OncoImmunology 2:9, e25595; September 2013; © 2013 Landes Bioscience

Trial Watch
Anticancer radioimmunotherapy

Erika Vacchelli,[1,2,3,†] Ilio Vitale,[4,5,†] Eric Tartour,[6,7,8] Alexander Eggermont,[2] Catherine Sautès-Fridman,[7,8,9] Jérôme Galon,[7,10,11,12] Laurence Zitvogel,[2,13] Guido Kroemer[3,7,8,14,15,‡,*] and Lorenzo Galluzzi[1,7,14,‡,*]

[1]Gustave Roussy; Villejuif, France; [2]Université Paris-Sud/Paris XI; Le Kremlin-Bicêtre, France; [3]INSERM, U848; Villejuif, France; [4]Regina Elena National Cancer Institute; Rome, Italy; [5]National Institute of Health; Rome, Italy; [6]INSERM, U970; Paris, France; [7]Université Paris Descartes/Paris V; Sorbonne Paris Cité; Paris, France; [8]Pôle de Biologie, Hôpital Européen Georges Pompidou; Assistance Publique-Hôpitaux de Paris; Paris, France; [9]Equipe 13, Centre de Recherche des Cordeliers; Paris, France; [10]Equipe 15, Centre de Recherche des Cordeliers; Paris, France; [11]INSERM, U872; Paris, France; [12]Université Pierre et Marie Curie/Paris VI; Paris, France; [13]INSERM, U1015; Villejuif, France; [14]Equipe 11 labelisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers; Paris, France; [15]Metabolomics and Cell Biology Platforms; Gustave Roussy; Villejuif, France

[†]These authors equally contributed to this article.

[‡]These authors share senior co-authorship.

Keywords: brachytherapy, immunogenic cell death, intensity-modulated radiation therapy, radionuclide, stereotactic body radiation therapy, stereotactic radiosurgery

Abbreviations: 3D-CRT, 3D-conformal radiation therapy; ACT, adoptive cell transfer; AGER, advanced glycosylation end product-specific receptor; APC, antigen-presenting cell; CRT, calreticulin; CT, computed tomography; CRC, colorectal carcinoma; CTLA4, cytotoxic T lymphocyte-associated protein 4; DAMP, damage-associated molecular pattern; DC, dendritic cell; EBRT, external-beam radiation therapy; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; GM-CSF, granulocyte macrophage colony-stimulating factor; HMGB1, high mobility group box 1; HNC, head and neck carcinoma; ICAM1, intercellular cell adhesion molecule 1; ICD, immunogenic cell death; IFN, interferon; IFRT, involved-field radiation therapy; IGRT, image-guided radiation therapy; IL, interleukin; IMRT, intensity-modulated radiation therapy; MIP-1α, macrophage inflammatory protein 1α; MRI, magnetic resonance imaging; PANX1, pannexin 1; PET, positron emission tomography; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; SRS, stereotactic radiosurgery; RIPK1, receptor-interacting protein kinase 1; RCC, renal cell carcinoma; RNS, reactive nitrogen species; ROS, reactive oxygen species; TBI, total body irradiation; TGFβ1, transforming growth factor β1; TLR, toll-like receptor; TNF, tumor necrosis factor; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor

Radiotherapy has extensively been employed as a curative or palliative intervention against cancer throughout the last century, with a varying degree of success. For a long time, the antineoplastic activity of X- and γ-rays was entirely ascribed to their capacity of damaging macromolecules, in particular DNA, and hence triggering the (apoptotic) demise of malignant cells. However, accumulating evidence indicates that (at least part of) the clinical potential of radiotherapy stems from cancer cell-extrinsic mechanisms, including the normalization of tumor vasculature as well as short- and long-range bystander effects. Local bystander effects involve either the direct transmission of lethal signals between cells connected by gap junctions or the production of diffusible cytotoxic mediators, including reactive oxygen species, nitric oxide and cytokines. Conversely, long-range bystander effects, also known as out-of-field or abscopal effects, presumably reflect the elicitation of tumor-specific adaptive immune responses. Ionizing rays have indeed been shown to promote the immunogenic demise of malignant cells, a process that relies on the spatiotemporally defined emanation of specific damage-associated molecular patterns (DAMPs). Thus, irradiation reportedly improves the clinical efficacy of other treatment modalities such as surgery (both in neo-adjuvant and adjuvant settings) or chemotherapy. Moreover, at least under some circumstances, radiotherapy may potentiate anticancer immune responses as elicited by various immunotherapeutic agents, including (but presumably not limited to) immunomodulatory monoclonal antibodies, cancer-specific vaccines, dendritic cell-based interventions and Toll-like receptor agonists. Here, we review the rationale of using radiotherapy, alone or combined with immunomodulatory agents, as a means to elicit or boost anticancer immune responses, and present recent clinical trials investigating the therapeutic potential of this approach in cancer patients.

*Correspondence to: Guido Kroemer and Lorenzo Galluzzi; Email: kroemer@orange.fr and deadoc@vodafone.it
Submitted: 06/28/13; Accepted: 06/28/13
Citation: Vacchelli E, Vitale I, Tartour E, Eggermont A, Sautès-Fridman C, Galon J, et al. Trial watch: Anticancer radioimmunotherapy. OncoImmunology 2013; 2:e25595; http://dx.doi.org/10.4161/onci.25595

Introduction

Origins and use of radiation oncology. In 1895, the German physicist Wilhelm Conrad Röntgen was the first to produce and detect an electromagnetic radiation with a wavelength corresponding to modern X-rays, marking the beginning of a decade that witnessed several pioneering discoveries in the same field, including that of natural radioactivity by the French physicist Antoine Henri Becquerel (in the same year) and that of radium as a natural source of γ-rays by the Polish physicist and chemist Marie Curie (in 1898).[1] As soon as in 1903, the Royal Swedish Academy of Sciences awarded Henri Becquerel, Marie Curie and her French husband Pierre the Nobel Prize in Physics, "in recognition of the extraordinary services they have rendered by their joint researches on the radiation phenomena."[1] Incredibly, no more than 60 d after Röntgen's discovery, the American physician Emil Grubbe employed X-rays to treat a woman bearing recurrent breast carcinoma, de facto establishing the field of radiation oncology.[1]

Throughout the last century, along with huge technological advances that allowed for the increasingly more accurate (in both anatomical and quantitative terms) delivery of X and γ-rays, or charged particles (i.e., protons and electrons) to malignant lesions, irradiation has been extensively employed as an antineoplastic intervention, either alone or in combination with other therapeutic modalities, with a variable degree of success.[1,2] Thus, according to current estimates, approximately 50% of all cancer patients have already received or will receive some form of radiation therapy, either as a curative intervention (i.e., aimed at eradicating a tumor and/or preventing recurrence) or as a palliative maneuver (i.e., intended to relieve the pain/discomfort caused by neoplastic lesions at specific anatomical locations, such as bones as well as peri-esophageal, peri-spinal, and cerebral areas).[3,4] Nowadays, ionizing irradiation is frequently administered in the context of chemotherapeutic regimens and/or surgery, either as a neo-adjuvant, an intraoperative, or an adjuvant intervention. In particular, radiotherapy is employed prior to surgery as a means to reduce tumor size, hence (1) allowing for, or minimizing the anatomical/esthetic impact of, the procedure; and (2) reducing the likelihood of disease recurrence owing to residual neoplastic cells. Intraoperative radiation therapy is advantageous (1) since it sometimes allow for the treatment of neoplastic lesions that are anatomically too close to healthy tissue/organs; and (2) as nearby normal tissues can be properly shielded from irradiation. Finally, adjuvant radiotherapy frequently represents an efficient means of reducing the risk of recurrence, for instance among breast carcinoma patients subjected to lumpectomy of radical mastectomy.[5,6]

Types of radiotherapy. Depending on how the source of radioactivity is employed to specifically target malignant lesions, radiotherapy can be roughly sub-divided into 2 large groups: (1) external-beam radiation therapy (EBRT), including a wide range of technical variants; and (2) internal radiotherapy, which can be further discriminated into brachytherapy and systemic radiation therapy.[2,7] EBRT most often involves a linear accelerator, i.e., a machine that generates X- or γ-rays that are collimated on malignant lesions across the intact skin. Conversely, brachytherapy relies on the seeding of tiny radioactive pellets within the tumor mass (interstitial brachytherapy), in a adjacent cavity—be it surgical or natural—via needles or catheters (intracavitary brachytherapy), while systemic radiation therapy is based on the oral or intravenous administration of a radionuclide, frequently coupled to a tumor-targeting monoclonal antibody.[7,8] A peculiar type of intracavitary brachytherapy is represented by plaque radiotherapy, which is frequently employed for the management of uveal and choroidal melanoma.[9-11] This approach involves a thin, concave metal plate containing radioactive seeds (often of ^{125}I) that is sewn to the outer surface of the ocular globe. For how it is constructed (with radioactive seeds facing inward), this medical device allows for the relatively focused delivery of ionizing radiation to the eye (and hence the tumor) while protecting other tissues from exposure.[9-11]

Common types of EBRT include (1) 3D-conformal radiation therapy (3D-CRT), which relies on a sophisticated computer software to deliver X- or γ-rays to precisely defined target areas;[12,13] (2) intensity-modulated radiation therapy (IMRT), using hundreds of (stationary or mobile) collimators to treat different zones of the malignant lesions or nearby tissues (see below) with different beam intensities;[14,15] (3) image-guided radiation therapy (IGRT), during which repeated scans by computed tomography (CT), positron emission tomography (PET), or magnetic resonance imaging (MRI) are performed to monitor changes in the size and precise location of the tumor, allowing to adjust dose and patient's position if required;[16-18] (4) tomotherapy, a peculiar type of image-guided IMRT based on a machine that can completely rotate around the patient, thus resembling a normal CT scanner;[19] (5) stereotactic radiosurgery (SRS), which uses an extremely accurate image-guided tumor targeting and patient positioning to deliver high doses of X- or γ-rays to small neoplastic lesions;[20-22] (6) stereotactic body radiation therapy (SBRT), delivering X- or γ-rays to small, isolated tumors, often in fewer sessions while using smaller radiation fields and higher doses than 3D-CRT;[23,24] (7) involved-field radiation therapy (IFRT), which specifically targets tumor-affected tissues (a radiotherapeutic mode frequently employed for the treatment of lymphoma patients);[25,26] and (8) proton or electron therapy, in which neoplastic lesions are treated with charged particles (photons) instead of a purely electromagnetic wave.[27,28] Along similar lines, brachytherapy can be performed in various modalities, for instance as a low vs. high dose-rate treatment, or based on temporary vs. permanent sources of radioactivity. The MammoSite® system (commercialized by Hologic, Inc.) is a well-known device for the delivery of high dose-rate, temporary brachytherapy to breast carcinoma patients.[29] Finally, systemic radiotherapy can be based on naked radionuclides such as ^{131}I, which is specifically taken up by thyrocytes and hence can be used for the treatment of thyroid carcinoma,[30] or on radionuclides coupled to tumor-targeting monoclonal antibodies. Two prominent examples of this approach—which is also known as selective internal radiation therapy (SIRT)—are provided by ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, 2 radionuclide-coupled anti-CD20 monoclonal antibodies that are currently approved for the treatment of lymphoma patients.[31,32] Each of these radiotherapeutic modalities

is associated with specific advantages and drawbacks that render it particularly suitable for the treatment of a specific subset of tumors. A detailed discussion of these aspects largely exceeds the scope of the present Trial Watch and can be found in refs. 2 and 7.

