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Abscopal Effect of Radiation Therapy: Current Concepts and Future Applications

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1. Introduction

Radiation therapy is one of the most important treatment tools in cancer therapy. It has a wide variety of indications for many malignant tumors, mostly for local control, whether a curative or palliative outcome is the intent, or as pre- or post-operative treatment as either neoadjuvant or adjuvant therapy. Radiation therapy is commonly used along with hormone therapy or chemotherapy. The full scope of the capabilities of radiation therapy is achieved particularly in combination settings with various anti-tumor modalities, the so-called multidisciplinary approach. To enhance the therapeutic efficacy of radiation sufficiently, one may choose radiation therapy in combination with cytotoxic chemotherapeutic agents or with warming devices used for hyperthermia treatment or utilize newly developing physical approaches as typified by intensity modulated radiation therapy, stereotactic radiation therapy, brachytherapy and image-guided radiation therapy. Moreover, an immunoenhancing agent might be selected in combination with radiation therapy from the standpoint of immunobiology in the treatment of cancer. Some promising data have been shown on the basis of immunological activation with ionizing radiation, demonstrating cytotoxic T lymphocyte (CTL) amplification and dendritic cell (DC) stimulation or maturation (Demaria, et al., 2004,Ganss, et al., 2002,Nikitina and Gabrilovich, 2001,Schuler, et al., 2003).

Radiation therapy plays a crucial role in enhancing tumor immunogenicity by promoting cross-priming and eliciting anti-tumor T-cell responses, and generates inflammatory signals via induction of tumor cell death (Hong, et al., 1999,Quarmby, et al., 1999,Watters, 1999). Thus, ionizing radiation can achieve not only direct cancer cell death but also has an indirect and systemic anti-tumor mechanism outside of the irradiated field, which has been reported in some clinical settings (Antoniades, et al., 1977,Ehlers and Fridman, 1973,Kingsley, 1975,Nobler, 1969,Perego and Faravelli, 2000,Rees, 1981,Rees and Ross, 1983,Sham, 1995). Local irradiation resulted in an anti-tumor effect at a non-irradiated location in a patient with hepatocellular carcinoma that regressed after palliative local radiotherapy for pain control of bone metastases (Ohba, et al., 1998). This rare phenomenon is known as the abscopal effect and is defined as a reaction following irradiation but occurring outside the zone of actual radiation absorption (Mole, 1953). The word “abscopal” is derived from the Latin prefix “ab,” meaning “away from,” and the Greek word “scopos,” meaning “target.”

The abscopal mechanism of action remains to be clarified, although a variety of underlying biological events can be hypothesized, mainly those induced by the immune system (Macklis, et al., 1992,Uchida, et al., 1989). Thus far, immunological activation with local irradiation has been explained by multiple possible mechanisms (Awwad and North, 1990,Cameron, et al., 1990,Chiang, et al., 1997,Dybal, et al., 1992,Younes, et al., 1995,Younes, et al., 1995).

This chapter gives an overview of theoretical mechanisms of the abscopal effect being progressively elucidated in the development of multidisciplinary approaches for cancer therapy.

2. Speculation on the mechanism of the abscopal effect

2.1 Possible cytokine contribution

Historically, the abscopal effect has been described in various tumors with possible underlying mechanisms explaining each observed case. A 76-year-old patient with hepatocellular carcinoma was irradiated to control his bone metastases as palliative, not curative, therapy. Yet following this palliative radiotherapy the primary liver tumor regressed (Ohba, et al., 1998). Ohba *et al.* also found in this patient an increase in blood levels of tumor necrosis factor alpha (TNF-α), which has known anti-tumor activity. They suggested that the primary tumor regression might have been caused by an immune response spearheaded by TNF-α. TNF-α has a paradoxical role in cancer by promoting growth, invasion, and metastasis in some tumors, while having a reverse effect in other cancers through destruction of blood vessels and cell-mediated killing. One wonderful review of the relation between TNF-α and cancer is found in the Lancet Oncology (Szlosarek and Balkwill, 2003).

