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Stereotactic Ablative Radiotherapy (SABR): Impact on the Immune System and Potential for Future Therapeutic Modulation

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Abstract

Stereotactic ablative radiotherapy (SABR) has been demonstrated to provide excellent local control in several malignancies. Recent reports have suggested that this ablative dose may impact disease outside of the radiated area. Furthermore, these studies have implicated immune modulation as the primary mechanism of disease response outside the irradiated area. More specifically, T-cell stimulation and tumor necrosis factor-α modulation following high dose irradiation have been suggested as the responsible components of this phenomenon. In addition, the “abscopal effect” may play a role in disease response outside of the radiated area. We review the current literature regarding the effects of ablative radiation therapy, the potential for immune modulation from it, and the mechanisms of the distant effects it elicits.

Keywords

Ablative Radiotherapy; Immune Response; Therapeutic Modulation

Introduction

Stereotactic radiosurgery (SRS) has been used as an alternative to surgery for benign and malignant tumors of the brain for decades (1). It was initially developed in the 1950’s by the Swedish neurosurgeon, Lars Leksell, to ablate deep-seated tumors that were otherwise inoperable (2). SRS did not come to the forefront until the mid-1980’s, when investigators at the University of Pittsburgh brought the technology to the United States (3).

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Conflicts of interest
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In addition, the integration of 3-dimensional imaging, specifically computed tomography and magnetic resonance imaging, in combination with the ability of treating with pinpoint accuracy (< 0.3 mm), increased the attractiveness of this novel modality resulting in surgical-like tumor control in select patients with brain tumors. Over the past several decades, SRS has evolved as a success story for patients with brain metastases by improving local control, quality of life, and survival similar to surgery (4). The most apparent advantage for SRS is that it is a non-invasive, outpatient procedure that can be performed without the need for general anesthesia. In addition, it allows for safe delivery of extremely high doses of radiation to small areas. Subsequently, for patients with asymptomatic small metastases this approach has become the standard of care.

SRS outside the brain, also known as stereotactic body RT (SBRT) or the more recently coined stereotactic ablative radiotherapy (SABR), is more challenging (5). Unlike intracranial targets, extracranial organ and tumor motion become critical concerns raising uncertainties about appropriate dose coverage of the target volume. These uncertainties require treating a cuff of normal tissue (i.e. a margin) which, for small targets, can make a significant difference in the volume of tissue receiving the same dose of radiation as the tumor. Theoretically, treating this larger volume increases the risk of normal tissue toxicity and side effects (6). Over the past15 years, technical advancements and solutions to these uncertainties have allowed SABR to treat tumors outside the brain (7) (8) with success just as impressive as that seen in the brain. In fact, a multi-institutional phase II trial from the Radiation Therapy Oncology Group published in JAMA showed a 98% local control rate at 3 years for patients with medically inoperable non-small cell lung cancer (9). These encouraging “surgical like” results from a completely noninvasive treatment have led investigators to challenge the paradigm of surgery as the standard of care for patients with small lung cancers (10).

Radiobiologically, these non-invasive approaches were initially designed to deliver treatment that was equivalent to the then-standard dose of fractionated radiotherapy (70 Gy over 7 weeks) with a hypofractionated schedule. The results, however, demonstrated more than equivalence; in fact they led to significantly improved local control prompting investigators to explore the biology of these high dose fractions. As a possible explanation, Fukset. al. (11) initially suggested that contrary to conventional (1.8–3 Gy) fractionation, high dose radiation (>8–10 Gy per fraction) specifically impacts more robust endothelial apoptosis and microvascular dysfunction, which in turn leads to increased cell death. Furthermore, hypoxia resulting from standard fractionated radiotherapy regimens results in a burst of pro-angiogenic activity in the tumor microenvironment, generating HIF-1α, VEGF and other vasculogenic factors which, in turn attenuate radiation induced apoptosis in endothelial cells.