Side effects of radiotherapy. As all other antineoplastic agents, radiotherapy is associated with both acute and chronic side effects, stemming from the inevitable (though increasingly more controlled) irradiation of healthy tissues.[33-36] Acute side effects mainly reflect the damage of highly proliferating cells that reside in anatomical regions exposed to irradiation, in a majority of cases including the skin. In addition, irradiated patients often experience fatigue, regardless of the exposed part of the body, and nausea/vomiting, especially when the abdomen and brain are treated.[7,37] All these side effects generally resolve within a few days/weeks upon the interruption of radiation therapy. In some cases, however, the damage to highly proliferating cell compartments is permanent, potentially resulting in chronic diarrhea, intestinal bleeding, and infertility. Moreover, radiotherapy is associated with a quantifiable increase in the risk of developing a secondary, treatment-induced cancer later in life.[38-40] Such a risk is generally highest among patients who have been exposed to radiation therapy as children or adolescents.[41,42] Of note, a small rim of normal tissue immediately surrounding neoplastic lesions is always irradiated on purpose, for 2 reasons: first, to accommodate for some degree of displacement of the tumor mass that may normally result from breathing or from the physiological movement of internal organs; and second, to reduce the likelihood of disease recurrence owing to malignant cells that have invaded adjacent tissues.[1,43]

Throughout the last 50 y, several approaches have been developed to minimize the acute and chronic side effects of radiation therapy, including technical/strategic improvements as well as chemicals that operate as "radiosensitizers," thus exacerbating the propensity of malignant cells to succumb to irradiation, or "radioprotectors," shielding non-transformed cells side from the cytotoxic effects of radiotherapy.[2,44-46] The common aim of all these strategies is to minimize the amount of damage experienced by normal tissues (to limit side effects), while maximizing that experienced by malignant cells (to improve efficacy), i.e., to widen the therapeutic window of radiation therapy.[46,47] By far the most commonly employed means to achieve this goal is fractionation, i.e., the delivery of radiotherapy in multiple sessions (spaced by at least 6 h) over several weeks, which is advantageous mainly as (1) it increases the likelihood of malignant cells to be exposed to irradiation when they are more vulnerable to it (i.e., not in the S phase of the cell cycle, see below); (2) it efficiently compensates for accelerated repopulation, i.e., the propensity of the neoplastic cells that survive radiotherapy to proliferate at increased rates; and (3) it allows time to normal cells for repairing irradiation-induced damage.[1] In addition, several distinct molecules have been demonstrated (in preclinical models) to efficiently sensitize cancer cells to the cytotoxic effects of radiation therapy, including DNA-damaging agents, cell cycle checkpoint inhibitors, and chemicals that increase oxygenation (see below). Along similar lines, a consistent experimental effort has been dedicated to the development of distinct strategies for radioprotection, including the (local) administration of radical scavengers (which minimize radiotherapy-induced damage at the molecular level, see below),[48-51] apoptosis inhibitors (to arrest the cellular demise of irradiated normal cells),[52-54] growth factors (which stimulate tissue reconstitution),[55-58] and immunomodulatory agents (to prevent the establishment of a cytotoxic inflammatory milieu).[59-63] This said, amifostine (a radical scavenger also known as Ethyol®) is the only drug currently approved by FDA for use in humans as a radioprotector.[64-66]

How radiation therapy works. Irradiated cells (be they malignant or normal) absorb high amounts of energy in the form of photons or charged particles, promoting some extent of direct macromolecular damage as well as the generation of highly diffusible reactive oxygen and nitrogen species (ROS and RNS, respectively), which de facto underpin the cytotoxic potential of radiation therapy.[43,67] Indeed, both free radicals and molecular oxygen appear to be required for the stabilization of DNA damage, a concept known as the "oxygen fixation" hypothesis.[68-70] Thus, a good level of oxygenation is a conditio sine qua non for neoplastic cells to respond to radiotherapy, in vitro and in vivo.[71-75] Oxygen concentrations less than 0.02% (0.15 mmHg) decrease the vulnerability of cancer cells to ionizing radiation by 2- to 3-fold,[76] and even milder degrees of hypoxia (oxygen concentration 1%, 8 mmHg)—which are commonly found in human tumors—produce an appreciable level of radio- (and chemo-) resistance.[77] In line with this notion, various strategies have been developed in the attempt to radiosensitize neoplastic lesions by means of an increased supply of oxygen, including the ventilation of irradiated patients with hyperbaric oxygen (most often a 95% O_2, 5% CO_2 mix)[78,79] and the administration of drugs that reduce the binding of oxygen to hemoglobin, such as efaproxiral.[80,81] Both these approaches exert radiosensitizing effects as they reduce the so-called "hypoxic fraction," i.e., the percentage of tumor cells exposed to subphysiological oxygen tensions. Alternatively, radiosensitization has been achieved with compounds that selectively target hypoxic cells, such as the 5-nitroimidazole nimorazole and tirapazamine analogs.[82-84]

The damage inflicted by radiation therapy to macromolecules, in particular DNA and lipids, generally activates the intrinsic pathway of apoptosis, which executes cell death upon the irreversible permeabilization of mitochondrial membranes.[85,86] As an alternative, irradiated cells enter senescence, a permanent proliferative arrest manifesting with a series of stereotyped phenotypic and biochemical traits.[87-89] Both these processes can be under the control of p53[90-92] and often, but not always, ensue the activation of mitotic catastrophe, an oncosuppressive mechanism ensuring the elimination of mitosis-incompetent cells.[93,94] In addition, both DNA damaging agents and oxidative stress have been shown to induce instances of programmed necrosis,[95-97] including the receptor-interacting protein kinase 1 (RIPK1)-dependent necrotic modality known as necroptosis.[98-100]

It is therefore not surprising that for decades the therapeutic effects of ionizing radiation have been entirely (but incorrectly) ascribed to the direct cytotoxic or cytostatic activity of X- and γ-rays.[1] However, robust preclinical and clinical evidence indicates that (at least part of) the therapeutic efficacy of irradiation

results from local and long-range bystander effects.[67,101] The former can originate from the transmission of lethal signals via gap junctions,[102] multimeric pores that allow for the exchange of 1000–1500 kDa molecules, including nucleotides, Ca^{2+} ions and ROS, between adjacent cells.[103,104] In addition, local bystander effects can ensue the release by irradiated (neoplastic and immune) cells of soluble mediators that exert a direct or indirect cytotoxic activity on non-irradiated neighboring cells, including ROS,[105] RNS,[106,107] and several cytokines such as interleukin (IL)-6,[108] IL-8,[109] transforming growth factor β1 (TGFβ1),[110] and tumor necrosis factor α (TNFα).[111] Conversely, long-range bystander effects, also known as out-of-field or abscopal effects, are thought to reflect the elicitation of an adaptive immune response against malignant cells.[112,113] Similar to some chemotherapeutic and photodynamic therapy,[114,115] ionizing irradiation promotes indeed the immunogenic demise of malignant cells,[85,115-117] a process that relies on the spatiotemporally-defined emission of specific damage-associated molecular patterns (DAMPs).[115,118,119]

Radiotherapy has also been shown to favor the normalization of the tumor vasculature,[120] hence (1) facilitating the delivery of chemotherapeutic agents administered via the systemic route and (2) promoting the infiltration of malignant lesions by effector (as opposed to regulatory) immune cells.[121,122] At least in part, the ability of ionizing radiation to stimulate the recruitment of immune cells to the tumor microenvironment reflects the fact that irradiated endothelial cells express increased levels of intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1) on their surface.[123] Whether the upregulation of adhesion molecules on the surface of irradiated endothelial cells results from a strictly cell-intrinsic mechanism or involves the secretion of autocrine/paracrine mediators remains to be elucidated. Thus, the local (and perhaps also the long-range) therapeutic effects of radiotherapy appear to involve a prominent vascular component.[122]

Following the tradition of our monthly Trial Watch series,[124-140] here we discuss the rationale of using radiotherapy, alone or combined with immunomodulatory interventions, as a means to elicit or boost anticancer immune responses, and review recent clinical trials investigating the therapeutic potential of this approach in cancer patients. Besides being used as an antineoplastic intervention, high-dose radiotherapy—most often in the form of total body irradiation (TBI)—is routinely employed as a conditioning regimen in patients bearing hematological malignancies allocated to receive hematopoietic stem cell transplantation.[141,142] The therapeutic value of radiation therapy in this settings stems from the ability of TBI to directly kill neoplastic progenitors in the bone marrow and promote a severe state of immunodeficiency (rather than immunostimulatory effects), which is required for engraftment.[141-143] Thus, the use of TBI as a pre-transplantation conditioning regimen will not be further discussed here.

Immunogenic Effects of Radiotherapy

As mentioned above, an increasing amount of preclinical and clinical evidence indicates that the therapeutic potential of ionizing irradiation does not simply reflect the cytotoxic activity of X- and γ-rays, but rather involves local and/or distant bystander effects.[67,101,112,144,145] Thus, therapeutic (as opposed to unwarranted) abscopal reactions have been documented in patients bearing a wide variety of neoplasms, including (but presumably not limited to) lymphoma,[146-150] melanoma,[151-154] primary and metastatic breast carcinoma,[155-158] adenocarcinoma,[159,160] sarcoma[161] hepatocellular carcinoma,[162,163] Merkel cell carcinoma,[164] renal cell carcinoma (RCC),[165] and uterine cancer.[166]

Initially, clinicians tended to consider the abscopal effect as a straightforward systemic consequence of the local release of immunostimulatory and cytotoxic cytokines, mainly TNFα[163] and IL-18,[162] by irradiated (malignant and immune) cells. However, it is now clear that—at least under specific circumstances—radiation therapy elicits an adaptive immune response against malignant cells that is capable of mediating robust antineoplastic effects on non-irradiated lesions.[167-170] At least 3 distinct lines of evidence support this interpretation. First, an elevation in the circulating levels of immunomodulatory cytokines including TNFα and IL-18 would be expected to cause a rather unspecific activation of the immune system, and hence to have a very limited (if any) impact on neoplasms other than melanoma and RCC, which are per se extremely immunogenic and immunosensitive.[127,139,171-173] In line with this notion, the administration of recombinant cytokines (notably IL-2) as standalone therapeutic interventions has been associated with considerable rates of objective clinical responses only among melanoma and RCC patients,[127,139] while abscopal effects have been documents in individuals bearing several other neoplasms (see above). Second, the abscopal effect can be boosted by various immunostimulatory preparations, including (but presumably not limited to) bone marrow-derived dendritic cells (DCs),[174] IL-2,[175,176] an active variant of macrophage inflammatory protein 1α (MIP-1α),[177] Toll-like receptor (TLR) agonists,[157,178,179] TGFβ1-blocking strategies,[180] and monoclonal antibodies specific for immunological checkpoint regulators such as cytotoxic T lymphocyte-associated protein 4 (CTLA4).[154,181-184] Third, abscopal effects have been correlated with the induction of interferon γ (IFNγ)-producing $CD8^+$ T lymphocytes[181,185] and have been shown to rely on the presence of both $CD4^+$ and $CD8^+$ T cells.[177]

The mechanisms whereby radiotherapy elicits tumor-specific immune responses have just begun to emerge. Indeed, the (most often) apoptotic demise of irradiated cancer cells has long been viewed as an immunologically silent—if not tolerogenic—event, reflecting the textbook notion that apoptotic corpses are rapidly taken up by professional phagocytes while delivering robust anti-inflammatory signals.[186-188] Rather, it is now clear that—in response to specific stimuli—malignant cells can undergo apoptosis while emitting a spatiotemporally-defined sequence of danger signals that the immune system translates into a tumor-specific adaptive immune response.[115,119] Importantly, together with anthracyclines (e.g., doxorubicin, mitoxantrone), oxaliplatin, cyclophosphamide, and hypericin-based photodynamic therapy, ionizing irradiation constitutes a bona fide inducer of immunogenic cell death (ICD), i.e., is capable of killing neoplastic cells while transforming them into a vaccine that efficiently protects syngeneic mice against a subsequent challenge with cancer cells of the same type.[114,189-191]

ICD has been shown to rely on (at least) 3 main determinants: (1) the pre-apoptotic exposure of the endoplasmic reticulum (ER) chaperone calreticulin (CRT) on the outer leaflet of the plasma membrane, constituting a prominent "eat-me signal" for professional antigen-presenting cells (APCs), including DCs;[189,192-194] (2) the autophagy-dependent and pannexin 1 (PANX1)-mediated secretion of ATP in the blebbing phase of apoptosis, operating both as a "find-me signal" for APCs and as a potent pro-inflammatory cue;[195-202] and (3) the post-apoptotic release of the non-histone chromatin-binding protein high mobility group box 1 (HMGB1), which—in its oxidized form—reportedly conveys pro-inflammatory stimuli upon ligation of TLR4 and/or advanced glycosylation end product-specific receptor (AGER).[203-206] In addition, dying cells expose or release several other DAMPs that per se are not immunogenic, yet operate as potent adjuvants, such as various mitochondrial products.[118] In conditions in which CRT, ATP, and HGMB1 (and perhaps other DAMPs) cannot be properly emitted by dying cancer cells, cannot be sensed by APCs, or cannot be translated into an adaptive immune response, the therapeutic efficacy of various ICD inducers is significantly reduced.[115,197,202] Intriguingly, this holds true in some, but not all, preclinical and clinical settings,[207] implying that some tumors may be more susceptible than others to immune responses, be them natural or elicited by therapy, and hence to the abscopal effect. The precise impact of specific DAMPs in the therapeutic efficacy of radiation therapy in vivo, however, has not yet been systematically investigated.

Irrespective of this hitherto poorly characterized aspect of the immunogenic demise of cancer cells as induced by X- and γ-rays, these observations indicate that (a large fraction of) the therapeutic efficacy of ionizing irradiation stems from its ability to provoke ICD coupled to the release of potent pro-inflammatory mediators, de facto eliciting a robust tumor-specific immune response.