2.2 Hyperthermia-related abscopal effect

Abscopal effects are usually associated with radiation therapy, however, one could sometimes see after other treatments as well, such as surgery or even hyperthermia. For example, in an experiment conducted in India, administering hyperthermia to the hind leg of a mouse for 40 min before transplanting a fibrosarcoma reduced the growth of the tumor in the heated leg (Vartak, et al., 1993). More surprisingly, it inhibited the growth of a tumor transplanted to the unheated leg as well. Actually, two to three weeks after hyperthermic treatment, tumor growth retardation had ceased in the leg that had been heated, but was still noticeable in the leg that had not been heated. Although the mechanism for this effect had not been investigated, the abscopal effect from hyperthermia turned out to be greater than its direct effect on the local target tumor. The authors concluded that local hyperthermia induced both direct and abscopal anti-tumor effects that might probably be the result of a systemic effect of hyperthermia in the host animal.

2.3 Radiation-related abscopal effect

In the clinical setting, Konoeda *et al.* conducted a practical study to investigate the mechanism of the abscopal effect in patients with breast cancer (Konoeda, 1990). Study subjects were 62 women with advanced breast cancer who received radiation therapy before surgery and then underwent mastectomy or tumor resection. Physical examination,

including palpation, indicated an abscopal effect on metastatic lymph nodes in 15 out of 42 cases (35.7%). Pathologic findings revealed an even greater tendency for regression, with an abscopal effect demonstrated in tissue samples from 22 of 42 cases (52.4%). Thus, more than half of these patients with advanced breast cancer exhibited some sort of abscopal effect following irradiation and surgery. The incidence of the abscopal effect was significantly higher in patients under 55 years old and was most frequent in patients who had "infiltrating lymphocytes around the degenerated cancer cells in the irradiated primary tumor nests." In other words, under the favorable condition of a vigorous immune reaction to the tumor as indicated by the presence of abundant lymphocytes, the host was more likely to attack the tumor and bring about an abscopal response as a result. Among the types of lymphocytes, the authors claimed that the most prevalent cells had been identified as primarily CD8 and CD4 lymphocytes, which play a role in cellular defense against pathogens, malignant cells, and other foreign substances. According to the authors, their findings suggested that the abscopal effect was caused by activated cellular immunity in the hosts. Although the study was not large enough for data to yield statistically significant results, the survival rate among patients who exhibited the abscopal effect was higher than among those patients who showed no such reaction.

The logical inference from this research is that the abscopal effect is a desirable and common systemic reaction to localized cancer treatment. Since the abscopal effect is dependent on a healthy immune system, one might infer that immune-damaging treatments should be kept to a minimum. In terms of this point, the trend in most parts of the world is in the undesirable direction, and immunosuppressive chemotherapy is given at every opportunity. The recruitment of leukocytes may have been inhibited by the antitumor chemotherapeutic agents, which would support the assumption that some types of recruited leukocytes play a role in the enhancement of the efficacy of radiation and the abscopal effect.

2.4 Surgery-related abscopal effect

Blay *et al.* reported that higher pretreatment interleukin (IL)-6 and C-reactive protein (CRP) levels in renal cell carcinoma were associated with a diminished response to cytokine therapy and poorer survival. Survival appeared to be better in those patients that had elevated CRP values that decreased to normal levels after nephrectomy compared to those whose CRP did not decrease to normal. For those whose pre-treatment CRP was within normal limits, there was no difference in survival between those who did or did not undergo nephrectomy (Blay, et al., 1992). Fujikawa *et al.* proposed that an IL-6-induced inflammatory response might inhibit the immune anti-tumor response. They suggested the following mechanism: in the setting of metastatic renal cell carcinoma and a primary tumor predominantly expressing IL-6, an associated drop in CRP following nephrectomy appears to curb the inflammatory response while simultaneously inducing immune activation (Fujikawa, et al., 2000).

