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Is There More to Radiotherapy than Hitting the Target?

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Description

One in two cancer patients are routinely treated with radiotherapy, using a linear accelerator to deliver the radiation dose. Conventionally, a treatment meets guidelines when the tumour is uniformly irradiated, but the surrounding normal tissue is avoided [1]. However, our recent study upsets this radiation therapy "dogma" [2]. We have shown that a radiation field with many high dose gradients may have an advantage over a uniform field [2], because it is more lethal to cancer cells than to normal cells. We attribute this effect predominantly to the production, diffusion and response to radiation induced bystander signals, which is consistent with previous reports of up to 60% of cell death following irradiation being attributed to bystander effects [3,4].

The use of a radiation field that delivers a non-uniform dose with high dose gradients is not new. Spatially fractionated radiotherapy or grid therapy, delivers radiation through a collimating grid block or by using the multileaf collimator of a linear accelerator. This approach creates an alternating peak and valley dose across the body surface with a spatial period of a few centimeters. At depth, the dose gradients will smear out and be reduced. Such fields have been known to allow a higher dose to the tumour at depth, while sparing normal tissue at shallower depths. Even though only a limited number of grid therapy cases are carried out in the clinic today, the responses have been encouraging with the achievement of a higher therapeutic ratio [5].

Another technique, which by design incorporates high dose gradients within the treatment field, is microbeam radiation therapy (MRT), where the field is created as a composite of micro-scale beams using an x-ray synchrotron. The medical beam line of a synchrotron creates non-divergent photon beams with far higher dose rates than a linear accelerator, therefore delivering a high dose quickly, while maintaining dose modulation [6,7]. To date, only *in-vitro* [8] and *in-vivo* animal studies have been performed using MRT, achieving exceptional therapeutic outcomes with preferential tumour toxicity and high normal tissue tolerance [9]. The peak dose in the micro-sized beam is over a hundred times greater than conventional radiotherapy and the outcomes are difficult to explain using the conventional dogma of radiation therapy. The success of MRT has been attributed to the differential response between tumour and normal tissue, particularly in their vasculature [10], but this factor does not explain the *in-vitro* therapeutic advantages.

Synchrotron facilities are currently not suitable for human cancer treatment, but it is feasible that the therapeutic advantages of MRT may in part be translated to the clinic using new generation linear accelerators. We questioned whether a radiation field created with linear accelerators, to give the finest possible collimated beams and therefore high dose gradients, could achieve a better therapeutic outcome than the conventional uniform field. By using the high definition micro-multileaf collimator (HD-mMLC) of a linear accelerator, where each collimator leaf projects to 2.5 mm at the isocentre, an alternating open and closed field is created resulting in a pattern of spatial modulation with a periodicity of 5.0 mm. The resulting beam modulation is much coarser than the synchrotron-generated microbeams, but far finer than used in traditional grid therapy. Even though the HD-mMLC generated beam characteristics are dosimetrically similar to those of grid therapy, the target prescription field and rationale for doing so follows closely to that of MRT.

Recently there has been an increased interest in the mechanism by which radiation stimulates the release of cytokines into the tumour microenvironment, which then induces an immune response [11,12]. In the first instance, the survival of a cell will depend on the radiation dose received, which will depend on its spatial position in the radiation field as a consequence of the dose modulation. However, the survival pattern will also be affected by cytokines, growth factors and other metabolites released into the microenvironment by neighbouring irradiated cells. This effect, also known as the *radiation induced bystander effect* has been reported to be an expression of factors released from cells upon irradiation and can travel outside the target volume, giving rise to the observed non-targeted response [13,14]. Bystander responses have been reported to vary depending on conditions and cell type [15] and can manifest as either a proliferative or cytotoxic effect [16,17].

In a uniform field, the secretion and diffusion of molecules leading to bystander effects will have an even distribution. However, in a highly-modulated field, the released factors are

driven as a result of dose gradients and the separate contributions of radiation and bystander effect can be discriminated. The biological effects of spatially fractionated fields for both grid therapy and MRT have been suggested to involve bystander responses [18,19].

In our study 'Grid therapy using high definition multileaf collimators: realizing benefits of the bystander effect', we found that spatial modulation of the radiation beam was more toxic to cancer cells, but had no additional effect on normal cells, compared to irradiation with a uniform field to the same average dose. The finest striped field modulation, which created an array of 2.5mm wide beams at the cell layer, gave a significant effect, indicating that sharp dose gradients are important in driving the bystander effect. This finding is consistent with the synchrotron MRT data, which shows that a finer modulation of each microbeam leads to a better therapeutic outcome in tumour suppression [20]. To confirm that the mechanism behind this effect was indeed the radiation induced bystander effect, we developed a simple model based on the assumption that the dose gradients in the field were responsible for the effects and showed that the model predictions were consistent with the experimental results for three human cancer and normal cell lines. The model will be useful for developing treatment strategies using fine dose modulation.

These results demonstrate that there is a hidden potential in the linear accelerator treatments routinely used in most cancer centres. Fine collimation of the beams can release cancer-suppressing molecules to increase the effectiveness of treatments without an increase in the radiation dose. Our result demonstrates the opportunity to improve the therapeutic ratio in the clinic, acquiring advantages of MRT without the need for a synchrotron.

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