Clinical Development of Radioimmunotherapy

For a long time, the term "radioimmunotherapy" has been used to specifically denote SIRT, i.e., the use of radionuclides coupled to (tumor-targeting) monoclonal antibodies, such as the FDA-approved agents ^{90}Y-ibritumomab tiuxetan (Zevalin®; Cell Therapeutics Inc.) and ^{131}I-tositumomab (Bexxar®; GlaxoSmithKline LLC).[208-211] Along with the recent expansion of anticancer immunotherapy, which embraces a large (and incessantly growing) panel of approaches, this expression has gained an ampler meaning and is nowadays employed to refer to the combinatorial or sequential administration of virtually any immunotherapeutic agent plus irradiation.[212] As EBRT is licensed by FDA and other international regulatory agencies as a neoadjuvant, intraoperative or adjuvant intervention against a majority of neoplasms, the number of clinical studies that de facto rely on an radioimmunotherapeutic approach, irrespective of whether this was explicitly envisioned a priori or not, is exponentially growing. Thus, interrogating PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) with the string "cancer AND radiotherapy AND patients AND immunotherapy," on June 13, 2013, returned a total of 3698 entries, of which more than 15% were published after January 1, 2011. In the same period, i.e., during the last 30 mo, no less than 400 distinct clinical trials have been launched to investigate the safety and antineoplastic potential of radioimmunotherapy, all types confounded (source www.clinicaltrials.gov). Of note, (1) the vast majority of these trials also relies on one or more chemotherapeutic agents and/or surgery; and (2) a consistent fraction of these studies does not specifically aim at evaluating the clinical potential of radiotherapy, but rather involves (most often external-beam) irradiation as part of conventional therapeutic regimens. In this setting, radiation therapy is administered only to the active comparator arm of the trial or to both arms (at least in one of which combined with the immunotherapeutic agent that is under investigation).

As it stands, official sources list no less than 177 ongoing (not withdrawn, suspended, terminated or completed on the day of submission) clinical trials initiated during the last 30 mo (that is, after, January 1, 2011) to assess the safety profile and antineoplastic activity of radioimmunotherapeutic regimens (source www.clinicaltrials.gov). Of these, 77 involve tumor-targeting or immunostimulatory monoclonal antibodies, such as the epidermal-growth factor receptor (EGFR)-specific agent cetuximab[213,214] and the anti-CTLA4 antibody ipilimumab;[215-217] 51 immunogenic chemotherapeutics (i.e., cyclophosphamide, anthracyclines, oxaliplatin);[114,115] 5 DC-based approaches, including the FDA-approved cell preparation known as sipuleucel-T®;[130,218-220] 3 immunostimulatory cytokines (e.g., IL-2, IFN-α2b);[127,139] 4 FDA-approved or experimental TLR agonists, such as imiquimod and SD-101,[128,129,140,221] 4 adoptive cell transfer (ACT) protocols;[126,137] 1 peptide vaccines;[132,222-224] 1 oncolytic viruses,[138,225,226] and 31 combinatorial strategies comprising at least 2 distinct types of immunotherapy (**Table S1**).

Neoadjuvant or adjuvant irradiation is routinely employed in the clinics to treat patients affected by multiple variants of head and neck carcinoma (HNC), alone or in combination with chemotherapeutic regimens based on platinum derivatives, most often cisplatin.[227-231] In line with this notion, no less than 35 clinical trials initiated in the last 30 mo are currently evaluating the clinical potential of various radioimmunotherapeutic approaches in HNC patients. With 3 notable exceptions, namely NCT01821495 (in which radiotherapy is combined with the administration of DCs and cytokine-induced killer cells), NCT01584284 (testing EBRT coupled to the intravenous administration of an oncolytic virus) and NCT01728480 (investigating the radioprotective potential of a TLR5 agonist), all these studies involve EGFR-targeting antibodies, most often the FDA-approved drug cetuximab or the hitherto experimental agent nimotuzumab (**Table 1**; **Table S1**). Irradiation is a frequent therapeutic choice also for anal and colorectal carcinoma (CRC) patients, especially when primary lesions have already metastasized or are attached to internal organs, rendering their complete removal by surgery virtually impossible.[232-234] Accordingly, official sources list 29 ongoing clinical trials initiated after January 1, 2011, to test the safety profile and efficacy of radioimmunotherapy in subjects bearing anal, colorectal, or rectal carcinoma. In this setting, the immunotherapeutic component

Table 1. Current trends of anticancer radioimmunotherapy*

Cancer type	Phase	N°	Notes
Breast carcinoma	I–III	9	A heterogeneous panel of radioimmunotherapeutic strategies is being tested in this clinical scenario
CRC	I–III	29	In a majority of cases, EBRT is administered in the context of the FOLFOX regimen or together with bevacizumab
Gastresophageal carcinoma	I–III	19	EBRT is often employed in combination with anti-EGFR monoclonal antibodies or oxaliplatin-based chemotherapy
Hematological tumors	I–III	24	EBRT is frequently administered as a consolidation therapy, in combination with immunogenic chemotherapeutics or the CD20-targeting monoclonal antibody rituximab
HNC	I–IV	35	Most studies combine IMRT with monoclonal antibodies specific for EGFR, such as cetuximab or nimotuzumab.
Melanoma	I–II	8	The most prominent approach involves one form of EBRT, often SBRT, combined with ipilimumab
Neuroectodermal and CNS tumors	I–III	18	Many of these studies involve the combination of EBRT with conventional chemotherapy plus bevacizumab
Pancreatic carcinoma	I–III	16	Patients are often allocated to receive one form of EBRT combined with oxaliplatin-based chemotherapy.
Prostate cancer	II	4	EBRT is often given in combination with sipuleucel-T®
Sarcoma	I–II	6	Most often, one variant of EBRT is combined with cyclophosphamide- or oxaliplatin-based chemotherapy
Others	I–IV	9	^{90}Y-based radioembolization is frequently investigated for the treatment of HCC and cholangiocarcinoma patients

CNS, central nervous system; CRC, colorectal carcinoma; EBRT, external-beam radiation therapy; EGFR, epidermal growth factor receptor; FOLFOX, 5-flurouracil, folinic acid and oxaliplatin; HCC, hepatocellular carcinoma; HNC, head and neck carcinoma; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy. *Based on clinical trials started after January 1, 2011, and not withdrawn, terminated, or suspended at the day of submission (source www.clinicaltrials.gov). See also **Table S1**.

of the combinatorial regimen is frequently represented by oxaliplatin (a bona fide ICD inducer) and/or by the vascular endothelial growth factor (VEGF)-blocking antibody bevacizumab, both of which are approved by FDA for use in CRC patients. NCT01839539 (in which radiotherapy is combined with conventional chemotherapeutic agents, DCs, and cytokine-induced killer cells), NCT01539824 (investigating the immunostimulatory potential of SBRT given in combination with IMM-101, a TLR2/TLR4 mixed agonist), and NCT01320683 (involving an ^{90}Y-conjugated monoclonal antibody specific for the carcinoembryonic antigen) constitute prominent exceptions to this trend (**Table 1**; **Table S1**). No less than 24 ongoing clinical trials have been launched during the last 30 mo to assess the safety and efficacy of radioimmunotherapy in individuals affected by hematological neoplasms (mainly lymphoma). In this case, EBRT is often employed as a consolidative treatment upon the administration of a chemotherapeutic regimen involving, among other drugs, cyclophosphamide and doxorubicin (2 ICD inducers). Alternatively, lymphoma patients are frequently allocated to receive ^{90}Y-ibritumomab tiuxetan (which specifically targets CD45) or EBRT in combination with various chemotherapeutic regimens involving the FDA-approved anti-CD20 antibody rituximab (**Table 1**; **Table S1**).

Most among the 18 clinical trials initiated after January 1, 2011, to assess the safety profile and efficacy of radioimmunotherapy in subjects affected by neuroectodermal and central nervous system tumors involve EBRT given in combination with temozolomide (an alkylating agent) and/or bevacizumab. Only a few among these studies, such as NCT01798004, NCT01526603, and NCT01857934, were initiated to test EBRT as a consolidative therapy upon autologous stem cell transplantation. Along similar lines, a majority of the 19 clinical studies launched during the last 30 mo to test radioimmunotherapeutic approaches in patients with gastric or esophageal carcinoma relies on EBRT in combination with a tumor-targeting monoclonal antibody, most often cetuximab or panitumumab (another FDA-approved EGFR-specific agent). Alternatively, the immunotherapeutic component of such combinatorial approaches is represented by oxaliplatin (**Table 1**; **Table S1**). Sixteen clinical trials initiated in the same period aim at investigating the antineoplastic activity of radioimmunotherapy in individuals affected by pancreatic carcinoma. With a few notable exceptions such as NCT01342224 (which involves a telomerase-targeting peptide vaccine given in combination with the granulocyte macrophage colony-stimulating factor [GM-CSF])[235,236] and NCT01298401 (testing the safety and efficacy of 3D-CRT combined with conventional chemotherapy and ganitumab, an experimental monoclonal antibody specific for the insulin-like growth factor 1 receptor), all these studies involve an oxaliplatin-containing chemotherapeutic cocktail. Of particular interest in this setting is NCT01581307, testing the clinical activity of small glass microspheres (20–30 μm in diameter) containing ^{90}Y (TheraSphere®, a preparation that is partially approved by FDA for the treatment of hepatocellular carcinoma)[237,238] administered (via radioembolization)[239] in the context of second line FOLFOX (5-flurouracil, folinic acid, and oxaliplatin) to patients bearing gemcitabine-refractory pancreatic carcinoma with liver metastases (**Table 1**; **Table S1**).

During the last 30 mo, additional 36 clinical trials have been launched to test the safety and anticancer activity of several radioimmunotherapeutic protocols in cohorts of patients bearing breast carcinoma (9 studies), melanoma (8 studies), sarcoma (6 studies), prostate carcinoma (4 studies), or other solid tumors (9 studies). The immunotherapeutic component of clinical studies

involving breast carcinoma patients is relatively heterogeneous, including the FDA-approved ERBB2-specific monoclonal antibody trastuzumab,[240-243] the TLR7 agonist imiquimod,[129,244,245] and ICD inducers such as cyclophosphamide and doxorubicin. Conversely, in this setting melanoma patients are near to invariably allocated to receive one variant of EBRT in combination with ipilimumab. A standalone exception to this trend is represented by NCT01416831, testing whether SBRT can improve the antineoplastic potential of high-dose IL-2. The radioimmunotherapeutic approach is also relatively homogeneous among prostate cancer-related clinical trials, with a majority of studies involving sipuleucel-T®. In addition, a rather heterogeneous panel of radiotherapeutic and immunotherapeutic regimens is currently under investigation for the treatment of patients with sarcoma, non-small cell lung carcinoma, pleuropulmonary blastoma, Merkel cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, and other solid tumors. In this context, some interest appears to be spurred by the use of ^{90}Y-based transarterial radioembolization as an alternative to transarterial chemoembolization for the treatment of hepatocellular carcinoma (NCT01381211; NCT01798160) and cholangiocarcinoma (NCT01798147) (**Table 1**; **Table S1**).

Concluding Remarks

Nowadays, combinatorial anticancer therapy is an affirmed clinical practice, reflecting the fact that—perhaps with a few notable exceptions—standalone chemo- or radiotherapeutic regimens are generally unable to control neoplastic lesions. As combining therapeutic agents with dissimilar mechanisms of action potentially results in synergistic antineoplastic effects, this approach presents several advantages over the use of monotherapeutic regimens, including (1) a decrease in the incidence and severity of adverse effects (as in this setting drugs as generally employed at reduced dosages); and (2) a lowered propensity of malignant cells to become chemo- or radioresistant.[246]

Along with the realization that most (if not all) clinically successful anticancer agents operate—at least in part—by eliciting or boosting tumor-specific immune responses,[213,247] and with the development of efficient means to (re)instate anticancer immunity, great interest has been spurred by the possibility to combine chemo-, radio-, and immunotherapeutic regimens.[213,248,249] Thus, several preclinical and clinical studies are underway to investigate whether and under which conditions various immunostimulatory agents can be used in combination with each other or with conventional antineoplastic regimens to achieve improved response rates and/or to minimize side effects.[250-252]

Radioimmunotherapy constitutes a rather peculiar case of this general approach. Indeed, radiation therapy has been extensively used as a conventional anticancer regimen throughout the last century, mostly as it was thought to mediate direct cytotoxic/cytostatic effects on malignant cells.[1,2] Preclinical and clinical evidence, however, indicates that the antineoplastic activity of irradiation exceeds that of a merely cytotoxic/cytostatic intervention and rather involves the (re)activation of tumor-specific cellular immune responses.[143] Thus, radiotherapy may per se constitute a combinatorial anticancer regimen, de facto inducing the death of cancer cells while exerting robust immunostimulatory effects. It is therefore tempting to speculate that combining radiation therapy with specific immunostimulatory interventions, such as immunological checkpoint inhibitors or TLR agonists, may result in superior antineoplastic effects, at least in a subset of cancer patients. Well-designed clinical trials are required to formally address this hypothesis.