3. Basic research for induction of radiation-related abscopal effect

3.1 Basic research on the basis of immunological mechanisms

Fms-like tyrosine kinase receptor 3 ligand (Flt3-L) is a growth factor that stimulates production of DCs and has been shown to induce antitumor immunity to several mouse

tumors, although its effects as a single agent are limited to early and more immunogenic tumors (Maraskovsky, et al., 1996,Maraskovsky, et al., 1997). The first study to test the combination of Flt3-L with local irradiation used the Lewis lung model of metastatic carcinoma (Chakravarty, et al., 1999). When Flt3-L was administered after the ablation of the primary tumor by high-dose local irradiation with 60 Gy, lung metastasis formation was inhibited and disease-free survival was enhanced compared with that of mice treated with irradiation or Flt3-L alone. Importantly, the anti-metastatic effect required T cells because this effect was not observed in nude (T cell-deficient) mice. These results provide preliminary evidence in support of the hypothesis that radiation-induced tumor cell death can release antigens for DCs to present to T cells. The high single dose of radiation used in this study limits its clinical applicability in addition to the fact that the intrinsic tumor immunogenicity could explain these responses. Nevertheless, these studies provided initial proof of the principle and stimulated some groups to further investigate whether more clinically relevant radiation doses could be used to elicit systemic antitumor immunity in combination with Flt3-L.

Demaria *et al.* used mouse mammary carcinoma 67NR, a moderately immunogenic syngeneic tumor. A radiation dose sufficient to cause growth delay of the irradiated tumor, in this case 2 Gy, was able to induce a systemic antitumor effect only in combination with Flt3-L administration. Inhibition of tumor growth outside of the irradiated field was specific and required T cells, confirming that it was immune-mediated (Demaria, et al., 2004).

Other groups have used a slightly different approach based on the same hypothesis, that radiation can free tumor-derived antigens for DC uptake and presentation. Nikitina *et al.* used *in vitro* bone marrow-derived DCs that were injected i.v. and s.c. around the tumor after local irradiation (Nikitina and Gabrilovich, 2001) whereas Teitz-Tennenbaum *et al.* used intratumoral injection of DCs (Teitz-Tennenbaum, et al., 2003). In both cases, the administration of DCs after radiation therapy was able to induce a potent antitumor immune response. Yasuda *et al.* reported intratumoral IL-2 injection after irradiation to colon adenocarcinoma enhances antitumor local control and abscopal metastatic inhibition via CD4 positive lymphocytes (Yasuda, et al., 2011). In another study, p53 appeared to mediate a radiation-induced abscopal effect in mice that was dose dependent (Camphausen, et al., 2003). Table 1 summarizes the possible underlying mechanisms for the abscopal effects observed preclinically or clinically.

Table 1. Type of malignancies in relation to abscopal effect reported and possible underlying mechanism.

Author	Tumor type	Treated sites (treatment)	Observed abscopal effect	Putative intrinsic mediator that induces abscopal effect
Preclinical				
Vartak *et al*.	fibrosarcoma	hind leg (HT)	tumor growth inhibition of unheated leg	unknown
Chakravarty *et al*.	LLC	primary tumor (RT)	lung metastasis regression	DC
Demaria *et al*.	mammary carcinoma 67NR	primary tumor (RT)	distant tumor growth inhibition	DC
Teitz-Tennenbaum *et al*.	melanoma/sarcoma	primary tumor (RT)	lung metastasis regression	DC
Camphausen *et al*.	LLC/fibrosarcoma	hind leg (RT)	distant tumor growth inhibition	p53
Shiraishi *et al*.	colon adenocarcinoma/LLC/fibrosarcoma	primary tumor (RT)	distant tumor growth inhibition/longer survival	CD8 and CD4 lymphocytes/NK
Iida *et al*.	hepatocellular carcinoma	primary tumor (RFA)	distant tumor growth inhibition	DC
Yasuda *et al*.	colon adenocarcinoma	primary tumor (RT)	liver metastasis inhibition	CD4 lymphocytes
Clinical				
Ohba *et al*.	hepatocellular carcinoma	bone metastasis (RT)	primary tumor regression	TNF-a
Konoeda *et al*.	breast cancer	breast (RT)	metastatic lymph node regression	CD8 and CD4 lymphocytes
Blay *et al*.	renal cell cacinoma	nephrectomy (surgery)	longer survival	IL-6 and CRP
Fujikawa *et al*.	metastatic renal cell carcinoma	nephrectomy (surgery)	longer survival	IL-6

Abbreviations: RT, radiation therapy; HT, hyperthermia; RFA, radiofrequency ablation; LLC, Lewis lung carcinoma; DC ,dendritic cells; NK, natural killer; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive prot

Table 1. Possible mechanisms for the abscopal effect

Important factor is that radiation therapy appears to cause less immunosuppression compared to surgery or other invasive treatment modalities. Therefore, radiation therapy potentially should have the more favorable biological activity for inducing an abscopal effect than surgical procedures if the major underlying mechanism is based upon immune activation.

