Radiobiology of stereotactic radiotherapy

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ABSTRACT

This paper focuses on the radiobiological mechanisms underlying the effects of stereotactic radiotherapy (SRT) which, despite SRT expansion, have not yet been fully elucidated. Some authors postulated that radiobiology principles, as applied to conventional fractionations (5R: reoxygenation, repair, repopulation, redistribution, radioresistance), suffice in themselves to account for the excellent clinical results of SRT; others argued that the role of the 5R was limited. Recent preclinical data showed that hypofractionated ablative treatments altered the microenvironment, thus determining cell death either directly or indirectly. Furthermore, dead tumor cells released quantities of antigens, which stimulated antitumor immunity, thus reducing the risk of relapse and metastasis. Better understanding of the radiobiological mechanisms underlying response to high-dose radiation treatment is essential for predicting its short- and long-term effects on the tumor and surrounding healthy tissues and, consequently, for improving its related therapeutic index.

Key words: stereotactic radiotherapy; radiobiology; radiosurgery

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Introduction

Despite expansion of stereotactic radiotherapy (SRT), i.e., hypo-fractionated treatments with high doses per fraction, the radiobiological mechanisms underlying their effects have not yet been fully elucidated. Some authors postulated that radiobiology principles, as applied to conventional fractionations (5R: reoxygenation, repair, repopulation, redistribution and radioresistance), are enough to account for their excellent clinical results [1]; others argued that in the ablative hypofractionated setting, the role of the 5R was limited [2–7]. Recent preclinical data showed that hypofractionated ablative treatments altered the microenvironment, thus determining cell death either directly or indirectly [2–5]. Furthermore, dead tumor cells released quantities of antigens, which stimulated antitumor immunity, thus reducing the risk of relapse and metastasis [6, 7].

Better understanding of the radiobiological mechanisms underlying response to high-dose radiation treatment is essential for predicting its short- and long-term effects on the tumor and surrounding healthy tissues and, consequently, for improving its related therapeutic index. Beside the present article, this topic was recently explored in depth in excellent review articles which we refer the reader to [8–11].

The “5Rs” of radiobiology

The “5Rs” of radiobiology play a controversial role in hypofractionated schemes, especially with high doses per fraction [1, 4, 5].
Re-oxygenation is believed to play little or no role in tumor response after single-fraction ablative treatments which are associated with widespread vascular destruction of tumors. Conversely, massive cell death with its drop in oxygen consumption, could favor re-oxygenation of surviving hypoxic cells [12]. Furthermore, vascular damage may be irrelevant after hypofractionation with doses of 3-8 Gy per fraction, which might thus lead to some reoxygenation [13, 14].

The hypofractionated schedules require prolonged delivery times, which were associated with around 10% loss of biological efficacy, particularly when they lasted over 30 minutes [15, 16]. They may interfere with sublethal damage repair, overwhelming repair mechanisms due to enzymatic pool depletion [17].

High single-dose fractionation blocks the cell in the cycle phase, thus interfering with redistribution. However, some cells may slowly progress to G2 and then die [2, 18, 19].

SRT hypofractionated schedules do not provide enough time for repopulation. In fact, the proliferation of surviving cells generally occurs 3–4 weeks after the start of radiation treatment [18]. Cell depletion could, however, determine some degree of repopulation which occurs 3–4 weeks afterwards, i.e., earlier than with conventional treatments [18].

The linear quadratic model

Mathematical formulas [biologically effective dose (BED), equivalent dose in 2 Gy fractions (EQ2)] based on the linear quadrant (LQ) model calculate the iso-effective doses for unconventional single fractions. As the LQ model derives mainly from in vitro studies, it does not perfectly reflect in vivo observations [20]. Although valid for fractions ranging from 1 to 5 Gy, its validity is doubtful when higher doses are used per fraction [20]. In vitro observations suggested the LQ model overestimated cell killing because it predicted a survival curve that continuously bent downward at high single doses whereas experimental data showed a constant slope [20]. In fact, lethal damage (linear component) predominated at large doses per fraction.

The LQ model does not take into account in vivo vascular damage after a single fraction high dose [20] or tumor stem cells which maintain the tumor pool and were associated with radioresistance [21]. Despite these data, experimental models and some clinical trials reported that the LQ model adapted adequately to SRT treatment response and was reliable for single fractions up to 10 Gy, becoming progressively less accurate as doses rose [1, 17]. As cell death is mediated directly and indirectly [18], the LQ formula, may not overestimate its rate but may well approximate the total SRT-induced cell death. Although the LQ model is still the most common, other models, such as the Universal Survival Curve (USC), were developed to compare conventional and high dose hypofractionated schemes [22, 23], and to provide empirical and clinical rationales for SRT [23].

Are tumor or endothelial cells the main radiobiological target of high-dose radiotherapy?