Some studies indicate that immunosuppressive cells, including $CD4^+CD25^+FOXP3^+$ regulatory T cells (which potently antagonize antitumor immune responses), may be highly resistant to the cytotoxic effects of ionizing radiation, favoring their preferential increase in the course of therapy.[253] In line with notion, experimental approaches aimed at specifically depleting regulatory T cells appear to greatly potentiate the antineoplastic potential of radiation therapy in murine tumor models.[253,254] Several chemotherapeutic agents have been shown to specifically subvert the immunosuppressive functions of regulatory T cells, including gemcitabine and cyclophosphamide (especially when administered according to a metronomic schedule).[213,255] Thus, it will be particularly interesting to see the results of multiple clinical trials that are currently underway to evaluate the safety and antineoplastic profile of cyclophosphamide-based radioimmunotherapeutic regimens in cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Authors are supported by the European Commission (ArtForce); European Research Council (ERC); Agence National de la Recherche (ANR); Ligue Nationale contre le Cancer; Fondation pour la Recherche Médicale (FRM); Institut National du Cancer (INCa); Associazione Italiana per la Ricerca sul Cancro (AIRC); Association pour la Recherche sur le Cancer (ARC), LabEx Immuno-Oncologie; Fondation de France; Fondation Bettencourt-Schueller; AXA Chair for Longevity Research; Cancéropôle Ile-de-France, Paris Alliance of Cancer Research Institutes (PACRI), and Cancer Research for Personalized Medicine (CARPEM).

Supplemental Material

Supplemental materials may be found here:
http://www.landesbioscience.com/journals/oncoimmunology/article/25595

References

1. Bernier J, Hall EJ, Giaccia A. Radiation oncology: a century of achievements. Nat Rev Cancer 2004; 4:737-47; PMID:15343280; http://dx.doi.org/10.1038/nrc1451
2. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gérard JP. Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol 2013; 10:52-60; PMID:23183635; http://dx.doi.org/10.1038/nrclinonc.2012.203
3. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005; 104:1129-37; PMID:16080176; http://dx.doi.org/10.1002/cncr.21324

4. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62:220-41; PMID:22700443; http://dx.doi.org/10.3322/caac.21149
5. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al.; European Organization for Research and Treatment of Cancer Radiotherapy and Breast Cancer Groups. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001; 345:1378-87; PMID:11794170; http://dx.doi.org/10.1056/NEJMoa010874
6. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol 1997; 15:963-8; PMID:9060534
7. Ahmad SS, Duke S, Jena R, Williams MV, Burnet NG. Advances in radiotherapy. BMJ 2012; 345:e7765; PMID:23212681; http://dx.doi.org/10.1136/bmj.e7765
8. DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles & Practice of Oncology. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins, 2008.
9. Bellmann C, Lumbroso-Le Rouic L, Levy C, Plancher C, Dendale R, Sastre-Garau X, et al. Uveal melanoma: management and outcome of patients with extraocular spread. Br J Ophthalmol 2010; 94:569-74; PMID:19965816; http://dx.doi.org/10.1136/bjo.2009.165423
10. Lumbroso-Le Rouic L, Charif Chefchaouni M, Levy C, Plancher C, Dendale R, Asselain B, et al. 125I plaque brachytherapy for anterior uveal melanomas. Eye (Lond) 2004; 18:911-6; PMID:15002010; http://dx.doi.org/10.1038/sj.eye.6701361
11. Al Mahmoud T, Mansour M, Deschênes J, Edelstein C, Burnier M, Marcil M, et al. Iodine-125 radiotherapy for choroidal melanoma. Ann N Y Acad Sci 2008; 1138:15-8; PMID:18837877; http://dx.doi.org/10.1196/annals.1414.003
12. Bucci MK, Bevan A, Roach M 3rd. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin 2005; 55:117-34; PMID:15761080; http://dx.doi.org/10.3322/canjclin.55.2.117
13. Mohan R. Field Shaping for Three-Dimensional Conformal Radiation Therapy and Multileaf Collimation. Semin Radiat Oncol 1995; 5:86-99; PMID:10717132; http://dx.doi.org/10.1016/S1053-4296(95)80003-4
14. Group IMRTCW; Intensity Modulated Radiation Therapy Collaborative Working Group. Intensity-modulated radiotherapy: current status and issues of interest. Int J Radiat Oncol Biol Phys 2001; 51:880-914; PMID:11704310; http://dx.doi.org/10.1016/S0360-3016(01)01749-7
15. Blockhuys S, Vanhoecke B, De Wagter C, Bracke M, De Neve W. From clinical observations of intensity-modulated radiotherapy to dedicated in vitro designs. Mutat Res 2010; 704:200-5; PMID:20178859; http://dx.doi.org/10.1016/j.mrrev.2010.02.003
16. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. Nat Rev Clin Oncol 2012; 9:688-99; PMID:23165124; http://dx.doi.org/10.1038/nrclinonc.2012.194
17. Heron DE, Smith RP, Andrade RS. Advances in image-guided radiation therapy--the role of PET-CT. Med Dosim 2006; 31:3-11; PMID:16551524; http://dx.doi.org/10.1016/j.meddos.2005.12.006
18. Ling CC, Yorke E, Fuks Z. From IMRT to IGRT: frontierland or neverland? Radiother Oncol 2006; 78:119-22; PMID:16413622; http://dx.doi.org/10.1016/j.radonc.2005.12.005
19. Fenwick JD, Tomé WA, Soisson ET, Mehta MP, Rock Mackie T. Tomotherapy and other innovative IMRT delivery systems. Semin Radiat Oncol 2006; 16:199-208; PMID:17010902; http://dx.doi.org/10.1016/j.semradonc.2006.04.002
20. Whyte RI. Stereotactic radiosurgery for lung tumors. Semin Thorac Cardiovasc Surg 2010; 22:59-66; PMID:20813318; http://dx.doi.org/10.1053/j.semtcvs.2010.04.001
21. Calcerrada Díaz-Santos N, Blasco Amaro JA, Cardiel GA, Andradas Aragonés E. The safety and efficacy of robotic image-guided radiosurgery system treatment for intra- and extracranial lesions: a systematic review of the literature. Radiother Oncol 2008; 89:245-53; PMID:18760852; http://dx.doi.org/10.1016/j.radonc.2008.07.022
22. Christie NA, Pennathur A, Burton SA, Luketich JD. Stereotactic radiosurgery for early stage non-small cell lung cancer: rationale, patient selection, results, and complications. Semin Thorac Cardiovasc Surg 2008; 20:290-7; PMID:19251167; http://dx.doi.org/10.1053/j.semtcvs.2008.12.001
23. Salama JK, Kirkpatrick JP, Yin FF. Stereotactic body radiotherapy treatment of extracranial metastases. Nat Rev Clin Oncol 2012; 9:654-65; PMID:23007273; http://dx.doi.org/10.1038/nrclinonc.2012.166
24. Grimm J, LaCouture T, Croce R, Yeo I, Zhu Y, Xue J. Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. J Appl Clin Med Phys 2011; 12:3368; PMID:21587185
25. Behre G, Christopeit M, Weber T. Involved field radiation therapy and donor lymphocyte infusion for relapsed or refractory non-Hodgkin lymphoma after allogeneic hematopoietic stem cell transplantation. Int J Hematol 2008; 88:463-4; PMID:18836792; http://dx.doi.org/10.1007/s12185-008-0174-4
26. Wendland MM, Smith DC, Boucher KM, Asch JD, Pulsipher MA, Thomson JW, et al. The impact of involved field radiation therapy in the treatment of relapsed or refractory non-Hodgkin lymphoma with high-dose chemotherapy followed by hematopoietic progenitor cell transplant. Am J Clin Oncol 2007; 30:156-62; PMID:17414465; http://dx.doi.org/10.1097/01.coc.0000251242.32763.35
27. De Ruysscher D, Mark Lodge M, Jones B, Brada M, Munro A, Jefferson T, et al. Charged particles in radiotherapy: a 5-year update of a systematic review. Radiother Oncol 2012; 103:5-7; PMID:22326572; http://dx.doi.org/10.1016/j.radonc.2012.01.003
28. Durante M, Loeffler JS. Charged particles in radiation oncology. Nat Rev Clin Oncol 2010; 7:37-43; PMID:19949433; http://dx.doi.org/10.1038/nrclinonc.2009.183
29. Dickler A, Kirk MC, Chu J, Nguyen C. The MammoSite breast brachytherapy applicator: a review of technique and outcomes. Brachytherapy 2005; 4:130-6; PMID:15893266; http://dx.doi.org/10.1016/j.brachy.2004.12.003
30. Divgi C. Targeted systemic radiotherapy of pheochromocytoma and medullary thyroid cancer. Semin Nucl Med 2011; 41:369-73; PMID:21803187; http://dx.doi.org/10.1053/j.semnuclmed.2011.05.004
31. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002; 20:2453-63; PMID:12011122; http://dx.doi.org/10.1200/JCO.2002.11.076
32. Kaminski MS, Estes J, Zasadny KR, Francis IR, Ross CW, Tuck M, et al. Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 2000; 96:1259-66; PMID:10942366
33. Milano MT, Constine LS, Okunieff P. Normal tissue tolerance dose metrics for radiation therapy of major organs. Semin Radiat Oncol 2007; 17:131-40; PMID:17395043; http://dx.doi.org/10.1016/j.semradonc.2006.11.009
34. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol 2003; 4:529-36; PMID:12965273; http://dx.doi.org/10.1016/S1470-2045(03)01191-4
35. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13:176-81; PMID:12903007; http://dx.doi.org/10.1016/S1053-4296(03)00031-6
36. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21:109-22; PMID:2032882; http://dx.doi.org/10.1016/0360-3016(91)90171-Y
37. Jereczek-Fossa BA, Marsiglia HR, Orecchia R. Radiotherapy-related fatigue. Crit Rev Oncol Hematol 2002; 41:317-25; PMID:11880207; http://dx.doi.org/10.1016/S1040-8428(01)00143-3
38. Travis LB, Ng AK, Allan JM, Pui CH, Kennedy AR, Xu XG, et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. J Natl Cancer Inst 2012; 104:357-70; PMID:22312134; http://dx.doi.org/10.1093/jnci/djr533
39. Berrington de Gonzalez A, Curtis RE, Kry SF, Gilbert E, Lamart S, Berg CD, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 2011; 12:353-60; PMID:21454129; http://dx.doi.org/10.1016/S1470-2045(11)70061-4
40. Tubiana M. Can we reduce the incidence of second primary malignancies occurring after radiotherapy? A critical review. Radiother Oncol 2009; 91:4-15, discussion 1-3; PMID:19201045; http://dx.doi.org/10.1016/j.radonc.2008.12.016
41. Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010; 102:1083-95; PMID:20634481; http://dx.doi.org/10.1093/jnci/djq238
42. Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009; 27:2356-62; PMID:19255307; http://dx.doi.org/10.1200/JCO.2008.21.1920
43. Hall EJ. Radiobiology for the Radiologist. Philadelphia, PA: Lippincott Williams & Wilkins, 2006.
44. Movsas B, Vikram B, Hauer-Jensen M, Moulder JE, Basch E, Brown SL, et al. Decreasing the adverse effects of cancer therapy: National Cancer Institute guidance for the clinical development of radiation injury mitigators. Clin Cancer Res 2011; 17:222-8; PMID:21047979; http://dx.doi.org/10.1158/1078-0432.CCR-10-1402
45. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010; 76(Suppl):S10-9; PMID:20171502; http://dx.doi.org/10.1016/j.ijrobp.2009.07.1754
46. Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009; 9:134-42; PMID:19148183; http://dx.doi.org/10.1038/nrc2587
47. Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer 2011; 11:239-53; PMID:21430696; http://dx.doi.org/10.1038/nrc3007

