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Mini-review

High dose bystander effects in spatially fractionated radiation therapy

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ABSTRACT

Traditional radiotherapy of bulky tumors has certain limitations. Spatially fractionated radiation therapy (GRID) and intensity modulated radiotherapy (IMRT) are examples of advanced modulated beam therapies that help in significant reductions in normal tissue damage. GRID refers to the delivery of a single high dose of radiation to a large treatment area that is divided into several smaller fields, while IMRT allows improved dose conformity to the tumor target compared to conventional three-dimensional conformal radiotherapy. In this review, we consider spatially fractionated radiotherapy approaches focusing on GRID and IMRT, and present complementary evidence from different studies which support the role of radiation induced signaling effects in the overall radiobiological rationale for these treatments.

1. Introduction

The success of traditional radiotherapy of bulky or deep-seated tumors is limited by poor blood flow, hypoxia in the tumor, poor depth dose distribution and toxicity to the skin and surrounding normal tissue. Normal tissue cannot tolerate the large radiation doses required to treat the increase in tumor volume, associated with bulky tumors, successfully. Although significant reductions in normal tissue complication have been afforded through the implementation of advanced modulated beam therapies such as intensity modulated radiotherapy (IMRT) in the clinic, emerging evidence suggests additional benefit may be gained by delivering a decreased number of higher dose fractions in some tumor types [1,2]. An additional approach which has the potential to offer further improvement is spatially fractionated radiation therapy (GRID). GRID describes the delivery of a single high dose fraction to a large treatment area which has been divided into several smaller fields with steep dose gradients thus reducing the overall toxicity of the treatment [3,4]. In this review, we consider spatially fractionated radiotherapy approaches focusing on GRID and IMRT, and present complementary evidence from different studies which support the role of radiation induced signaling effects in the overall radiobiological rationale for these treatments.

2. Classification of radiation induced signaling effects

The efficacy of ionizing radiation in cancer therapy stems from its ability to induce cell death as a consequence of DNA damage due to energy deposition in the cellular environment. Cellular radiobiological responses are mediated largely through direct energy deposition in cellular DNA or indirectly through reactive oxygen species (ROS) and other free radicals formed during the radiolysis of water [5].

The classical paradigm in radiation biology which focused on nuclear DNA as the sole target of radiation induced damage has been challenged over the last 25 years with an increasing amount of evidence demonstrating radiobiological effects in cells which are not directly traversed by the radiation field. These effects, termed radiation induced bystander effects (RIBEs) generally describe a range of radiation induced signaling effects that have been observed under different *in vitro* and *in vivo* exposure conditions.

RIBEs were first identified by Nagasawa and Little [6] who observed chromosome damage in the form of sister chromatid exchanges in more than 30% of a cell population under conditions in which only 1% of cell nuclei had been targeted using α-particles. Since then, RIBEs have been demonstrated using a range of experimental systems with multiple biological endpoints. Despite increasing evidence in a growing number of model systems, the implications of RIBEs for radiotherapy and cancer risk remain to be fully determined. Whilst conventional approaches to study RIBEs have used techniques somewhat removed from clinical exposure scenarios including media transfer [7] and co-culture models [8,9], characterization of RIBEs occurring in response to advanced clinical exposures such as intensity modulated radiotherapy (IMRT) and GRID will provide additional understanding of their importance in overall radiobiological response.

RIBEs are primarily radiation induced signaling effects that have been shown to be mediated through direct physical cell contact via gap junction intercellular communication (GJIC) [8] or through the

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secretion of diffusible signaling molecules into the surrounding medium [10,11,12]. The underlying mechanisms mediating response have been extensively studied in a number of model systems and shown to include reactive oxygen and nitrogen species (ROS/NOS) including nitric oxide (NO), cytokines such as transforming growth factor-β (TGF-β) and interleukin-8 (IL-8), which initiate multiple downstream signaling pathways including the mitogen activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) [13].

Classification of RIBEs is often dependent on the experimental model and exposures conditions which are being investigated. A recent framework for the classification of more general radiation induced signaling effects based on human radiation exposure scenarios was proposed by Blythe and Sykes [14,15] in which effects were classified into three categories; bystander, abscopal and cohort effects. Within this framework, bystander effects are defined for human exposure scenarios as radiation induced, signal mediated effects in unirradiated cells adjacent to a target volume that are exposed to only very low levels of scatter radiation, if any [14,15,16]. These effects are relevant for whole and partial body exposures to very low doses, such as those from background radiation, high altitude flights and ingested radioactive potassium.

The second class of effects are abscopal effects, defined as radiation induced effects in unirradiated tissues occurring distinctly outside of an irradiated volume. Abscopal effects have been observed for more than 60 years as systemic radiation effects in some patients following radiotherapy. They do not appear to be dose dependent, making them particularly relevant to the partial body exposures typically delivered during conformal radiotherapy. Abscopal effects are rarely recognized in the clinic and so their importance in radiotherapy response remains controversial [17].