The abscopal effect apparently operates through mechanisms that are paralleled in gene therapy, local immunotherapy, hyperthermia, and post-surgical distant bystander effects. Recently, some investigators have suggested that the definition of the abscopal effect should have been broadened to include other forms of local therapy that have systemic effects, *i.e.*, a distant bystander effect (Perego and Faravelli, 2000,Vartak, et al., 1993). Whether or not the definition should be extended to include local therapies other than radiation therapy that have a distant effect is a matter of debate. However, to unravel the abscopal effect of radiation, it seems prudent to evaluate other directed therapies that are associated with systemic effects (Kaminski, et al., 2005). Since the literal meaning is the same for abscopal and distant bystander, the terms could be used interchangeably to refer to any local therapy with a distant impact.

3.2 Possible mechanisms via DC activation

In recent years, the crucial role played by innate immunity, and in particular by DCs in enhancing T cell activation, has been widely clarified. DCs are lineage-negative, bone marrow-derived mononuclear cells found in peripheral blood or in many organs (O'Neill, et al., 2004). DCs can be broadly divided into myeloid or plasmacytoid DCs (MDCs and PDCs, respectively) on the basis of phenotypic, morphologic, and functional differences. Antigens acquired both endogenously (*i.e.*, synthesized within the DC cytosol) or exogenously (acquired from the extracellular environment) are processed into peptides, which are loaded onto major histocompatibility complex class I and II (MHC I and II) molecules and transported to the cell surface for recognition by antigen-specific T cells. DCs most efficiently capture antigens when they are in the immature phase. The terminal process of differentiation termed as *maturation* transforms DCs with weak immunostimulatory properties for antigen capture into cells specialized for T cell stimulation in the lymphoid organ. This process is accompanied by cytoskeletal reorganization, loss of adhesiveness, acquisition of cellular motility with development of characteristic cytoplasmic extensions, migration to lymphoid tissues, reduced phagocytic uptake, and T cell activation potential (O'Neill, et al., 2004). Natural killer (NK) cells are activated by type I interferon (IFN) produced from tumor tissues as a "danger signal" to attack tumor cells. Immature DCs uptake tumor tissue-derived products such as apoptotic bodies and necrotic bodies with tumor-associated antigens (Moretta, 2002). Mature DCs can secrete chemokines and cytokines that attract other immune cells and activate resting T cells. DCs can prime resting NK cells via proinflammatory cytokines such as IL-12 or IL-15 and NK-inducing chemokines such as IL-8 or macrophage inflammatory protein 1-alpha (MIP-1α), and enhance their own maturation by attachment with activated NK cells. However, NK cells negatively regulate the function of DCs also by killing immature DCs in peripheral tissues. Moreover, a subset of NK cells, after migration to secondary lymphoid tissues, might have a role in the editing of mature DCs based on the selective killing of mature DCs that do not express optimal surface densities of MHC class I molecules. Maturation of DCs can be

induced by a growing number of exogenous and endogenous molecular signals, generally referred to as "danger signals" (Matzinger, 1994). Danger signals include host-derived proinflammatory cytokines, such as TNF, IL-1, IL-6, and type I IFN, and a variety of molecules released not only by microbes but also by damaged host tissues, including tumor involvement (Skoberne, et al., 2004). These noncytokine molecules signal primarily through transmembrane receptors related to Drosophila Toll protein, known as Toll-like receptors (TLR) (Kopp and Medzhitov, 2003), which are expressed by DCs.