48. Mahmood J, Jelveh S, Calveley V, Zaidi A, Doctrow SR, Hill RP. Mitigation of radiation-induced lung injury by genistein and EUK-207. Int J Radiat Biol 2011; 87:889-901; PMID:21675818; http://dx.doi.org/10.3109/09553002.2011.583315
49. Jiang J, Stoyanovsky DA, Belikova NA, Tyurina YY, Zhao Q, Tungekar MA, et al. A mitochondria-targeted triphenylphosphonium-conjugated nitroxide functions as a radioprotector/mitigator. Radiat Res 2009; 172:706-17; PMID:19929417; http://dx.doi.org/10.1667/RR1729.1
50. Andreassen CN, Grau C, Lindegaard JC. Chemical radioprotection: a critical review of amifostine as a cytoprotector in radiotherapy. Semin Radiat Oncol 2003; 13:62-72; PMID:12520465; http://dx.doi.org/10.1053/srao.2003.50006
51. Xavier S, Yamada K, Samuni AM, Samuni A, DeGraff W, Krishna MC, et al. Differential protection by nitroxides and hydroxylamines to radiation-induced and metal ion-catalyzed oxidative damage. Biochim Biophys Acta 2002; 1573:109-20; PMID:12399020; http://dx.doi.org/10.1016/S0304-4165(02)00339-2
52. Atkinson J, Kapralov AA, Yanamala N, Tyurina YY, Amoscato AA, Pearce L, et al. A mitochondria-targeted inhibitor of cytochrome c peroxidase mitigates radiation-induced death. Nat Commun 2011; 2:497; PMID:21988913; http://dx.doi.org/10.1038/ncomms1499
53. Meyn RE, Milas L, Ang KK. The role of apoptosis in radiation oncology. Int J Radiat Biol 2009; 85:107-15; PMID:19280463; http://dx.doi.org/10.1080/09553000802662595
54. Belka C, Budach W. Anti-apoptotic Bcl-2 proteins: structure, function and relevance for radiation biology. Int J Radiat Biol 2002; 78:643-58; PMID:12194748; http://dx.doi.org/10.1080/09553000210137680
55. Farrell CL, Bready JV, Rex KL, Chen JN, DiPalma CR, Whitcomb KL, et al. Keratinocyte growth factor protects mice from chemotherapy and radiation-induced gastrointestinal injury and mortality. Cancer Res 1998; 58:933-9; PMID:9500453
56. Le QT, Kim HE, Schneider CJ, Muraközy G, Skladowski K, Reinisch S, et al. Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: a randomized, placebo-controlled study. J Clin Oncol 2011; 29:2808-14; PMID:21670453; http://dx.doi.org/10.1200/JCO.2010.32.4095
57. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med 2004; 351:2590-8; PMID:15602019; http://dx.doi.org/10.1056/NEJMoa040125
58. Zheng H, Wang J, Koteliansky VE, Gotwals PJ, Hauer-Jensen M. Recombinant soluble transforming growth factor beta type II receptor ameliorates radiation enteropathy in mice. Gastroenterology 2000; 119:1286-96; PMID:11054386; http://dx.doi.org/10.1053/gast.2000.19282
59. Wang ZD, Qiao YL, Tian XF, Zhang XQ, Zhou SX, Liu HX, et al. Toll-like receptor 5 agonism protects mice from radiation pneumonitis and pulmonary fibrosis. Asian Pac J Cancer Prev 2012; 13:4763-7; PMID:23167416; http://dx.doi.org/10.7314/APJCP.2012.13.9.4763
60. Burdelya LG, Gleiberman AS, Toshkov I, Aygun-Sunar S, Bapardekar M, Manderscheid-Kern P, et al. Toll-like receptor 5 agonist protects mice from dermatitis and oral mucositis caused by local radiation: implications for head-and-neck cancer radiotherapy. Int J Radiat Oncol Biol Phys 2012; 83:228-34; PMID:22000579; http://dx.doi.org/10.1016/j.ijrobp.2011.05.055
61. Vijay-Kumar M, Aitken JD, Sanders CJ, Frias A, Sloane VM, Xu J, et al. Flagellin treatment protects against chemicals, bacteria, viruses, and radiation. J Immunol 2008; 180:8280-5; PMID:18523294
62. Burdelya LG, Krivokrysenko VI, Tallant TC, Strom E, Gleiberman AS, Gupta D, et al. An agonist of toll-like receptor 5 has radioprotective activity in mouse and primate models. Science 2008; 320:226-30; PMID:18403709; http://dx.doi.org/10.1126/science.1154986
63. Haabeth OA, Bogen B, Corthay A. A model for cancer-suppressive inflammation. Oncoimmunology 2012; 1:1146-55; PMID:23170261; http://dx.doi.org/10.4161/onci.21542
64. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009; 27:127-45; PMID:19018081; http://dx.doi.org/10.1200/JCO.2008.17.2627
65. Schuchter LM, Hensley ML, Meropol NJ, Winer EP; American Society of Clinical Oncology Chemotherapy and Radiotherapy Expert Panel. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2002; 20:2895-903; PMID:12065567; http://dx.doi.org/10.1200/JCO.2002.04.178
66. Brizel DM, Wasserman TH, Henke M, Strnad V, Rudat V, Monnier A, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 2000; 18:3339-45; PMID:11013273
67. Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy. Nat Rev Cancer 2009; 9:351-60; PMID:19377507; http://dx.doi.org/10.1038/nrc2603
68. Bertout JA, Patel SA, Simon MC. The impact of O_2 availability on human cancer. Nat Rev Cancer 2008; 8:967-75; PMID:18987634; http://dx.doi.org/10.1038/nrc2540
69. Barilla J, Lokajícek M. The role of oxygen in DNA damage by ionizing particles. J Theor Biol 2000; 207:405-14; PMID:11082309; http://dx.doi.org/10.1006/jtbi.2000.2188
70. Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. Cancer Metastasis Rev 2007; 26:225-39; PMID:17440684; http://dx.doi.org/10.1007/s10555-007-9055-1
71. Overgaard J. Hypoxic radiosensitization: adored and ignored. J Clin Oncol 2007; 25:4066-74; PMID:17827455; http://dx.doi.org/10.1200/JCO.2007.12.7878
72. Menegakis A, Eicheler W, Yaromina A, Thames HD, Krause M, Baumann M. Residual DNA double strand breaks in perfused but not in unperfused areas determine different radiosensitivity of tumours. Radiother Oncol 2011; 100:137-44; PMID:21821302; http://dx.doi.org/10.1016/j.radonc.2011.07.001
73. Wouters BG, Brown JM. Cells at intermediate oxygen levels can be more important than the "hypoxic fraction" in determining tumor response to fractionated radiotherapy. Radiat Res 1997; 147:541-50; PMID:9146699; http://dx.doi.org/10.2307/3579620
74. Gray LH, Conger AD, Ebert M, Hornsey S, Scott OC. The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br J Radiol 1953; 26:638-48; PMID:13106296; http://dx.doi.org/10.1259/0007-1285-26-312-638
75. Nordsmark M, Overgaard M, Overgaard J. Pretreatment oxygenation predicts radiation response in advanced squamous cell carcinoma of the head and neck. Radiother Oncol 1996; 41:31-9; PMID:8961365
76. Wouters BG, Skarsgard LD. Low-dose radiation sensitivity and induced radioresistance to cell killing in HT-29 cells is distinct from the "adaptive response" and cannot be explained by a subpopulation of sensitive cells. Radiat Res 1997; 148:435-42; PMID:9355868; http://dx.doi.org/10.2307/3579320
77. Trédan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 2007; 99:1441-54; PMID:17895480; http://dx.doi.org/10.1093/jnci/djm135
78. Ogawa K, Kohshi K, Ishiuchi S, Matsushita M, Yoshimi N, Murayama S. Old but new methods in radiation oncology: hyperbaric oxygen therapy. Int J Clin Oncol 2013; 18:364-70; PMID:23463521; http://dx.doi.org/10.1007/s10147-013-0537-6
79. Bennett MH, Feldmeier J, Smee R, Milross C. Hyperbaric oxygenation for tumour sensitisation to radiotherapy. Cochrane Database Syst Rev 2012; 4:CD005007; PMID:22513926
80. Suh JH, Stea B, Nabid A, Kresl JJ, Fortin A, Mercier JP, et al. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. J Clin Oncol 2006; 24:106-14; PMID:16314619; http://dx.doi.org/10.1200/JCO.2004.00.1768
81. Viani GA, Manta GB, Fonseca EC, De Fendi LI, Afonso SL, Stefano EJ. Whole brain radiotherapy with radiosensitizer for brain metastases. J Exp Clin Cancer Res 2009; 28:1; PMID:19126230; http://dx.doi.org/10.1186/1756-9966-28-1
82. Overgaard J, Hansen HS, Overgaard M, Bastholt L, Berthelsen A, Specht L, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. Radiother Oncol 1998; 46:135-46; PMID:9510041; http://dx.doi.org/10.1016/S0167-8140(97)00220-X
83. Rischin D, Peters LJ, O'Sullivan B, Giralt J, Fisher R, Yuen K, et al. Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group. J Clin Oncol 2010; 28:2989-95; PMID:20479425; http://dx.doi.org/10.1200/JCO.2009.27.4449
84. Le QT, Moon J, Redman M, Williamson SK, Lara PN Jr., Goldberg Z, et al. Phase II study of tirapazamine, cisplatin, and etoposide and concurrent thoracic radiotherapy for limited-stage small-cell lung cancer: SWOG 0222. J Clin Oncol 2009; 27:3014-9; PMID:19364954; http://dx.doi.org/10.1200/JCO.2008.21.3868
85. Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, et al. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ 2012; 19:107-20; PMID:21760595; http://dx.doi.org/10.1038/cdd.2011.96
86. Kroemer G, Galluzzi L, Brenner C. Mitochondrial membrane permeabilization in cell death. Physiol Rev 2007; 87:99-163; PMID:17237344; http://dx.doi.org/10.1152/physrev.00013.2006
87. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol 2007; 8:729-40; PMID:17667954; http://dx.doi.org/10.1038/nrm2233
88. Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest 2013; 123:966-72; PMID:23454759; http://dx.doi.org/10.1172/JCI64098
89. Verheij M. Clinical biomarkers and imaging for radiotherapy-induced cell death. Cancer Metastasis Rev 2008; 27:471-80; PMID:18470482; http://dx.doi.org/10.1007/s10555-008-9131-1
90. Vigneron A, Vousden KH. p53, ROS and senescence in the control of aging. Aging (Albany NY) 2010; 2:471-4; PMID:20729567
91. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol 2007; 8:275-83; PMID:17380161; http://dx.doi.org/10.1038/nrm2147