In addition to excellent local control, high dose radiotherapy using SABR also appears to impact disease outside the radiated volume. This is best exemplified by a retrospective experience from William Beaumont Hospital (12) which compared patients who were treated with either a sublobar resection or SABR during the same time period. SABR not only resulted in a drastically lower local failure rate (5% versus 24%, p=0.05), but more unexpectedly had a lower regional lymph node failure rate (18 vs 0%, p<0.05). Given that

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patients treated using SABR have a very small (tumor plus margin) volume of tissue irradiated, and few if any lymph nodes included in the treatment field, this was a surprising finding. Furthermore, when considering that patients were more accurately staged in the surgical group with 71% undergoing a mediastinoscopy or lymph node dissection as opposed to only 20% in the SABR group, these results seem even more intriguing. One possible explanation of this phenomenon is the stimulation of T-cell immunity by SABR, leading to the eradication of occult regional micrometastases. In contrast to SABR, minimally invasive surgery and open thoracotomy are associated with transient post-operative decreases in circulating $CD8^+$ T-cells (13). This may contribute to the increased incidence of regional failure observed with wedge resection compared with SBRT (14). The lower rate of regional nodal failures after SBRT may be due to increased $CD4^+$ and $CD8^+$ T-cell immunity.

The immune system has long been known to play a critical role in tumor surveillance and control (15). It is thought that tumors develop by escaping immune detection, either by down regulating surface recognition antigens or by releasing immunomodulatory cytokines that dampen the immune response, and are found in greater prevalence in immunosuppressed populations. Conversely, a robust immune response, associated with cytotoxic immune cell populations, is associated with improved tumor control (16). Radiotherapy, in its classic delivery with standard fractionation, has traditionally been viewed as an immunosuppressive modality (17). However, the actual effects on the immune system are extremely complex with conflicting reports on whether they promote or interfere with tumor reduction (18). Just as in the dichotomous modulation of angiogenesis, the immune response may be differentially affected by standard and high dose regimens.

High Dose Radiotherapy and SFGRT/SABR

Spatially fractionated GRID radiation treatment (SFGRT) is a technique that utilizes a “GRID” pattern of “multiple, small non-confluent pencil beams” as a means of overcoming limitations of acute and late normal tissue tolerance. SFGRT was routinely used from the 1900–1950s (prior to the development of megavoltage radiation) to deliver 12–20Gy in a single treatment. This approach was developed to decrease toxicity to the superficial tissues, while portions of the tumor would receive high dose radiation (19). Upon the development of megavoltage radiation, with its potential for skin sparing and better dose distributions, SFGRT became obsolete as a clinical method for delivering high dose radiation. However, SFGRT demonstrated impressive response rates, far better than would have been anticipated by classic radiobiology calculations, especially given that the entire tumor was not treated (see Figure 1). Given the high dose per fraction utilized in SFGRT, the mechanism of action appears to parallel that seen with SABR and may be related to priming the immune system.

Comprehension of the mechanism of immune regulation following treatment with SFGRT or SABR is an evolving process. Data suggests that several cytokines, serum protein products and enzymes appear to be secreted by tumor cells exposed to SFGRT. In a previously published experience, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ceramide levels in patients exposed to SFGRT were assessed by ELISA before and at 24, 48,

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72 hours after radiation (20) (21). Eleven of 37 patients had low or undetectable levels of TNF-α before treatment, but showed induction of TNF-α after SFGRT. In twenty-three cases, TNF-α was undetectable pre and post treatment at all time points examined. Clinical complete response (cCR) to SFGRT was seen in 12/37 (32%) patients, and partial response (cPR) in 18/37 (49%) patients. A strong correlation was observed between clinical cCR rate and TNF-α induction. The rate of cCR was 6/11 (55%) in patients where TNF-α was induced as compared to 6/26 (23%) in patients were TNF-α induction was not seen (p=0.022). TGF-β, EGF, and VEGF levels before or after factors have been implicated (22) as critical mediators of enhanced endothelial apoptosis to radio-induction (22). The authors concluded that high dose SFGRT results in significant induction of TNF-α that can be measured in serum of some patients 24 – 72 hours after radiation. Importantly, cCR strongly correlated with the induction of TNF-α levels in the serum.

