

Praca poglądowa/Review paper

Biological Effects of Advanced Radiotherapy Techniques Beyond the Irradiated Target Volume

Igor Piotrowski¹¹Radiobiology Laboratory, Greater Poland Cancer Centre, Poznan, Poland

Abstract

Radiotherapy is used in the treatment of approximately half of all patients with cancer, and technological advances over the past decades have progressively improved the precision with which the radiation dose can be matched to the target volume. Techniques such as three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, and volumetric modulated arc therapy (VMAT) allow better sparing of healthy tissue and have enabled the introduction of schedules implementing higher radiation doses, including hypofractionated stereotactic body radiotherapy (SBRT), and boost techniques including intraoperative radiotherapy (IORT). However, delivering higher radiation doses with modern techniques such as VMAT expose tissues distant from the target volume to low, out-of-field doses of radiation of varying energy, and the biological consequences of this exposure have not been fully characterized. Similarly, although IORT reduces the dose delivered to healthy tissue while irradiating the tumour bed directly during surgery, its influence on the postoperative wound microenvironment and on the behaviour of residual tumour cells is incompletely understood. This review summarizes in vitro evidence addressing these two questions.

Keywords: radiotherapy; volumetric modulated arc therapy; stereotactic body radiotherapy; intraoperative radiotherapy; out-of-field effects; radiation-induced bystander effect; wound microenvironment; prostate cancer; breast cancer

Adres do korespondencji

Igor Piotrowski

Radiobiology Laboratory, Greater Poland Cancer Centre, Poznan,

Telefon. +48 61 885 0474

e-mail: igor.piotrowski@wco.pl

Advanced Radiotherapy Techniques: From Rationale to Biological Evidence

Radiotherapy is one of the most widely used methods of treating cancer. Worldwide, it is used in the management of approximately 50% of patients with malignant disease, in both radical and palliative settings (1, 2). Over the past several decades, radiotherapy has undergone substantial technological development. Until the 1990s, treatment planning relied on two-dimensional radiographic imaging, with dose distributions calculated in a single plane, and treatment typically used two to four beams with a rectangular or circular cross-section to irradiate the entire tumour volume. Such techniques are now rarely used because of their relatively low accuracy and the high doses they deliver to healthy tissue (3). In most cases they have been replaced by considerably more precise approaches, such as three-dimensional conformal radiotherapy (3D-CRT) (4). More advanced techniques that provide even better sparing of healthy tissue are now most commonly used (5, 6), including intensity-modulated radiation therapy (IMRT), which allows a closer match between the dose distribution and the target volume (7). One development within IMRT is volumetric modulated arc therapy (VMAT), in which modulation of beam shape and intensity is combined with rotational movement of the treatment head, reducing the dose received by organs at risk (OAR). Because irradiation occurs continuously during gantry rotation, however, a larger volume of healthy tissue receives low doses of radiation (8).

Techniques that improve the match between the dose distribution and the target volume while reducing the dose to OAR have enabled the introduction of modified fractionation schedules, including a reduction in the number of fractions combined with an increase in the dose per fraction (hypofractionation), which makes treatment less burdensome for patients.

In oncology delivering radiotherapy in fractions allows for the healthy tissues to regenerate between fractions, while tumour cells are continuously eliminated. Depending on the regenerative capacity of the cancer cells and the surrounding healthy tissue, for some cancers radiotherapy with more lower-dose fractions (hyperfractionation) or fewer higher-dose fractions (hypofractionation) may be beneficial (9). Hypofractionation is particularly advantageous for tumours with a low α/β ratio, such as prostate cancer (10). In prostate cancer, hypofractionation not only increases the probability of cure while maintaining a low risk of complications in normal tissue, but also shortens the overall duration of radiotherapy (11). Hypofractionated stereotactic body radiotherapy (SBRT), delivered using techniques such as VMAT, is increasingly used for prostate cancer (11). VMAT-based SBRT achieves satisfying treatment outcomes with a low risk of complications in the bladder and rectum. However, the use of technologically advanced multi-beam, including rotational, techniques results in radiation doses being delivered to various regions of the patient's body, including sites distant from the target volume. These doses are relatively small, typically up to 1–2 Gy, and arise both from secondary radiation scattered within the body and the treatment head, and from the fact that a large proportion of the body is exposed to the primary radiation of one or multiple beam components as the gantry rotates. Until recently, the biological response of distant OAR to the exposure and doses arising from these effects during VMAT-based SBRT had not been investigated.