92. Galluzzi L, Kepp O, Kroemer G. TP53 and MTOR crosstalk to regulate cellular senescence. Aging (Albany NY) 2010; 2:535-7; PMID:20876940
93. Vitale I, Galluzzi L, Castedo M, Kroemer G. Mitotic catastrophe: a mechanism for avoiding genomic instability. Nat Rev Mol Cell Biol 2011; 12:385-92; PMID:21527953; http://dx.doi.org/10.1038/nrm3115
94. Vitale I, Galluzzi L, Senovilla L, Criollo A, Jemaà M, Castedo M, et al. Illicit survival of cancer cells during polyploidization and depolyploidization. Cell Death Differ 2011; 18:1403-13; PMID:21072053; http://dx.doi.org/10.1038/cdd.2010.145
95. Baritaud M, Cabon L, Delavallée L, Galán-Malo P, Gilles ME, Brunelle-Navas MN, et al. AIF-mediated caspase-independent necroptosis requires ATM and DNA-PK-induced histone H2AX Ser139 phosphorylation. Cell Death Dis 2012; 3:e390; PMID:22972376; http://dx.doi.org/10.1038/cddis.2012.120
96. Cabon L, Galán-Malo P, Bouharrour A, Delavallée L, Brunelle-Navas MN, Lorenzo HK, et al. BID regulates AIF-mediated caspase-independent necroptosis by promoting BAX activation. Cell Death Differ 2012; 19:245-56; PMID:21738214; http://dx.doi.org/10.1038/cdd.2011.91
97. Wang Y, Kim NS, Haince JF, Kang HC, David KK, Andrabi SA, et al. Poly(ADP-ribose) (PAR) binding to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos). Sci Signal 2011; 4:ra20; PMID:21467298; http://dx.doi.org/10.1126/scisignal.2000902
98. Vandenabeele P, Galluzzi L, Vanden Berghe T, Kroemer G. Molecular mechanisms of necroptosis: an ordered cellular explosion. Nat Rev Mol Cell Biol 2010; 11:700-14; PMID:20823910; http://dx.doi.org/10.1038/nrm2970
99. Galluzzi L, Kroemer G. Necroptosis: a specialized pathway of programmed necrosis. Cell 2008; 135:1161-3; PMID:19109884; http://dx.doi.org/10.1016/j.cell.2008.12.004
100. Galluzzi L, Vanden Berghe T, Vanlangenakker N, Buettner S, Eisenberg T, Vandenabeele P, et al. Programmed necrosis from molecules to health and disease. Int Rev Cell Mol Biol 2011; 289:1-35; PMID:21749897; http://dx.doi.org/10.1016/B978-0-12-386039-2.00001-8
101. Mothersill C, Seymour CB. Radiation-induced bystander effects--implications for cancer. Nat Rev Cancer 2004; 4:158-64; PMID:14964312; http://dx.doi.org/10.1038/nrc1277
102. Azzam EI, de Toledo SM, Little JB. Direct evidence for the participation of gap junction-mediated intercellular communication in the transmission of damage signals from alpha -particle irradiated to nonirradiated cells. Proc Natl Acad Sci U S A 2001; 98:473-8; PMID:11149936
103. Hervé JC, Bourmeyster N, Sarrouilhe D, Duffy HS. Gap junctional complexes: from partners to functions. Prog Biophys Mol Biol 2007; 94:29-65; PMID:17507078; http://dx.doi.org/10.1016/j.pbiomolbio.2007.03.010
104. Goodenough DA, Paul DL. Beyond the gap: functions of unpaired connexon channels. Nat Rev Mol Cell Biol 2003; 4:285-94; PMID:12671651; http://dx.doi.org/10.1038/nrm1072
105. Lehnert BE, Goodwin EH, Deshpande A. Extracellular factor(s) following exposure to alpha particles can cause sister chromatid exchanges in normal human cells. Cancer Res 1997; 57:2164-71; PMID:9187116
106. Shao C, Furusawa Y, Aoki M, Matsumoto H, Ando K. Nitric oxide-mediated bystander effect induced by heavy-ions in human salivary gland tumour cells. Int J Radiat Biol 2002; 78:837-44; PMID:12428924; http://dx.doi.org/10.1080/09553000210149786
107. Shao C, Stewart V, Folkard M, Michael BD, Prise KM. Nitric oxide-mediated signaling in the bystander response of individually targeted glioma cells. Cancer Res 2003; 63:8437-42; PMID:14679007
108. Chou CH, Chen PJ, Lee PH, Cheng AL, Hsu HC, Cheng JC. Radiation-induced hepatitis B virus reactivation in liver mediated by the bystander effect from irradiated endothelial cells. Clin Cancer Res 2007; 13:851-7; PMID:17289877; http://dx.doi.org/10.1158/1078-0432.CCR-06-2459
109. Narayanan PK, LaRue KE, Goodwin EH, Lehnert BE. Alpha particles induce the production of interleukin-8 by human cells. Radiat Res 1999; 152:57-63; PMID:10381841; http://dx.doi.org/10.2307/3580049
110. Iyer R, Lehnert BE, Svensson R. Factors underlying the cell growth-related bystander responses to alpha particles. Cancer Res 2000; 60:1290-8; PMID:10728689
111. Zhou H, Ivanov VN, Gillespie J, Geard CR, Amundson SA, Brenner DJ, et al. Mechanism of radiation-induced bystander effect: role of the cyclooxygenase-2 signaling pathway. Proc Natl Acad Sci U S A 2005; 102:14641-6; PMID:16203985; http://dx.doi.org/10.1073/pnas.0505473102
112. Kroemer G, Zitvogel L. Abscopal but desirable: The contribution of immune responses to the efficacy of radiotherapy. Oncoimmunology 2012; 1:407-8; PMID:22754758; http://dx.doi.org/10.4161/onci.20074
113. Gupta A, Sharma A, von Boehmer L, Surace L, Knuth A, van den Broek M. Radiotherapy supports protective tumor-specific immunity. Oncoimmunology 2012; 1:1610-1; PMID:23264910; http://dx.doi.org/10.4161/onci.21478
114. Dudek AM, Garg AD, Krysko DV, De Ruysscher D, Agostinis P. Inducers of immunogenic cancer cell death. Cytokine Growth Factor Rev 2013; In press; PMID:23391812; http://dx.doi.org/10.1016/j.cytogfr.2013.01.005.
115. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013; 31:51-72; PMID:23157435; http://dx.doi.org/10.1146/annurev-immunol-032712-100008
116. Kono K, Mimura K. Immunogenic tumor cell death induced by chemoradiotherapy in a clinical setting. Oncoimmunology 2013; 2:e22197; PMID:23482346; http://dx.doi.org/10.4161/onci.22197
117. Garg AD, Krysko DV, Vandenabeele P, Agostinis P. The emergence of phox-ER stress induced immunogenic apoptosis. Oncoimmunology 2012; 1:786-8; PMID:22934283; http://dx.doi.org/10.4161/onci.19750
118. Galluzzi L, Kepp O, Kroemer G. Mitochondria: master regulators of danger signalling. Nat Rev Mol Cell Biol 2012; 13:780-8; PMID:23175281; http://dx.doi.org/10.1038/nrm3479
119. Krysko DV, Garg AD, Kaczmarek A, Krysko O, Agostinis P, Vandenabeele P. Immunogenic cell death and DAMPs in cancer therapy. Nat Rev Cancer 2012; 12:860-75; PMID:23151605; http://dx.doi.org/10.1038/nrc3380
120. Ganss R, Ryschich E, Klar E, Arnold B, Hämmerling GJ. Combination of T-cell therapy and trigger of inflammation induces remodeling of the vasculature and tumor eradication. Cancer Res 2002; 62:1462-70; PMID:11888921
121. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005; 307:58-62; PMID:15637262; http://dx.doi.org/10.1126/science.1104819
122. Tartour E, Pere H, Maillere B, Terme M, Merillon N, Taieb J, et al. Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. Cancer Metastasis Rev 2011; 30:83-95; PMID:21249423; http://dx.doi.org/10.1007/s10555-011-9281-4
123. Heckmann M, Douwes K, Peter R, Degitz K. Vascular activation of adhesion molecule mRNA and cell surface expression by ionizing radiation. Exp Cell Res 1998; 238:148-54; PMID:9457067; http://dx.doi.org/10.1006/excr.1997.3826
124. Galluzzi L, Vacchelli E, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, et al. Trial Watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2012; 1:28-37; PMID:22720209; http://dx.doi.org/10.4161/onci.1.1.17938
125. Vacchelli E, Galluzzi L, Fridman WH, Galon J, Sautès-Fridman C, Tartour E, et al. Trial watch: Chemotherapy with immunogenic cell death inducers. Oncoimmunology 2012; 1:179-88; PMID:22720239; http://dx.doi.org/10.4161/onci.1.2.19026
126. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial Watch: Adoptive cell transfer immunotherapy. Oncoimmunology 2012; 1:306-15; PMID:22737606; http://dx.doi.org/10.4161/onci.19549
127. Vacchelli E, Galluzzi L, Eggermont A, Galon J, Tartour E, Zitvogel L, et al. Trial Watch: Immunostimulatory cytokines. Oncoimmunology 2012; 1:493-506; PMID:22754768; http://dx.doi.org/10.4161/onci.20459
128. Galluzzi L, Vacchelli E, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial Watch: Experimental Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:699-716; PMID:22934262; http://dx.doi.org/10.4161/onci.20696
129. Vacchelli E, Galluzzi L, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial watch: FDA-approved Toll-like receptor agonists for cancer therapy. Oncoimmunology 2012; 1:894-907; PMID:23162757; http://dx.doi.org/10.4161/onci.20931
130. Galluzzi L, Senovilla L, Vacchelli E, Eggermont A, Fridman WH, Galon J, et al. Trial watch: Dendritic cell-based interventions for cancer therapy. Oncoimmunology 2012; 1:1111-34; PMID:23170259; http://dx.doi.org/10.4161/onci.21494
131. Senovilla L, Vacchelli E, Galon J, Adjemian S, Eggermont A, Fridman WH, et al. Trial watch: Prognostic and predictive value of the immune infiltrate in cancer. Oncoimmunology 2012; 1:1323-43; PMID:23243596; http://dx.doi.org/10.4161/onci.22009
132. Vacchelli E, Martins I, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial watch: Peptide vaccines in cancer therapy. Oncoimmunology 2012; 1:1557-76; PMID:23264902; http://dx.doi.org/10.4161/onci.22428
133. Vacchelli E, Eggermont A, Galon J, Sautès-Fridman C, Zitvogel L, Kroemer G, et al. Trial watch: Monoclonal antibodies in cancer therapy. Oncoimmunology 2013; 2:e22789; PMID:23482847; http://dx.doi.org/10.4161/onci.22789
134. Menger L, Vacchelli E, Kepp O, Eggermont A, Tartour E, Zitvogel L, et al. Trial watch: Cardiac glycosides and cancer therapy. Oncoimmunology 2013; 2:e23082; PMID:23525565; http://dx.doi.org/10.4161/onci.23082
135. Vacchelli E, Senovilla L, Eggermont A, Fridman WH, Galon J, Zitvogel L, et al. Trial watch: Chemotherapy with immunogenic cell death inducers. Oncoimmunology 2013; 2:e23510; PMID:23687621; http://dx.doi.org/10.4161/onci.23510
136. Senovilla L, Vacchelli E, Garcia P, Eggermont A, Fridman WH, Galon J, et al. Trial watch: DNA vaccines for cancer therapy. Oncoimmunology 2013; 2:e23803; PMID:23734328; http://dx.doi.org/10.4161/onci.23803
137. Vacchelli E, Eggermont A, Fridman WH, Galon J, Tartour E, Zitvogel L, et al. Trial Watch: Adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2013; 2:e24238; PMID:23762803; http://dx.doi.org/10.4161/onci.24238
138. Vacchelli E, Eggermont A, Sautès-Fridman C, Galon J, Zitvogel L, Kroemer G, et al. Trial Watch: Oncolytic viruses for cancer therapy. OncoImmunology 2013; 2:e24612; http://dx.doi.org/10.4161/onci.24612

