer cells in the tumor mass and, possibly, in other regions of the organism.

rophages through chemokines and/or cytokines, which point the other elements of the immune system to intervene and remove the origin of the distress signals and attempt to promote homeostasis and healing (17, 85-91).

There are many other factors that derive from radiation-induced injuries of cancer cells, which release certain components that affect several other cells via bystander effects (**table I**). For example, before dying irradiated cells quite often secrete cytotoxic mediators based on reactive oxygen and nitrogen species (21, 92, 93), together with certain cytokines, such as tumor necrosis factor α (TNF α /interleukin (IL)-6, IL-8 and transforming growth factor β 1 (TGF β 1) (94-97). The cytotoxic mediators are responsible for short range bystander effects, which involve non-irradiated malignant cells that are contiguous to irradiated cells (16, 98, 99).

The interpretation of the influence of ionizing radiations on tumor vascularization is rather controversial (100-106). Radiation therapy has also been designed to affect the tumor microenvironment, which is an important regulator of tumor vascularization (102). Therefore, the irradiation of the tumor niche should result in the inhibition of neoangiogenesis in the areas that surround the tumor mass. However, the analysis of the irradiation-induced clinical effects on tumor vascularization has provided some unexpected findings (106). In this respect, a clinical study on the effects of radiation therapy on neovascularization observed the reformation of blood vessels around relapsing tumor masses (104). Additional studies revealed that radiations also have the potential to increase the epithelial-mesenchymal transition of cancer cells, along with enhanced migration, metastasis, invasion and angiogenesis (106). Some clinical trials are combining radiation therapy with antiangiogenic factors to make the targeting of the tumor microenvironment more effective and to avoid the reconstitution of neovascularization (98, 107-109).

ABSCOPAL EFFECTS IN RADIATION THERAPY

As already discussed, the combination of immune checkpoints inhibitors with radiation therapy provided a substantial increment of abscopal effects among oncological patients.

Systemic immune responses were reported in two clinical trials, in which patients with melanoma were treated with the CTLA4 inhibitor termed ipilimumab and radiation therapy (110, 111). In one trial, the clinical outcome of the patient exhibited tumor mass reduction, a rise in CD4⁺ ICOS^{high} T cells counts and antibodies-mediated responses to the cancer-testis antigen NY-ESO-1 (110). The other trial dealt with the treatment of a patient with melanoma, who had brain and nodal metastasis and was treated with ipilimumab and stereotactic radiosurgery into the brain metastasis (111). A complete brain tumor remission was observed, along with the resolution of nodal metastases (111).

Enhanced systemic immune responses were reported among patients with advanced melanoma, who received radiation therapy in combination with ipilimumab (112). The total number of patients enrolled in the trial was 101. A cohort of 70 patients received the double treatment of radiations and ipilimumab, whereas a second cohort of 31 patients was treated with ipilimumab alone (112). No differences in toxicity were observed between the two groups of patients. The rates of complete responses were in the double treatment group was 25.7%, whereas the complete responses rates of the single treatment group were 6.5% (112).

Thirty-five patients with standard therapy refractory metastasized solid tumors either in the lung, or in the liver were enrolled in a phase I clinical trial, which used ipilimumab in combination with SABR (20). Significant clinical benefits were reported in 7

INTRACELLULAR FACTORS	Mixed lineage kinase domain-like (MLKL)-protein and the receptor-interacting protein kinase 3 (RIPK3) axis.	Poly(ADP-ribose) polymerase 1 (PARP1) and the apoptosis-inducing factor mitochondrion-associated 1 (AIFM1) axis (parthanatos).	Tumor suppressor protein p53
EXTRACELLULAR FACTORS	Danger associated molecular pattern molecules (DAMPs) and toll-like receptors (TLRs).	Bystander effects induced by: • reactive oxygen and nitrogen species; • tumor necrosis factor α (TNFα); • interleukin (IL)-6 and IL-8; • transforming growth factor β1 (TGFβ1).	-

Table I. List of factors that regulate the necroptotic pathways induced by traumatic cell death.

patients, who exhibited either a partial response, or a stable disease period that lasted more than 6 months (20). The cohort of patients with clinical benefits had substantial augment of peripheral blood CD8⁺ T cells (20).

Abscopal effects were also reported in clinical studies that utilized SABR alone (30). Twenty-eight patients with renal carcinoma were treated with SABR (113). Abscopal effects leading to tumor remissions were observed in 4 patients of the clinical study (113). A complete metastatic disease regression was reported in three patients that exhibited abscopal effects-related clinical benefits (111). In addition, no recurrence of the tumor was observed after the intervention in periods that ranged from 2 to 4 years (113).

SABR-related abscopal effects were observed in a patient with renal carcinoma (114). The out-of-field effects caused the remission of pulmonary metastases and of lymph nodes metastases (114). Regrettably, a contemporaneous relapse of the disease involved the brain, indicating that in this case abscopal effects were not able to pass through the blood-brain barrier (114).

A patient with synchronous primary lung cancer was treated with chemoradiation therapy to the primary adenocarcinoma situated in the left lung (115). Five months later, SABR was used to target the primary tumor mass in the right lung. Abscopal effects resulting in the remission of metastases were reported 5 months post-SABR treatment (115).