Biological effects of hypofractionation radiotherapy

Advanced radiotherapy techniques such as VMAT can increase the contribution of scattered radiation of varying energy outside the treated volume; using a 6 MV photon beam, Kirkby et al. showed that the proportion of low-energy electrons increases with distance from the target volume (12), and lower-energy radiation is generally able to induce biological effects more efficiently than higher-energy radiation (13). Radiation absorbed by tissue distant from the target volume may therefore produce a greater biological effect than would be expected from the measured dose alone, and until recently this out-of-field effect of VMAT-based SBRT had not been investigated directly. This gap was addressed in a phantom-based in vitro study of VMAT-based SBRT for prostate cancer, in which cellular damage was assessed both within the target volume and at the position of peripheral OAR (14). A clear radiobiological response was confirmed in cells positioned at the prostate, while cells positioned at the intestine showed only a small, non-significant increase in DNA damage and cell death. Importantly the intestinal tolerance

dose is considerably higher than the doses recorded in the study, and intestinal crypt stem cells can repair damage from doses of several Gy (15, 16); cells positioned at the lung and thyroid showed no radiation-related gene-expression response.

These results indicate that VMAT-based SBRT for prostate cancer does not induce a substantial radiobiological response in peripheral critical organs, although even doses that cause no measurable cellular damage cannot fully exclude a contribution to later genetic change (17). Even such low radiation doses may be of clinical significance due to the increased risk of developing secondary cancer. With modern conformal radiotherapy techniques, higher volume of tissues is irradiated with low radiation doses originating from leakage of the accelerator head, radiation scattered from the device and the patient's body (18). The risk of cancer induction increases with higher doses and has no threshold at low doses (19). The doses to OAR can reach even up to 1 Gy, inducing DNA damage and subsequent carcinogenesis (20, 21). While the relative risk of secondary cancers is rather low and organ and age-dependent, the severity of this side effect means it cannot be overlooked after radiotherapy (18).

Biological effects of intraoperative radiotherapy

For many tumour types, delivering a higher radiation dose to the tumour volume increases the probability of local control (22). However, the achievable dose is often limited by the proximity of healthy tissue, and even the most advanced external-beam techniques cannot completely eliminate the dose received by surrounding tissue. For select tumour types, intraoperative radiotherapy (IORT) allows the dose to healthy tissue to be reduced while the dose delivered to the target volume is increased (23). Clinical studies have shown that IORT can be used in breast cancer to irradiate the tumour bed after breast-conserving surgery (24), thereby increasing the dose of ionizing radiation delivered to the tumour bed while limiting the dose received by the surrounding healthy tissue (25, 26).

IORT delivers ionizing radiation directly to the target volume through an applicator, the position of which is verified in the operating theatre by the treatment team (23). Because the skin is retracted and the applicator is placed within the tumour bed, IORT substantially reduces the dose received by the patient's skin. In breast cancer, delivering a dose of 10–20 Gy with IORT shortens the overall duration of treatment and reduces the number of patient visits, and it reduces some of the side effects associated with radiotherapy; however, clinical trials to date have not demonstrated that the efficacy of IORT is, in general, superior to that of standard fractionated external-beam radiotherapy (24, 27, 28).

Several studies suggest that surgical excision of a tumour can alter its microenvironment and promote the growth of tumour cells remaining in the surgical bed, potentially contributing to local recurrence (29, 30). With standard postoperative external-beam radiotherapy for breast cancer, treatment begins several weeks after tumour excision, whereas intraoperative radiotherapy irradiates residual tumour cells immediately, before they can benefit from the favourable growth conditions of the healing wound; secretory factors present in this microenvironment are known to promote the proliferation of such residual cancer cells (29), and more recent studies suggest that IORT may reduce the pro-tumorigenic properties of the wound microenvironment (30), although the mechanism had not been established.