The final class of effects are defined as cohort effects. These describe the component of overall radiobiological response in irradiated cells which is not a consequence of direct energy deposition in the target cell but rather due to communication between cells within an irradiated volume. Cohort effects are relevant for any exposures where the majority of a cell population is exposed to significant dose and whilst this interpretation is relatively uncommon in the literature, there is increasing evidence that intercellular signaling plays a role in overall radiation response [16].

Although this framework clearly defines different classes of radiation induced signaling effects, which may potentially impact the overall radiobiological responses, it is unlikely that they occur independently in the advanced clinical scenario where patients are exposed to complex spatially and temporally modulated beam profiles with nearby cells receiving vastly different doses. It is consequently difficult to investigate either of these effects in isolation as they may stem from the same or similar cellular signaling origin and may be interpreted as different consequences of the same generalized RIBEs.

3. Observations of RIBEs under modulated beam conditions

3.1. Spatially fractionated radiotherapy (GRID)

Spatially fractionated radiotherapy (GRID) refers to the delivery of a single high dose fraction of radiation by dividing a large treatment area into several smaller fields, thus reducing the overall toxicity of the treatment [3,4]. GRID has been successfully used in the treatment of bulky and deep-seated tumors. GRID may be combined with traditional dose/time fractionated radiation therapy or used along with other treatment modalities, including chemotherapy to achieve better control of bulky tumors and it extends the treatment course minimally.

GRID is not a new technique. In the early 1900s, GRID irradiation was invented and performed originally by Köhler through a perforated screen to successfully deliver higher than normal doses of radiation, safely and without causing complication due to skin toxicity [3]. In the 1950s, GRID was routinely used along with orthovoltage radiation to treat deep seated tumors with minimal skin and subcutaneous tissue toxicity [18]. However, with the development of megavoltage radiation, better depth dose distribution and reduced skin toxicity could be achieved and this method was used in a GRID format to achieve a more efficient treatment of bulky and advanced tumors [19]. GRID involves delivery of high doses of radiation through a specially made GRID collimator or a multileaf collimator, such that the entire target does not receive a uniform radiation dose. Instead, only the target directly under the open areas receives irradiation. Recently, it has also been demonstrated that GRID could be applied to deep seated and irregular geometries using the advanced capabilities of a tomotherapy system [20].

Clinical results of GRID obtained thus far are very encouraging. Most importantly, implementing GRID therapy in a radiation oncology clinic does not require any additional clinical personnel. The already in place clinical staff (physician, medical physicist and dosimetrist) are sufficient to implement a GRID therapy program. In addition, GRID therapy can be easily delivered using a commercially available pre-fabricated cerrobend block with the required opening to opening distance (on/off ratio) and opening diameter. However, even a block such as this is not necessary since the procedure can be delivered with existing multi-leaf collimators on most linear accelerators in a step-and-shoot fashion. With respect to clinical outcomes, Mohiuddin et al. [21,22] constructed a special GRID collimator using 7 cm of lead consisting of 250 equidistant holes. Seventy-one patients with advanced bulky tumors were treated with 15 Gy (6 MV photons) radiation delivered by GRID to various sites including lung, head and neck, gastrointestinal, sarcomas, gynecologic, genitourinary and skin. The patients were treated with GRID alone or GRID followed by fractionated radiation therapy or GRID followed by fractionated radiation therapy and surgery. An overall 75.7% response rate was observed at the end of the study and 78% response rate was observed for palliative treatment and 72.5% for mass effect. A complete response of 16% was observed for all treatments. In a second study 79 patients with bulky tumors were treated spatially fractionated radiation [23]. The overall response in terms of pain and tumor mass management between groups treatment with GRID using a cerrobend block and a multi leaf collimator were found to be comparable. In another study, 27 patients with advanced head and neck cancer were treated with GRID along with radiation therapy (Group 1) or GRID followed by radiation therapy and planned neck dissection (Group 2) [24]. The overall neck control rate was 93% for Group 1 with a disease specific survival of 50% and morbidity was limited to mild soft tissue damage. In Group 2, an 85% pathologic complete response rate was observed, as well as, 92% neck control rate, 85% disease specific survival and surgical morbidity was limited to wound healing complications. Penagaricano et al. [4] used a multileaf collimator based GRID design in a cerrobend alloy 7 cm in thickness. Fourteen patients with advanced head and neck cancers were evaluated. These patients received GRID (6 MV photons) followed by chemo-radiotherapy. The overall control rate of the GRID treated tumor volume was 93%, overall neck and primary tumor control rate was 86%. The overall survival was 64% and disease specific survival was found to be 79% and 57% patients exhibited disease free survival. Other encouraging results have been reported from a clinical comparison of differing collimation approaches by Neuner et al. [23].

Although the GRID dose distribution is non-uniform, the regression of the tumor mass receiving GRID has exhibited uniform regression clinically [4,24]. One plausible explanation might be