On a similar theme, radiation oncologists have long used the term “abscopal effect” to describe distant effects seen after a local radiation treatment. More recently, it has been used to include distant bystander effects of local therapies. In the case of SFGRT or SABR, initiation of high dose bystander signaling responses appear to be the underlying mechanism involved. Specifically, significant induction of low density lipoprotein (LDL)-enriched ceramide, secretory sphingomyelinase (S-SMase), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and TNF-α in serum from patients treated with SFGRT suggests these bystander effects may have a role in overall tumor response (20–22). *In vitro* studies appear to confirm this observation. In a previous study, ionizing radiation-induced bystander effects were investigated in two lung cancer cell lines (23). A549 cells (a human lung cancer cell line isolated from a primary lung malignancy) were found to be more sensitive to radiation conditioned medium (RCM) obtained from H460 cells (another lung cancer cell line isolated from pleural effusion) exposed to 10 Gy as compared to RCM from A549 cells. Significant release of TNF- α and cell mortality was observed in A549 cells following RCM exposure; however, the poor survival was reversed when a neutralizing antibody against TNF-α was added to the RCM. In H460 cells, significant release of TRAIL, but not TNF-α, was observed in response to radiation, RCM exposure or RCM + 2Gy radiation. Addition of a neutralizing antibody against TRAIL diminished RCM-mediated clonogenic inhibition. Mechanistically, TNF-α present in 10 GyRCM of A549 was found to mediate NFkB translocation to nucleus, whereas, the soluble TRAIL present in 10 Gy RCM of H460 cells mobilized the nuclear translocation of PAR-4 (a pro-apoptotic protein). EGR-1, which regulates TNF-α, was functional in A549 cells but not in H460 cells. Thus, the high dose radiation-induced bystander responses, like those induced by low doses, are dependent on the genetic makeup of the target as well as the bystander cells. The functionality of EGR1 in mediating the expression of TNF-α is a pivotal genetic factor in the bystander signaling events mediated by high dose radiation in lung adenocarcinoma cells (23).

Role of $CD8^+$ T cells

It is well-known that CD8+ T-cell mediated targeting is a critical component of the cell mediated immune response and is thought to play a pivotal role in tumor control as well. Besides the role of cytokine-mediated bystander effects, it is also postulated that the lower than expected regional failure rate with SABR may be due to radiation-induced systemic

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stimulation of T-cell immune responses, leading to eradication of occult regional micrometastases. Support for this theory derives primarily from experiments in animal models. A recent study examined the effect of ablative doses of radiation therapy in a mouse melanoma model (24). In this study, mice with B16 melanoma tumors received 20Gy of radiation in a single fraction. Examination of the tumor microenvironment and lymphoid tissues 1–2 weeks post treatment demonstrated tumor regression and an increase of infiltrating T cells. When the experiment was repeated with athymic nude mice, which lack T cells, no statistically significant decrease in tumor volume was observed, suggesting that the effects were T-cell mediated. Taken together, these studies suggest that ablative doses of radiation alter the tumor microenvironment, causing T-cell infiltration resulting in vigorous priming and expansion of effector T-cells. The experiment was -repeated in wild-type mice with B16 tumors, which had been subjected to antibody mediated $CD8^+$ T cell depletion. The therapeutic benefit to the ablative radiation was diminished, and survival in this $CD8^+$ depleted group was decreased by 75%. In a separate experiment using a transplantable mouse 4T1 mammary carcinoma model (which mimics metastatic ability of breast cancer cells to lung, bone, liver etc.), ablative radiation therapy delivered to the primary tumor site led to a complete elimination of lung metastasis. This observation strongly suggests the induction of a potent anti-tumor immune response. Separate experiments utilizing CD8 depletion strategies demonstrate a relative increase in number of distant metastases, again suggesting that $CD8^+$ T cells are critical for mediating protection against tumors. Taken in combination, these studies suggest that $CD8^+$ T cells play a critical role in radiation induced anti-tumor immune responses (both locally and distantly), following ablative dose therapy.