Not just direct cell killing: RIBE and abscopal effects

Ionizing radiation effects can be transmitted from irradiated to non-irradiated cells through the radiation-induced bystander effect (RIBE), and this has since been demonstrated directly using surgical wound fluid collected from patients treated with IORT: applied to breast cancer cells in vitro, such fluid alters the radiobiological response of the cells, indicating that RIBE is one of the factors shaping the biological properties of postoperative wound fluid after IORT (31). Consistent with this, wound fluid collected after breast-conserving surgery was shown to induce a more aggressive, invasive phenotype in breast cancer cells, marked by features of cancer stem cells and epithelial-to-mesenchymal transition, and this pro-tumorigenic effect was considerably weaker when IORT had been administered during surgery (32). Together, these findings suggest that IORT may reduce the risk of local recurrence not only through direct irradiation of residual tumour cells, but also through RIBE-mediated changes in

the wound microenvironment. RIBE has also been observed in other types of cancer, although often in *in vitro* studies. Radiation induces the bystander effect in prostate cancer cell lines, with higher doses likely producing a more pronounced effect (33). Interestingly, the use of radiosensitizers, such as gold nanoparticles, can also boost RIBE in prostate cancer cells (34).

While RIBE is a more local phenomenon, radiotherapy can also induce changes on a systemic scale. The clinical effects of stereotactic radiotherapy techniques are not accurately described by the linear-quadratic model, suggesting a greater contribution of other mechanisms (35). High-dose fractionation radiotherapy was shown to induce more significant immune effects, especially related to cytotoxic T cell activation, mediating systemic antitumour response (36). This phenomenon, named abscopal effect, can even lead to regression of tumours present outside of treatment field, especially when combined with immune interventions (37). Some molecular studies suggest immune stimulation is also induced after prostate radiotherapy (38), however its immunosuppressive microenvironment may be responsible for reduced effectiveness. That is why combination of radiotherapy with immune checkpoint therapy might be especially beneficial for utilizing abscopal effect in prostate cancer treatment (39).

Discussion

These lines of evidence show that the biological effects of advanced radiotherapy techniques are not confined to the treated volume itself. During VMAT-based SBRT, low, out-of-field doses reach tissue distant from the prostate, but the resulting radiobiological response is minor and does not indicate a meaningful risk of radiotoxicity in the intestine, lung, thyroid, or other peripheral OAR. During intraoperative radiotherapy for breast cancer, by contrast, irradiation of the tumour bed appears to produce a biologically meaningful, favourable change in the postoperative wound microenvironment, at least in part through RIBE-mediated signalling, reducing the capacity of wound fluid to support tumour cell growth and invasion.

These findings support two complementary conclusions relevant to clinical practice: first, that VMAT-based SBRT for prostate cancer can be considered biologically safe with respect to peripheral OAR; and second, that the therapeutic effect of IORT in breast cancer may extend beyond direct cytotoxicity to residual tumour cells, through modulation of the wound microenvironment. Further studies are needed to clarify the mechanisms underlying RIBE-mediated changes in wound fluid, and to determine whether they can be exploited or enhanced to improve the efficacy of intraoperative radiotherapy.

Conclusions

In vitro evidence indicates that the biological effects of advanced radiotherapy techniques extend beyond the irradiated target volume. VMAT-based SBRT for prostate cancer produces only a minor, largely reparable radiobiological response in peripheral OAR, without evidence of substantial radiotoxicity. Intraoperative radiotherapy for breast cancer modifies the postoperative wound microenvironment in a manner unfavourable to residual tumour cells, an effect associated with the radiation-induced bystander effect. These findings support the biological safety of VMAT-based SBRT and point to bystander-mediated mechanisms as a potential target for improving the efficacy of intraoperative radiotherapy in breast cancer.

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