The major concern is whether ionizing radiation-induced apoptosis can increase tumor immunogenicity. The immunostimulatory activity associated with cell lysates (endogenous adjuvant activity) was shown to be elevated once the cells were stressed by ultraviolet radiation, indicating that injury can modulate this effect (Gallucci, et al., 1999,Shi, et al., 2000). Some examples exist in which apoptotic cells show immunostimulatory features (Rock, et al., 2005). Immunization with apoptotic cells or *in situ* induction of tumor cell apoptosis induced T cell responses *in vivo* as exemplified in some reports (Kotera, et al., 2001,Nowak, et al., 2003,Ronchetti, et al., 1999). Injection of immature DCs into tumor tissue after irradiation-induced tumor cell apoptosis can stimulate strong antitumor immunity (Kim, et al., 2004). These studies suggest that under some favorable conditions for an immunocompetent host, radiation-induced tumor cell death might be associated with the production of ideal maturation signals for DCs (Demaria, et al., 2005).

The possible contribution of radiation-induced apoptosis vs. necrosis to immunostimulation has not been fully elucidated, and no significant difference was seen in capabilities of both kinds of cell death for antigen presentation *in vitro* (Larsson, et al., 2001). Endogenous factors released from necrotic cells might be responsible for the ability of the necrotic body to activate DCs (Skoberne, et al., 2004). Examples of these are immunostimulatory self-DNA that binds TLR9, self-single-strand RNA that stimulates TLR7 and TLR8, secondary structures of messenger RNA that activate TLR3, and heat shock proteins that stimulate TLR4 (Demaria, et al., 2005). The induction of necrosis *in vivo* could be accompanied by the release not only of self-antigens but also inflammatory factors that may cause DC maturation and the whole immune response. Candidates for cell-associated antigens being cross-presented from dying cells could include heat shock protein-associated proteins, native proteins (Shen and Rock, 2004), peptides (Neijssen, et al., 2005), or other constituents. In general, it is considered that DC maturation signals are essential to convert cross-tolerance to cross-priming (Steinman and Nussenzweig, 2002).

Opinion is divided as to the ability of ionizing radiation to generate the signals required for DC maturation; however, the combined approach of inducing cell death by irradiation in combination with the administration of a chemotactic agent that activates DCs can lead to the priming or enhancement of antitumor responses (Shiraishi, et al., 2008).

3.3 Attempts to consistently induce the abscopal effect

Based on the theory of immunological activation with ionizing radiation, Shiraishi *et al.* have chosen MIP-1α in combination with radiotherapy and investigated whether MIP-1α could cause a broad-spectrum enhancement of the efficacy of radiotherapy in tumor-bearing mice. Although there are many reports concerning anti-cancer (Crittenden, et al., 2003,Nakashima, et al., 1996,Taub, et al., 1995,Zibert, et al., 2004) and anti-metastasis effects of MIP-1α (van

Deventer, et al., 2002), enhancement of radiation efficacy had not been investigated sufficiently. Radiation treatment at tumor bearing sites is known to induce strong inflammation in the irradiated field and to recruit tumor-specific T lymphocytes and DCs, which seem to play an important role in the remission of tumors (Friedman, 2002,Garnett, et al., 2004,Teitz-Tennenbaum, et al., 2003). MIP-1α or CCL3, is a chemokine known to be secreted from various leukocytes including T lymphocytes and activated macrophages, and to recruit CCR1- and/or CCR5-expressing leukocytes such as monocytes, DCs, NK cells and T lymphocytes (Rollins, 1997). It was also reported that MIP-1α could enhance survival of DCs (Sumida, et al., 2004) and primed T lymphocytes to generate IFN-γ (Lillard, et al., 2003).