139. Vacchelli E, Galluzzi L, Eggermont A, Galon J, Tartour E, Zitvogel L, et al. Trial Watch: Immunostimulatory cytokines. OncoImmunology 2012; 1:493-506; PMID:22754768
140. Vacchelli E, Eggermont A, Sautes-Fridman C, Galon J, Zitvogel L, Kroemer G, et al. Trial Watch: Toll-like receptor agonists for cancer therapy. OncoImmunology 2013; 2: In press.
141. Gough MJ, Crittenden MR. Combination approaches to immunotherapy: the radiotherapy example. Immunotherapy 2009; 1:1025-37; PMID:20635917; http://dx.doi.org/10.2217/imt.09.64
142. Hill-Kayser CE, Plastaras JP, Tochner Z, Glatstein E. TBI during BM and SCT: review of the past, discussion of the present and consideration of future directions. Bone Marrow Transplant 2011; 46:475-84; PMID:21113184; http://dx.doi.org/10.1038/bmt.2010.280
143. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 2013; 105:256-65; PMID:23291374; http://dx.doi.org/10.1093/jnci/djs629
144. Munro AJ. Bystander effects and their implications for clinical radiotherapy. J Radiol Prot 2009; 29(2A):A133-42; PMID:19454811; http://dx.doi.org/10.1088/0952-4746/29/2A/S09
145. Mancuso M, Pasquali E, Giardullo P, Leonardi S, Tanori M, Di Majo V, et al. The radiation bystander effect and its potential implications for human health. Curr Mol Med 2012; 12:613-24; PMID:22452594; http://dx.doi.org/10.2174/156652412800620011
146. Rees GJ. Abscopal regression in lymphoma: a mechanism in common with total body irradiation? Clin Radiol 1981; 32:475-80; PMID:7249526; http://dx.doi.org/10.1016/S0009-9260(81)80310-8
147. Nobler MP. The abscopal effect in malignant lymphoma and its relationship to lymphocyte circulation. Radiology 1969; 93:410-2; PMID:5822721
148. Antoniades J, Brady LW, Lightfoot DA. Lymphangiographic demonstration of the abscopal effect in patients with malignant lymphomas. Int J Radiat Oncol Biol Phys 1977; 2:141-7; PMID:403163; http://dx.doi.org/10.1016/0360-3016(77)90020-7
149. Robin HI, AuBuchon J, Varanasi VR, Weinstein AB. The abscopal effect: demonstration in lymphomatous involvement of kidneys. Med Pediatr Oncol 1981; 9:473-6; PMID:7029238; http://dx.doi.org/10.1002/mpo.2950090510
150. Horiuhi T, Nomura J, Okuda M, Ichinohasama R. Abscopal effect of small intestinal NK/T-cell lymphoma. Rinsho Ketsueki 2003; 44:940-5; PMID:14577314
151. Hiniker SM, Chen DS, Knox SJ. Abscopal effect in a patient with melanoma. N Engl J Med 2012; 366:2035, author reply 2035-6; PMID:22621637; http://dx.doi.org/10.1056/NEJMc1203984
152. Kingsley DP. An interesting case of possible abscopal effect in malignant melanoma. Br J Radiol 1975; 48:863-6; PMID:811297; http://dx.doi.org/10.1259/0007-1285-48-574-863
153. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012; 366:925-31; PMID:22397654; http://dx.doi.org/10.1056/NEJMoa1112824
154. Stamell EF, Wolchok JD, Gnjatic S, Lee NY, Brownell I. The abscopal effect associated with a systemic anti-melanoma immune response. Int J Radiat Oncol Biol Phys 2013; 85:293-5; PMID:22560555; http://dx.doi.org/10.1016/j.ijrobp.2012.03.017
155. Mikuriya S, Saito T, Konoeda K, Matsuba T, Torii A, Sato O, et al. Evaluation of abscopal effect observed in advanced cancer of breast treated with preoperative radiotherapy (author's transl). Nihon Gan Chiryo Gakkai Shi 1979; 14:997-1008; PMID:120402
156. Mikuriya S, Saito T, Matsuba T, Torii A, Sato O, Adachi H, et al. Pathologic and immunologic analysis for a case with carcinoma of aberrant breast of the axilla showed "abscopal effect" after the radiotherapy (author's transl). Nihon Gan Chiryo Gakkai Shi 1978; 13:406-13; PMID:712167
157. Okino T, Kan N, Nakanishi M, Satoh K, Mise K, Yamasaki S, et al. The therapeutic effects of OK-432 combined adoptive immunotherapy (AIT) against liver metastases of breast cancer. Gan To Kagaku Ryoho 1989; 16:1913-9; PMID:2730083
158. Konoeda K. Therapeutic efficacy of pre-operative radiotherapy on breast carcinoma: in special reference to its abscopal effect on metastatic lymph-nodes. Nihon Gan Chiryo Gakkai Shi 1990; 25:1204-14; PMID:2398302
159. Rees GJ, Ross CM. Abscopal regression following radiotherapy for adenocarcinoma. Br J Radiol 1983; 56:63-6; PMID:6185172; http://dx.doi.org/10.1259/0007-1285-56-661-63
160. Ehlers G, Fridman M. Abscopal effect of radiation in papillary adenocarcinoma. Br J Radiol 1973; 46:220-2; PMID:4706791; http://dx.doi.org/10.1259/0007-1285-46-543-220
161. Matsubara S, Horiuchi J, Okuyama T, Suzuki S, Miyazaki K. A case of reticulum cell sarcoma of the skin showing abscopal effect during radiotherapy (author's transl). Nihon Igaku Hoshasen Gakkai Zasshi 1975; 35:860-7; PMID:765959
162. Nakanishi M, Chuma M, Hige S, Asaka M. Abscopal effect on hepatocellular carcinoma. Am J Gastroenterol 2008; 103:1320-1; PMID:18477367; http://dx.doi.org/10.1111/j.1572-0241.2007.01782_13.x
163. Ohba K, Omagari K, Nakamura T, Ikuno N, Saeki S, Matsuo I, et al. Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. Gut 1998; 43:575-7; PMID:9824589; http://dx.doi.org/10.1136/gut.43.4.575
164. Cotter SE, Dunn GP, Collins KM, Sahni D, Zukotynski KA, Hansen JL, et al. Abscopal effect in a patient with metastatic Merkel cell carcinoma following radiation therapy: potential role of induced antitumor immunity. Arch Dermatol 2011; 147:870-2; PMID:21768497; http://dx.doi.org/10.1001/archdermatol.2011.176
165. Ishiyama H, Teh BS, Ren H, Chiang S, Tann A, Blanco AI, et al. Spontaneous regression of thoracic metastases while progression of brain metastases after stereotactic radiosurgery and stereotactic body radiotherapy for metastatic renal cell carcinoma: abscopal effect prevented by the blood-brain barrier? Clin Genitourin Cancer 2012; 10:196-8; PMID:22409865; http://dx.doi.org/10.1016/j.clgc.2012.01.004
166. Takaya M, Niibe Y, Tsunoda S, Jobo T, Imai M, Kotani S, et al. Abscopal effect of radiation on toruliform para-aortic lymph node metastases of advanced uterine cervical carcinoma--a case report. Anticancer Res 2007; 27(1B):499-503; PMID:17348433
167. Demaria S, Formenti SC. Role of T lymphocytes in tumor response to radiotherapy. Front Oncol 2012; 2:95; PMID:22937524; http://dx.doi.org/10.3389/fonc.2012.00095
168. Frey B, Rubner Y, Wunderlich R, Weiss EM, Pockley AG, Fietkau R, et al. Induction of abscopal anti-tumor immunity and immunogenic tumor cell death by ionizing irradiation - implications for cancer therapies. Curr Med Chem 2012; 19:1751-64; PMID:22414083; http://dx.doi.org/10.2174/092986712800099811
169. Kwilas AR, Donahue RN, Bernstein MB, Hodge JW. In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. Front Oncol 2012; 2:104; PMID:22973551; http://dx.doi.org/10.3389/fonc.2012.00104
170. Rubner Y, Wunderlich R, Rühle PF, Kulzer L, Werthmöller N, Frey B, et al. How does ionizing irradiation contribute to the induction of anti-tumor immunity? Front Oncol 2012; 2:75; PMID:22848871; http://dx.doi.org/10.3389/fonc.2012.00075
171. Clement JM, McDermott DF. The high-dose aldesleukin (IL-2) "select" trial: a trial designed to prospectively validate predictive models of response to high-dose IL-2 treatment in patients with metastatic renal cell carcinoma. Clin Genitourin Cancer 2009; 7:E7-9; PMID:19692326; http://dx.doi.org/10.3816/CGC.2009.n.014
172. Halama N, Zoernig I, Jaeger D. Advanced malignant melanoma: immunologic and multimodal therapeutic strategies. J Oncol 2010; 2010:689893; PMID:20224761; http://dx.doi.org/10.1155/2010/689893
173. Ngiow SF, von Scheidt B, Möller A, Smyth MJ, Teng MW. The interaction between murine melanoma and the immune system reveals that prolonged responses predispose for autoimmunity. Oncoimmunology 2013; 2:e23036; PMID:23524369; http://dx.doi.org/10.4161/onci.23036
174. Akutsu Y, Matsubara H, Urashima T, Komatsu A, Sakata H, Nishimori T, et al. Combination of direct intratumoral administration of dendritic cells and irradiation induces strong systemic antitumor effect mediated by GRP94/gp96 against squamous cell carcinoma in mice. Int J Oncol 2007; 31:509-15; PMID:17671676
175. Yasuda K, Nirei T, Tsuno NH, Nagawa H, Kitayama J. Intratumoral injection of interleukin-2 augments the local and abscopal effects of radiotherapy in murine rectal cancer. Cancer Sci 2011; 102:1257-63; PMID:21443690; http://dx.doi.org/10.1111/j.1349-7006.2011.01940.x
176. Seung SK, Curti B, Crittenden M, Urba W. Radiation and immunotherapy: Renewed allies in the war on cancer. Oncoimmunology 2012; 1:1645-7; PMID:23264923; http://dx.doi.org/10.4161/onci.21746
177. Shiraishi K, Ishiwata Y, Nakagawa K, Yokochi S, Taruki C, Akuta T, et al. Enhancement of antitumor radiation efficacy and consistent induction of the abscopal effect in mice by ECI301, an active variant of macrophage inflammatory protein-1alpha. Clin Cancer Res 2008; 14:1159-66; PMID:18281550; http://dx.doi.org/10.1158/1078-0432.CCR-07-4485
178. Brody JD, Ai WZ, Czerwinski DK, Torchia JA, Levy M, Advani RH, et al. In situ vaccination with a TLR9 agonist induces systemic lymphoma regression: a phase I/II study. J Clin Oncol 2010; 28:4324-32; PMID:20697067; http://dx.doi.org/10.1200/JCO.2010.28.9793
179. Hotz C, Bourquin C. Systemic cancer immunotherapy with Toll-like receptor 7 agonists: Timing is everything. Oncoimmunology 2012; 1:227-8; PMID:22720251; http://dx.doi.org/10.4161/onci.1.2.18169
180. Zhang M, Lahn M, Huber PE. Translating the combination of TGFβ blockade and radiotherapy into clinical development in glioblastoma. Oncoimmunology 2012; 1:943-5; PMID:23162765; http://dx.doi.org/10.4161/onci.19789
181. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res 2009; 15:5379-88; PMID:19706802; http://dx.doi.org/10.1158/1078-0432.CCR-09-0265
182. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1:1223-5; PMID:23243584; http://dx.doi.org/10.4161/onci.21335
183. Waitz R, Fassò M, Allison JP. CTLA-4 blockade synergizes with cryoablation to mediate tumor rejection. Oncoimmunology 2012; 1:544-6; PMID:22754781; http://dx.doi.org/10.4161/onci.19442
184. Verbrugge I, Galli M, Smyth MJ, Johnstone RW, Haynes NM. Enhancing the antitumor effects of radiotherapy with combinations of immunostimulatory antibodies. Oncoimmunology 2012; 1:1629-31; PMID:23264917; http://dx.doi.org/10.4161/onci.21652