Clinically, similarly suggestive observations have been reported in several tumor types, most notably in breast cancer. Mahmoud et al. (25) (26) recently demonstrated the influence of density and distribution of the cytotoxic $CD8^+$T cells in breast cancer patients. Using immunohistochemistry staining of tissue microarray cores, they established that infiltration of $CD8^+$ T cells into the distant stroma correlated with improved overall survival. In addition, the number of T regulatory cells, the ratio of $CD4^+$ to $CD8^+$ T cells, and the presence of T lymphocytes in the primary tumor correlated with grade, stage, and survival. Furthermore, several groups have demonstrated that the presence of tumor-associated lymphocytes in breast cancer is an independent predictor of response to anthracycline/ taxane-based chemotherapy (27). Other published studies by Paulson et. al. (28), have demonstrated that intratumoral$CD8^+$ lymphocyte infiltration was the most important predictor of outcomes in patients with merkel cell carcinoma. Interestingly, in this population, patients with tumors that demonstrated a robust $CD8^+$ lymphocyte infiltration were observed to have the largest improvements in regional and distant control as compared to local control.

In addition to intratumoral infiltration, immunomodulatory effects have also been detected in peripheral blood samples of patients treated with RT (29) (30). During conventionally fractionated RT, a shift is seen toward higher numbers of effector and memory cytotoxic T lymphocytes (CTLs) in the peripheral blood mononuclear cells. The functional responses of antigen-specific memory T cells are affected to a much lesser extent than general T cell proliferative or cytokine responses induced in an antigen-independent manner. Tumor–specific T cell responses become detectable shortly after the completion of RT. Together,

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these findings constitute an improved understanding of the complex immunologic events that follow RT administration and suggest the basis for novel therapeutic interventions that take into account the infiltration of CD8+ CTLs as well as relative resistance of memory T cells to RT.

Implications and Future Applications with SABR

Investigators (24) have shown the antitumor effects of the combination of radiotherapy and immunotherapy in 2 animal models. Mice bearing established 4T1 or B16-CCR7 tumors, which are both spontaneously metastatic tumor lines, were treated with either: radiation alone, immunotherapy alone, both radiotherapy and immunotherapy or no treatment. Tumors were then surgically removed on day 35, and a percentage of the mice were euthanized for tumor colonogenic assays from each group. No colonies were detected in the group treated with the combination of 12 Gy×2 followed by intratumoral injections of a known immunotherapy agent concomitantly with the 2nd day of radiation. Impressively, 86% of the mice treated with the combination showed prolonged survival (>100 days), as opposed to all mice from any of the other groups that all died within 60 days. This data demonstrates that the combination of immunotherapy and ablative doses of radiation can better control metastases, compared to either treatment alone.

In light of these encouraging results, investigators are now evaluating the combination of SABR and immunotherapy. One recent and prominent example is with ipilimumab, which is a monoclonal antibody to cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). The CTLA-4 receptor is present on CTLs and acts as a negative regulator of T cell activation. The anti-tumor immune response is suppressed by CTLA-4 binding more strongly to B7 rather than CD28. Ipilimumab prevents this binding, thereby resulting in an amplified immune mediated anti-tumor response. Hodi et al. (31) compared ipilimumab with gp100 versus either agent alone in patients with previously treated metastatic melanoma in a phase III randomized study. They found that ipilimumab significantly improved overall survival with an overall survival of 10 months with ipilimumab plus gp100, 10.1 months with ipilimumab alone and 6.4 months with gp100 alone. Grade 3–4 toxicities occurred in up to 15% of patients receiving ipilimumab. While ipilimumab has not been directly compared to interferon or other chemotherapeutic agents, its outcomes appear promising with a 10.9% overall response rate and with 60% of the responders having a durable response for at least 2 years. Given the knowledge about the role of immune cells (and in particular CTLs) in the response to ablative radiation doses, several investigators are combining SABR with ipilimumab in an attempt to improve the 10.9% response rate of ipilimumab alone. It is anticipated that this could increase the number of patients achieving a durable response.