Twenty-three cases of abscopal effects were identified in retrospective studies on radiation oncology clinical literature from 1960 until July 2014 (33). The searches were conducted in Medline and Embase. The patients had either solid tumors, or blood-related cancers and were treated either with radiation therapy alone, or in combination with immunotherapy (33).

Abscopal effects were also observed in another Medline search, for the retrospective study on patients with metastatic melanoma, who underwent radiation therapy combined with ipilimumab from 2009 until 2017 (116). The search identified 16 clinical trials that involved 451 patients. Abscopal effects were observed in an average of 26.5% of patients and the median overall survival was 19 months (116).

Clinical studies are currently characterizing the effects of hypofractionated radiation therapy combined with immune checkpoint inhibitors in patients with non-small cell lung cancer (117), whereas

a preclinical study reported an increase of abscopal effects in a mouse model for breast cancer, following fractionated doses of radiations combined with immune checkpoint inhibitors (118).

ABSCOPAL EFFECTS INDUCED BY OTHER THERAPEUTIC AGENTS

In addition to radiation therapy, immunogenic cell death-related abscopal effects can be triggered by a variety of therapeutic agents that lyse malignant cells. For instance, oncolytic viruses have been used either alone, or in combination with immune checkpoints inhibitors in some clinical studies for the treatment of various tumors (34, 119-125). Some oncolytic viruses were produced to encode immunomodulatory agents, such as cytokines (34). Following the entry into the malignant cells, the oncolytic viral-encoded cytokines are expressed and contribute to increase the host immune responses against tumor-associated antigens of lysed cancer cells (34). The oncolytic herpesvirus talimogene laherparepvec (T-vec) was utilized in a clinical trial for the treatment of patients with advanced melanoma (34). T-vec was engineered to encode the granulocyte-macrophage colony-stimulating factor (GM-CSF), which attracts the cells of the immune system and then stimulates their proliferation (127-131). However, the immunosuppression that affects most patients with cancer is a major obstacle for the effective application of oncolytic viruses in therapy (34). Therefore, immune checkpoints inhibitors were utilized in conjunction with oncolytic viruses to boost the host immune responses in oncological patients (34, 129, 130, 132-134). For instance, ipilimumab and T-vec were administered into patients with unresectable stage IIIB-IV melanoma (135). Complete remission was reported in 4 patients and the clinical data showed that the treatment was safe (135).

Preclinical studies were conducted in animal models to characterize the recombinant vaccinia virus VV_{WR}-TK-RR-Fcu1 (136) and the chimeric parapoxvirus CF189 (137). Targeting of secondary tumor masses in animals were observed in both studies. Another preclinical testing was carried out to study the anti-cancer effects of the oncolytic peptide LTX-315, which was administered into animals along with an immune checkpoint inhibitor to test their ability to clear subcutaneous implantations of tumor cell lines (138). The oncolytic peptide LTX-315 produces pores through the cellular membrane

and then attacks the mitochondria. At this stage, the targeted malignant cells release DAMPs and undergo immunogenic cell death (138).

An emerging technique in cancer therapy is based on high intensity focused ultrasound, which can be used to target the tumor microenvironment and to induce tissue damage to the tumor mass (139). Focused ultrasound delivers mechanical waves that are centered at small region of the target tissue and comprises four types of applications, such as histotripsy, mechanical perturbation, thermal ablation and hyperthermia/thermal stress (139). Consequently, the high density of the delivered energy is absorbed by the treated area. The local heating and/or mechanical stimulations may cause tissue damage to the irradiated tumor site, with resultant immunogenic cell death, followed by the release of tumor associated antigens and DAMPs (**figure 2**). High intensity focused ultrasound has been used for the treatment of patients with prostate cancer, with promising results at the time of the treatment (140, 142). However, it is too early for an evaluation of the long-term effects of the therapeutic applications in patients with prostate cancer, because the trials are recent.

CONCLUSIONS

The activation of the host immune system induced by immune checkpoints inhibitors, along with a localized therapeutic intervention that causes immunogenic cell death in the targeted malignant mass are the essential key elements that may lead to a systemic response against the tumor in oncological patients. Clinical trials and preclinical studies are currently in progress to optimize the efficiency of abscopal effects in patients with cancer. These studies involve a variety of therapeutic agents, which are utilized for the treatment of several types of malignancies. For the moment, a major emphasis has been placed on radiation therapy, chemotherapeutics and immunomodulators, followed by oncolytic viruses and focused ultrasound, while other promising therapeutic agents are currently under charac-

terization at the preclinical stage, such as oncolytic peptides. The current priority in the field of cancer therapy is the achievement of a more efficient induction of abscopal effects in patients with cancer. Unfortunately, molecular and/or genetic markers associated with the onset of abscopal effects in patients are currently missing (142). The identification and characterization of biomarkers for the prediction and optimization of abscopal effects are certainly challenging tasks for the oncologists.

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ETHICS

Fundings

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Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

All the data supporting the findings of this study are available within the article.

Authors' contribution

All the authors contributed equally to conception, data collection, analysis and writing of this paper.

Ethical approval

N/A

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