The radiobiological target of high-dose radiation treatments is highly debated. Even though Leith et al. calculated [24] at least 80–90 Gy in a single fraction were needed to control a 3 cm diameter brain tumor, many clinical studies showed that 18–25 Gy in a single fraction effectively controlled primary and metastatic central nervous system neoplasms [2–7, 15, 24–27]. Furthermore, when 5–7 cm liver tumors were treated with 54 Gy in 3 fractions, local control was over 90% at 2 years [28]. To justify these surprisingly better results [24], different radiobiological mechanisms were proposed. The main control point for irradiation-induced immune responses may be the vascular endothelium, which acted as a barrier regulating immune cell rolling on the vascular surface [29]. Several pieces of experimental evidence supported the hypothesis of endothelial cell damage [5, 30–32], with consequent tumor microenvironment deterioration and indirect hypoxia-related cell death [33]. Tumor endothelial cells were more radiosensitive than normal endothelial cells because of varying intrinsic radiosensitivity and structural differences [34, 35]. Doses over 10 Gy in a single fraction caused vascular damage like occlusion, vasodilation, vasoconstriction, and rupture [4, 5, 36–41] which reduced endotheliocytes in number and, consequently, perfusion [38, 42, 43]. Irradiation-induced endothelial cell death released anti-tumor signals, such as the TNF cytokine, which activated macrophages; the C-X-C motif chemokine ligand 6 (CXCL6) chemokine, which recruited immune cells and activated Toll-like receptors on dendritic cells [44]. The efficacy of SRT
when administered in hypoxic conditions was evaluated in pre-clinical and clinical studies. Compared with conventional fractionation, SRT reduced the cell killing of hypoxic cellular lines [45]. Furthermore, in an animal model, tumor control probability was lower when SRT was delivered to tumors irradiated at low partial pressure of oxygen (pO2) [46]. In the clinical setting, some studies confirmed that hypoxia, assessed by imaging, decreased the efficacy of SRT [47, 48]. Interestingly, in patients who had received SRT for the treatment of meningiomas, the expression of the endogenous marker of hypoxia hypoxia-inducible factor 1α (HIF-1α) negatively impacted on local control [49].

A single dose of 8–16 Gy increased acid sphingomyelinase (ASMase) expression, which contributed to post-irradiation inflammation and fibrosis. Within blood vessels, irradiation generated a prothrombotic state with platelet aggregation, microthrombosis and increased inflammatory-endothelial cell adhesion, with subsequent diapedesis to the perivascular space [50]. Endothelial cell exposure to radiation doses of > 0.5 Gy or < 10 Gy primarily caused their senescence [51].

In vivo studies supported the hypothesis that irradiation played an indirect role in vascular damage. Clonogenic survival was lower in tumor-bearing mice that were irradiated with single dose 10 Gy than in in vitro tumor samples [5, 33].

The dose for indirect death varied with factors, such as tumor type [4, 33] and vessel diameter, as small vessels seemed more vulnerable to radiation damage than large [52]. Despite these data, consensus is not unanimous on the main target in high dose hypofractionated treatments. In a recent murine model study, Moding et al. [53] argued it was the tumor rather than the endothelial cell, providing evidence that radioinduced tumor death did not change when endothelial cells were genetically engineered by deleting the Bax pro-apoptotic gene or the DNA damage response gene. While not excluding that other stromal cells may play a role in tumor eradication after SRT, the vascular damage contribution was reduced [53].

**Antigen-induced damage and immune response**

Other biological mechanisms are involved in the efficacy of high-dose ablative treatments. High dose hypofractionated irradiation was reported to promote antitumor immunity [6, 7], while low dose fractionated treatments suppressed host immunocompetence. Extensive cell death during hypofractionated irradiation increased expression of immunomodulatory molecules like the histocompatibility complex, adhesion molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines and tumor cell surface death receptors [7, 54]. The massive release of tumor antigens and cytokines enhanced the innate antitumor response. In a mouse model, with an induced B16 melanoma, single dose 15 Gy increased the number of antitumor immune cells, facilitating antigen presentation, T lymphocyte priming in lymph nodes and effector T lymphocyte trafficking in tumors [55]. When the 15 Gy dose was fractionated in the same murine model, the immune response was weaker. Increasing the single dose up to 20 Gy augmented the immune response towards the primary tumor [55, 56]. Hypofractionated radiation therapy significantly inhibited tumor growth in immunocompetent, but not immunocompromised, mice [57]. Compared with conventional fractionation, hypofractionation reduced tumor recruitment of myeloid-derived suppressor cells and decreased their expression of programmed death-ligand 1 (PD-L1) [57]. Antitumor immunity was observed in clinical trials. A recent phase 1 study showed that the combination of interleukin 2 (IL-2) and SRT enhanced the immune response more than radiation therapy alone [58]. Ipilimumab, a CTL-associated antigen 4 (CTLA-4) ligand, associated with SRT (9.5 Gy in 3 fractions) was linked to an abscopal effect in metastatic melanoma [59]. The time-frames are worth noting. Generally speaking, tumor-specific radio-induced immunity cannot underlie the secondary death of tumor cells 2–3 days after radiation treatment as it completely developed within 1–2 weeks. On the other hand, tumor-specific radio-induced immunity seemed to inhibit proliferation of surviving tumor cells, thus suppressing recurrences and metastases. As preclinical and clinical evidence continues to mount, immune-mediated tumor “rejection” is increasingly appreciated as the sixth “R” of radiobiology [60] and several clinical trials were initiated combining SRT with immunotherapy [61, 62].

The radiobiological immunologically effective dose (IED) model was recently developed for immuno-radiotherapy. Since the dose per fraction,
the time interval between fractions and the tumour radio sensitivity may all impact on the tumour antigen expression, the IED model was designed to predict the anti-tumour immune response after exposure to different RT schedules. Once this model is validated it may be used to select the most immunogenic RT schedules [63].

Conflicts of interest
The authors have no conflict of interest to declare.

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