A recently published report (32) appears to substantiate this combination of ipilimumab with SABR. In this case study, a patient with progressive metastatic melanoma receiving maintenance ipilimumab therapy was treated palliatively with SABR for a painful paraspinal mass. While there was no initial response, a single additional dose of ipilimumab not only significantly decreased the size of the paraspinal mass, but also caused regression of additional sites of metastatic disease which were considerable distance from the radiated paraspinal mass. Further analysis demonstrated that RT had increased antibodies to NY-

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ESO-1, an antigen associated with melanoma, by 30-fold. Since presence of antibodies to NY-ESO-1 had been associated with a more robust response to ipilimumab, this may explain why this patient had such an excellent response to disease within and outside the radiation portal. Furthermore, the RT regimen in this patient also led to a subsequent spike in inducible co-stimulator (ICOS), a marker of activated CTLs, suggesting an additional mechanism for the observed tumor control.

Conclusions

Ablative doses of radiation therapy (as delivered with SABR or SFGRT) appear to result in both local and distant control at rates far better than anticipated. While the exact mechanism for this phenomenon is subject of ongoing research, there appears to be a strong correlation between these improved results and the immune response induced by ablative doses of RT. These cytotoxic effects may be mediated by immune modulators including $CD8^+$ cells and TNF- α, and are appreciable in both the immediate tumor milieu and in more systemic manifestations. With immunomodulatory antibodies making a strong impact in cancer treatments, such as ipilimumab in metastatic melanoma, the observed increases in measurable cytotoxic immune mechanisms following ablative RT doses may represent an extremely effective future therapeutic intervention. Therefore, further delineation of mechanisms involved in the induction of effective immune responses due to high dose radiation therapy is likely to be a fruitful area of research.

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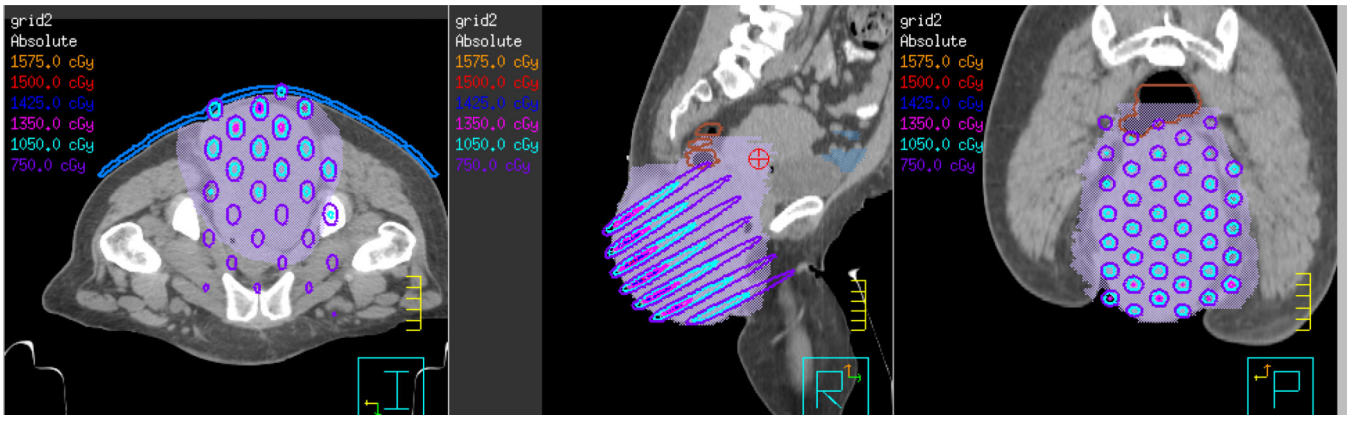


Figure 1. This is an example of GRID therapy for a patient with a large recurrent rectal cancer which delivers high doses of radiotherapy to portions of the tumor

This is in stark comparison to conventional radiation therapy which requires ensuring delivered dose to the entire tumor.