An active variant of human MIP-1α with improved pharmaceutical properties that carries a single amino acid substitution of the 26Asp to Ala was reported (Hunter, et al., 1995), which has a reduced tendency to form large aggregates at physiological pH and ionic strength. Myelosuppressive effect of the active variant (Arango, et al., 1999,Arango, et al., 2001,Gilmore, et al., 1999,Lord, et al., 1995) was investigated in several clinical trials of patients receiving chemotherapy (Bernstein, et al., 1997,Broxmeyer, et al., 1998,Clemons, et al., 1998,Marshall, et al., 1998). We previously showed that the recombinant MIP-1α variant, now called ECI301, strikingly enhanced the antitumor efficacy of subcutaneous tumor irradiation and induced an abscopal effect (Shiraishi, et al., 2008). Our study resulted in tumor-free mice with long-term survival without significant toxicity and complete rejection by surviving mice to a re-challenge with the same tumor cells. In accordance with our findings, no significant side effects of a compound with the same structure (BB-10010) had been reported previously when administered to human patients. Moreover, we observed a tumor-type- and mouse-strain-independent abscopal effect, indicating that the antitumor effect of ECI301 may be exerted via systemic inflammation and immune response. Marked infiltration of CD4+ and CD8+ cells was observed both in irradiated and non-irradiated sites. It was reported that DC precursors were mobilized into the circulation by administration of MIP-1α (Zhang, et al., 2004) and radiofrequency ablation-treated hepatocellular carcinomas (Iida, et al., 2010); however, we did not observe an increase in $CD11c^+$ cell infiltration into the tumor tissue in this model. Depletion of CD8+ T cells by antibodies diminished the effect of combination treatment at the irradiated site, indicating that CD8+ T cells are involved in the antitumor effect. Furthermore, rejection of the same tumor type in the cured mice may have been mediated by the presence of these types of lymphocytes. An increased number of splenocytes with tumor-specific IFN-γ-generating ability with the combination treatment also supports this assumption (Shiraishi, et al., 2010). Depletion of CD4+ T lymphocytes or NK1.1 cells by antibodies diminished the abscopal effect, indicating that these cells are involved in the remission either directly or indirectly. CD4+ T cells may play a role in generating cytokines such as IFN-γ, which may also activate other leukocytes (Dorner, et al., 2002,Pender, et al., 2005,Shiraishi, et al., 2008).

Further studies using C3H/HeN, C3H/HeJ and athymic mice will show whether the high mobility group box 1 (HMGB1) RNA level, an important mediator of local and systemic inflammation, is up-regulated at each tumor-bearing site (unpublished data). Results might clarify the underlying HMGB1-dependent mechanism for the abscopal effect via TLR4-mediated inflammation (Fig. 1).

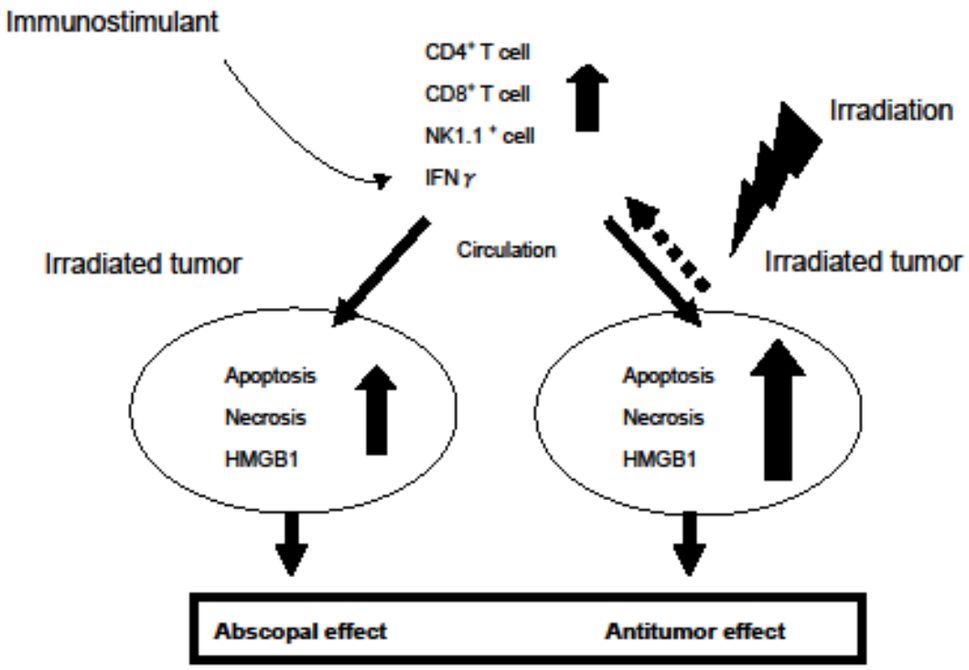

Fig. 1. Possible mechanism for radiation-induced abscopal effect.