185. Hodge JW, Sharp HJ, Gameiro SR. Abscopal regression of antigen disparate tumors by antigen cascade after systemic tumor vaccination in combination with local tumor radiation. Cancer Biother Radiopharm 2012; 27:12-22; PMID:22283603; http://dx.doi.org/10.1089/cbr.2012.1202
186. Krysko DV, D'Herde K, Vandenabeele P. Clearance of apoptotic and necrotic cells and its immunological consequences. Apoptosis 2006; 11:1709-26; PMID:16951923; http://dx.doi.org/10.1007/s10495-006-9527-8
187. Krysko DV, Vanden Berghe T, D'Herde K, Vandenabeele P. Apoptosis and necrosis: detection, discrimination and phagocytosis. Methods 2008; 44:205-21; PMID:18314051; http://dx.doi.org/10.1016/j.ymeth.2007.12.001
188. Martins I, Kepp O, Galluzzi L, Senovilla L, Schlemmer F, Adjemian S, et al. Surface-exposed calreticulin in the interaction between dying cells and phagocytes. Ann N Y Acad Sci 2010; 1209:77-82; PMID:20958319; http://dx.doi.org/10.1111/j.1749-6632.2010.05740.x
189. Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, Perfettini JL, et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat Med 2007; 13:54-61; PMID:17187072; http://dx.doi.org/10.1038/nm1523
190. Garg AD, Krysko DV, Verfaillie T, Kaczmarek A, Ferreira GB, Marysael T, et al. A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. EMBO J 2012; 31:1062-79; PMID:22252128; http://dx.doi.org/10.1038/emboj.2011.497
191. Obeid M, Panaretakis T, Joza N, Tufi R, Tesniere A, van Endert P, et al. Calreticulin exposure is required for the immunogenicity of gamma-irradiation and UVC light-induced apoptosis. Cell Death Differ 2007; 14:1848-50; PMID:17657249; http://dx.doi.org/10.1038/sj.cdd.4402201
192. Panaretakis T, Kepp O, Brockmeier U, Tesniere A, Bjorklund AC, Chapman DC, et al. Mechanisms of pre-apoptotic calreticulin exposure in immunogenic cell death. EMBO J 2009; 28:578-90; PMID:19165151; http://dx.doi.org/10.1038/emboj.2009.1
193. Panaretakis T, Joza N, Modjtahedi N, Tesniere A, Vitale I, Durchschlag M, et al. The co-translocation of ERp57 and calreticulin determines the immunogenicity of cell death. Cell Death Differ 2008; 15:1499-509; PMID:18464797; http://dx.doi.org/10.1038/cdd.2008.67
194. Sukkurwala AQ, Martins I, Wang Y, Schlemmer F, Ruckenstuhl C, Durchschlag M, et al. Immunogenic calreticulin exposure occurs through a phylogenetically conserved stress pathway involving the chemokine CXCL8. Cell Death Differ 2013; In press; PMID:23787997; http://dx.doi.org/10.1038/cdd.2013.73.
195. Aymeric L, Apetoh L, Ghiringhelli F, Tesniere A, Martins I, Kroemer G, et al. Tumor cell death and ATP release prime dendritic cells and efficient anticancer immunity. Cancer Res 2010; 70:855-8; PMID:20086177; http://dx.doi.org/10.1158/0008-5472.CAN-09-3566
196. Martins I, Tesniere A, Kepp O, Michaud M, Schlemmer F, Senovilla L, et al. Chemotherapy induces ATP release from tumor cells. Cell Cycle 2009; 8:3723-8; PMID:19855167; http://dx.doi.org/10.4161/cc.8.22.10026
197. Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, et al. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science 2011; 334:1573-7; PMID:22174255; http://dx.doi.org/10.1126/science.1208347
198. Michaud M, Sukkurwala AQ, Martins I, Shen S, Zitvogel L, Kroemer G. Subversion of the chemotherapy-induced anticancer immune response by the ecto-ATPase CD39. Oncoimmunology 2012; 1:393-5; PMID:22737627; http://dx.doi.org/10.4161/onci.19070
199. Martins I, Wang Y, Michaud M, Ma Y, Sukkurwala AQ, Shen S, et al. Molecular mechanisms of ATP secretion during immunogenic cell death. Cell Death Differ 2013; In press.
200. Chekeni FB, Elliott MR, Sandilos JK, Walk SF, Kinchen JM, Lazarowski ER, et al. Pannexin 1 channels mediate 'find-me' signal release and membrane permeability during apoptosis. Nature 2010; 467:863-7; PMID:20944749; http://dx.doi.org/10.1038/nature09413
201. Elliott MR, Chekeni FB, Trampont PC, Lazarowski ER, Kadl A, Walk SF, et al. Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature 2009; 461:282-6; PMID:19741708; http://dx.doi.org/10.1038/nature08296
202. Ghiringhelli F, Apetoh L, Tesniere A, Aymeric L, Ma Y, Ortiz C, et al. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat Med 2009; 15:1170-8; PMID:19767732; http://dx.doi.org/10.1038/nm.2028
203. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007; 13:1050-9; PMID:17704786; http://dx.doi.org/10.1038/nm1622
204. Yamazaki T, Hannani D, Poirier-Colame V, Ladoire S, Locher C, Sistigu A, et al. Defective immunogenic cell death of HMGB1-deficient tumors: compensatory therapy with TLR4 agonists. Cell Death Differ 2013; In press; PMID:23811849; http://dx.doi.org/10.1038/cdd.2013.72.
205. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 2002; 418:191-5; PMID:12110890; http://dx.doi.org/10.1038/nature00858
206. Tang D, Loze MT, Zeh HJ, Kang R. The redox protein HMGB1 regulates cell death and survival in cancer treatment. Autophagy 2010; 6:1181-3; PMID:20861675; http://dx.doi.org/10.4161/auto.6.8.13367
207. Vacchelli E, Galluzzi L, Rousseau V, Rigoni A, Tesniere A, Delahaye N, et al. Loss-of-function alleles of P2RX7 and TLR4 fail to affect the response to chemotherapy in non-small cell lung cancer. Oncoimmunology 2012; 1:271-8; PMID:22737602; http://dx.doi.org/10.4161/onci.18684
208. Goldsmith SJ. Radioimmunotherapy of lymphoma: Bexxar and Zevalin. Semin Nucl Med 2010; 40:122-35; PMID:20113680; http://dx.doi.org/10.1053/j.semnuclmed.2009.11.002
209. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005; 352:441-9; PMID:15689582; http://dx.doi.org/10.1056/NEJMoa041511
210. Leahy MF, Turner JH. Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. Blood 2011; 117:45-52; PMID:20864582; http://dx.doi.org/10.1182/blood-2010-02-269753
211. Mäkelä S, Poutanen M, Lehtimäki J, Kostian ML, Santti R, Vihko R. Estrogen-specific 17 beta-hydroxysteroid oxidoreductase type 1 (E.C. 1.1.1.62) as a possible target for the action of phytoestrogens. Proc Soc Exp Biol Med 1995; 208:51-9; PMID:7892295; http://dx.doi.org/10.3181/00379727-208-43831
212. Pouget JP, Navarro-Teulon I, Bardiès M, Chouin N, Cartron G, Pèlegrin A, et al. Clinical radioimmunotherapy--the role of radiobiology. Nat Rev Clin Oncol 2011; 8:720-34; PMID:22064461; http://dx.doi.org/10.1038/nrclinonc.2011.160
213. Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov 2012; 11:215-33; PMID:22301798; http://dx.doi.org/10.1038/nrd3626
214. Goldberg RM. Cetuximab. Nat Rev Drug Discov 2005; (Suppl): S10-1; PMID:15962524; http://dx.doi.org/10.1038/nrd1728
215. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012; 13:459-65; PMID:22456429; http://dx.doi.org/10.1016/S1470-2045(12)70090-6
216. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012; 30:2046-54; PMID:22547592; http://dx.doi.org/10.1200/JCO.2011.38.4032
217. Madan RA, Heery CR, Gulley JL. Combination of vaccine and immune checkpoint inhibitor is safe with encouraging clinical activity. Oncoimmunology 2012; 1:1167-8; PMID:23170267; http://dx.doi.org/10.4161/onci.20591
218. Higano CS, Small EJ, Schellhammer P, Yasothan U, Gubernick S, Kirkpatrick P, et al. Sipuleucel-T. Nat Rev Drug Discov 2010; 9:513-4; PMID:20592741; http://dx.doi.org/10.1038/nrd3220
219. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al.; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-22; PMID:20818862; http://dx.doi.org/10.1056/NEJMoa1001294
220. Tanimoto T, Hori A, Kami M. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:1966, author reply 1967-8; PMID:21067392; http://dx.doi.org/10.1056/NEJMc1009982
221. Holcmann M, Drobits B, Sibilia M. How imiquimod licenses plasmacytoid dendritic cells to kill tumors. Oncoimmunology 2012; 1:1661-3; PMID:23264929; http://dx.doi.org/10.4161/onci.22033
222. Walter S, Weinschenk T, Reinhardt C, Singh-Jasuja H. Single-dose cyclophosphamide synergizes with immune responses to the renal cell cancer vaccine IMA901. Oncoimmunology 2013; 2:e22246; PMID:23482454; http://dx.doi.org/10.4161/onci.22246
223. Johnson LE, Frye TP, McNeel DG. Immunization with a prostate cancer xenoantigen elicits a xenoantigen epitope-specific T-cell response. Oncoimmunology 2012; 1:1546-56; PMID:23264901; http://dx.doi.org/10.4161/onci.22564
224. Sawada Y, Sakai M, Yoshikawa T, Ofuji K, Nakatsura T. A glypican-3-derived peptide vaccine against hepatocellular carcinoma. Oncoimmunology 2012; 1:1448-50; PMID:23243625; http://dx.doi.org/10.4161/onci.21351
225. Grekova SP, Rommelaere J, Raykov Z. Parvoviruses-tools to fine-tune anticancer immune responses. Oncoimmunology 2012; 1:1417-9; PMID:23243613; http://dx.doi.org/10.4161/onci.21097
226. Cerullo V, Vähä-Koskela M, Hemminki A. Oncolytic adenoviruses: A potent form of tumor immunovirotherapy. Oncoimmunology 2012; 1:979-81; PMID:23162778; http://dx.doi.org/10.4161/onci.20172
227. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet 2008; 371:1695-709; PMID:18486742; http://dx.doi.org/10.1016/S0140-6736(08)60728-X
228. Brizel DM, Esclamado R. Concurrent chemoradiotherapy for locally advanced, nonmetastatic, squamous carcinoma of the head and neck: consensus, controversy, and conundrum. J Clin Oncol 2006; 24:2612-7; PMID:16763273; http://dx.doi.org/10.1200/JCO.2005.05.2829
229. Garden AS, Harris J, Trotti A, Jones CU, Carrascosa L, Cheng JD, et al. Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: a phase II trial of the radiation therapy oncology group (RTOG 99-14). Int J Radiat Oncol Biol Phys 2008; 71:1351-5; PMID:18640496; http://dx.doi.org/10.1016/j.ijrobp.2008.04.006

230. Nuyts S, Dirix P, Clement PM, Poorten VV, Delaere P, Schoenaers J, et al. Impact of adding concomitant chemotherapy to hyperfractionated accelerated radiotherapy for advanced head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2009; 73:1088-95; PMID:18707823; http://dx.doi.org/10.1016/j.ijrobp.2008.05.042

231. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, et al. Molecular mechanisms of cisplatin resistance. Oncogene 2012; 31:1869-83; PMID:21892204; http://dx.doi.org/10.1038/onc.2011.384

232. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al.; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 355:1114-23; PMID:16971718; http://dx.doi.org/10.1056/NEJMoa060829

233. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012; 23:2479-516; PMID:23012255; http://dx.doi.org/10.1093/annonc/mds236

234. Van Cutsem E, Borràs JM, Castells A, Ciardiello F, Ducreux M, Haq A, et al. Improving outcomes in colorectal cancer: Where do we go from here? Eur J Cancer 2013; In press; PMID:23642327; http://dx.doi.org/10.1016/j.ejca.2013.03.026.

235. Inderberg-Suso EM, Trachsel S, Lislerud K, Rasmussen AM, Gaudernack G. Widespread CD4+ T-cell reactivity to novel hTERT epitopes following vaccination of cancer patients with a single hTERT peptide GV1001. Oncoimmunology 2012; 1:670-86; PMID:22934259; http://dx.doi.org/10.4161/onci.20426

236. Brunsvig PF, Kyte JA, Kersten C, Sundstrøm S, Møller M, Nyakas M, et al. Telomerase peptide vaccination in NSCLC: a phase II trial in stage III patients vaccinated after chemoradiotherapy and an 8-year update on a phase I/II trial. Clin Cancer Res 2011; 17:6847-57; PMID:21918169; http://dx.doi.org/10.1158/1078-0432.CCR-11-1385

237. Murthy R, Nunez R, Szklaruk J, Erwin W, Madoff DC, Gupta S, et al. Yttrium-90 microsphere therapy for hepatic malignancy: devices, indications, technical considerations, and potential complications. Radiographics 2005; 25(Suppl 1):S41-55; PMID:16227496; http://dx.doi.org/10.1148/rg.25si055515

238. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010; 138:52-64; PMID:19766639; http://dx.doi.org/10.1053/j.gastro.2009.09.006

239. Kennedy A, Coldwell D, Sangro B, Wasan H, Salem R. Radioembolization for the treatment of liver tumors general principles. Am J Clin Oncol 2012; 35:91-9; PMID:22363944; http://dx.doi.org/10.1097/COC.0b013e3181f47583

240. Montemurro F, Aglietta M. Duration of trastuzumab for HER2-positive breast cancer. Lancet Oncol 2013; 14:678-9; PMID:23764182; http://dx.doi.org/10.1016/S1470-2045(13)70273-0

241. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al.; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011; 365:1273-83; PMID:21991949; http://dx.doi.org/10.1056/NEJMoa0910383

242. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344:783-92; PMID:11248153; http://dx.doi.org/10.1056/NEJM200103153441101

243. Kute T, Stehle JR Jr., Ornelles D, Walker N, Delbono O, Vaughn JP. Understanding key assay parameters that affect measurements of trastuzumab-mediated ADCC against Her2 positive breast cancer cells. Oncoimmunology 2012; 1:810-21; PMID:23162748; http://dx.doi.org/10.4161/onci.20447

244. Hoffman ES, Smith RE, Renaud RC Jr. From the analyst's couch: TLR-targeted therapeutics. Nat Rev Drug Discov 2005; 4:879-80; PMID:16299917; http://dx.doi.org/10.1038/nrd1880

245. Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. Nat Immunol 2002; 3:196-200; PMID:11812998; http://dx.doi.org/10.1038/ni758

246. Vacchelli E, Prada N, Kepp O, Galluzzi L. Current trends of anticancer immunochemotherapy. OncoImmunology 2013; 2:e25396; http://dx.doi.org/10.4161/onci.25396

247. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: Reinstating immunosurveillance. Immunity 2013; In press.

248. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol 2011; 8:151-60; PMID:21364688; http://dx.doi.org/10.1038/nrclinonc.2010.223

249. Prendergast GC. Immunological thought in the mainstream of cancer research: Past divorce, recent remarriage and elective affinities of the future. Oncoimmunology 2012; 1:793-7; PMID:23162746; http://dx.doi.org/10.4161/onci.20909

250. Lesterhuis WJ, Haanen JB, Punt CJ. Cancer immunotherapy--revisited. Nat Rev Drug Discov 2011; 10:591-600; PMID:21804596; http://dx.doi.org/10.1038/nrd3500

251. Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nat Rev Cancer 2012; 12:237-51; PMID:22437869; http://dx.doi.org/10.1038/nrc3237

252. Baxevanis CN, Perez SA, Papamichail M. Combinatorial treatments including vaccines, chemotherapy and monoclonal antibodies for cancer therapy. Cancer Immunol Immunother 2009; 58:317-24; PMID:18704409; http://dx.doi.org/10.1007/s00262-008-0576-4

253. Kachikwu EL, Iwamoto KS, Liao YP, DeMarco JJ, Agazaryan N, Economou JS, et al. Radiation enhances regulatory T cell representation. Int J Radiat Oncol Biol Phys 2011; 81:1128-35; PMID:21093169; http://dx.doi.org/10.1016/j.ijrobp.2010.09.034

254. Baba J, Watanabe S, Saida Y, Tanaka T, Miyabayashi T, Koshio J, et al. Depletion of radio-resistant regulatory T cells enhances antitumor immunity during recovery from lymphopenia. Blood 2012; 120:2417-27; PMID:22806892; http://dx.doi.org/10.1182/blood-2012-02-411124

255. Le DT, Jaffee EM. Regulatory T-cell modulation using cyclophosphamide in vaccine approaches: a current perspective. Cancer Res 2012; 72:3439-44; PMID:22761338; http://dx.doi.org/10.1158/0008-5472.CAN-11-3912