Ionizing radiation induces tumor cell death in the irradiated tumor, causes inflammation and activates the immune system via chemokines with HMGB1. Length of arrows means relative strength of the effects.

HMGB1 = high mobility group box 13.4 Implications for future therapies

For future development, further insights into the mechanisms underpinning abscopal signaling are required. Theoretical elucidation of the relevance of abscopal responses in radiation-induced carcinogenesis is also required, including molecular pathways and targets outside of directly exposed fields.

A balance between angiogenic and anti-angiogenic molecules seems to be one of the key factors behind tumor growth. For example, several experimental animal models indeed suggest that the growth of a primary tumor can inhibit the production of distant metastases, probably due to inhibition of angiogenesis (Gorelik, 1983,Prehn, 1991). In contrast, the angiogenic inhibitors, angiostatin and endostatin, are known to function in tumor inhibition (O'Reilly, et al., 1997,O'Reilly, et al., 1994). Hartford *et al.* reported that the effect of irradiation of a primary tumor on angiogenesis at a distal site may differ from the effect of surgical removal of the primary tumor with respect to angiostatin production (Hartford, et al., 2000). They clearly demonstrated that, unlike surgery, irradiation of a tumor might enhance angiogenic suppression at a distal site. The involvement of angiogenic regulation in a radiation-induced abscopal effect should be emphasized as a clinical advantage in contrast to other invasive procedures, which may reduce possible angiogenic inhibition.

4. Conclusion

In conclusion, data that possibly support an intriguing concept as an abscopal effect are reviewed. These data will encourage future therapeutic gain of immunostimulants utilization in the treatment of advanced or metastatic cancer. The development of safer, reasonable, and targeted therapies will be facilitated as we clarify the mechanisms for the abscopal effects. Future therapies will need to be optimized with tumor-type tailoring in consideration of various intra- or inter-tissue signals if these are to affect treatment outcome.

Hopefully, a more aggressive effort for investigating and developing a potentially novel application of ionizing radiation in combination with immunotherapy will be needed. When the effectiveness of "immunoradiotherapy" in a clinical setting is established in a desirable manner, it could lead to a new era of cancer treatment, with common availability of established modalities, without significant adverse events.

5. List of abbreviations and expansions in the order corresponding to apperances

CTL, cytotoxic T lymphocyte
DC, dendritic cell
TNF-α, tumor necrosis factor alpha
IL , interleukin
CRP, C-reactive protein
Flt3-L, fms-like tyrosine kinase receptor 3
MHC, major histocompatibility complex
NK, natural killer
IFN, interferon
MIP-1α, macrophage inflammatory protein 1-alpha
TLR, Toll-like receptors
HMGB1, high mobility group box 1

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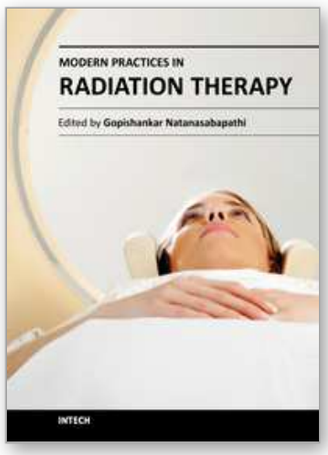

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Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. It is an enormous global health encumbrance, growing at an alarming pace. Global statistics show that in 2030 alone, about 21.4 million new cancer cases and 13.2 million cancer deaths are expected to occur, simply due to the growth, aging of the population, adoption of new lifestyles and behaviors. Amongst the several modes of treatment for cancer available, Radiation treatment has a major impact due to technological advancement in recent times. This book discusses the pros and cons of this treatment modality. This book "Modern Practices in Radiation Therapy" has collaged topics contributed by top notch professionals and researchers all around the world.

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