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Strategies to optimize radiotherapy based on biological responses of tumor and normal tissue (Review)

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Abstract. Rapid developments in radiation oncology are currently taking place. Radiation-induced responses are being increasingly used for radiotherapy modification based on advancements in radiobiology. In the process of radiation treatment, radiobiological responses of tumor and normal tissue in patients are monitored non-invasively by a variety of techniques including imaging, biological methods and biochemical assays. Information collected using these methods and data on responses are further incorporated into radiotherapy optimization approaches, which not only include the optimization of radiation treatment planning, such as dose distributions in targets and treatment delivery, but also include radiation sensitivity modification and gene radiotherapy of the tumor and normal tissue. Hence, the highest tumor control rate is obtained with the utmost protection being afforded to normal tissue under this treatment modality.

Contents

1. Introduction

Radiation oncology has undergone 100 years of development and has now entered the 'precision radiotherapy' era. New radiotherapy modalities, such as intensity modulated radiation therapy (IMRT), image guided radiotherapy (IGRT), volumetric modulated arc therapy (VMAT), biologically guided radiation therapy (BGRT), adaptive radiation therapy (ART) and hadron radiotherapy are emerging, each with unique characteristics (1). However, a discrepancy between supply and demand still exists; the current outcomes of radiation therapy are still far from the high demand of cancer patients for therapy efficacy and quality of life. Great advancements in radiation biology (2), radiation physics (3) and imaging technology (4) are bringing about new opportunities to further improve the outcomes of radiation treatment. In recent years, radiation-induced reponses of tumor and normal tissues have increasingly been used as feedback to modify radiotherapy in order to get the highest therapeutic gain. In this review, we briefly discuss how and why this new treatment strategy has come into being, as well as its current status and characteristics. Also, the future developments of this treatment modality are discussed.

2. Why response-modified radiation treatment?

Demand for individualized radiotherapy as a driving force. Accurate delivery of the ionizing radiation dose has greatly improved over the past 2-3 decades, allowing more precise deposition of therapeutic agents to the tumor while progressively reducing any unwanted dose to surrounding normal tissues. Such techniques allow the dose to the tumor to be increased to levels that would be unachievable without precise targeting (5,6). With the improvement of tumor control and survival, the requirements of improving quality of life have also increased. However, the challenge is that not only do the same types of tumor tissue from different patients show differences in sensitivity to radiation, but the sensitivity of tumor tissues of the same patient during radiotherapy also shows dynamic changes. All of these disparities in radiation sensitivity necessitate the use of different radiation doses. Thus, to achieve the greatest efficacy with minimal side effects, individualized response-guided radiation therapy is required (7).

Advances in understanding radiobiological responses have made 'response-modified radiation therapy' possible. Biology is a fast-growing branch of science. With the development of molecular biotechnologies, we gain deeper understanding of biological phenomena and mechanisms. This has led to advances in radiation biology, such as radiation-induced early responses, cell proliferation, hypoxia and inherent radiosensitivity, as well as screening of a series of specific molecular

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markers. To date, ATM, ADR, γ-H2AX, MDM2 and Bcl/Bax have been verified in preliminary clinical trials (8). We currently have a fairly comprehensive understanding of the biological responses of radiotherapy-induced molecules, cells, tissues and systems at all levels. All these data on radiobiological responses may be used to modify personalized radiotherapy.

Progression in radiation physics and bio-imaging technology provides technical support for response modified radiation treatment. Newly emerging biological/physiological imaging techniques, such as functional imaging, molecular imaging and metabolic imaging, differ from traditional anatomical imaging. The processes of physiology, biochemistry, metabolism and signal transduction of cells may be visualized through bio-imaging technology to generate real-time, dynamic biological information of tumor and normal tissues *in vivo* (9,10). Similarly, radiation physics has experienced significant development in recent years. A number of new localization and fixing techniques, dose calculation algorithms and treatment concepts make radiotherapy even more precise. With deeper understanding of the concepts of factors such as the biologically effective dose (BED), equivalent uniform dose (EUD), α/β, tumor control probability (TCP) and normal tissue complication probability (NTCP), biological responses could be translated into a means for radiation physics optimization (11-13).

To conclude, there is an urgent clinical need for this new radiation model, and its feasibility is based on growing knowledge regarding radiation responses and advances in modern radiation physics and imaging technology. Therefore, we believe that response modified radiotherapy will become the mainstream mode of radiation therapy.

3. How do radiation-induced responses modify radiotherapy?

The modality of response modified radiotherapy may be described as follows. Based on the biological responses to radiation of tumor and normal human tissues, the optimization of radiation treatment planning and modification of tissue sensitivity are carried out dynamically by adjusting to changes in responses to radiation, which will lead to the best therapeutic ratio (Fig. 1). Specifically, radiobiological responses include: i) molecular reactions such as DSB (14-18), ATM (19,20), ATR (21), NBS1 (22), BRCA1 (23), DNA-PK (24,25), HIF-1a (26,27), γ-H2AX (28,29), as well as the early response molecules such as Egr-1 (30) and c-fos (31); ii) cellular responses such as apoptosis (32), autophagy (16,33-35), cell proliferation rate (36) and changes in cell cycle (37-43); iii) tissue and organ level responses, including volume changes (44), inflammation, edema and fibrosis (8,45,46); and iv) the overall level of responses, including changes in expression of cytokines such as IL-1 (47), IL-6 (48), TNFα (49) and TGFβ (45). Radiation responses should be considered on multiple, comprehensive levels in the tumor and normal tissue, as well as in the early stage of acute response and the late stage tissue responses. Based on the above indicators of radiation response, the optimization of radiation therapy includes (Table I) i) the optimization of the radiation treatment planning, including the dose-painting techniques on regions with different sensitivity in the same target volume and the dose-fractionation model

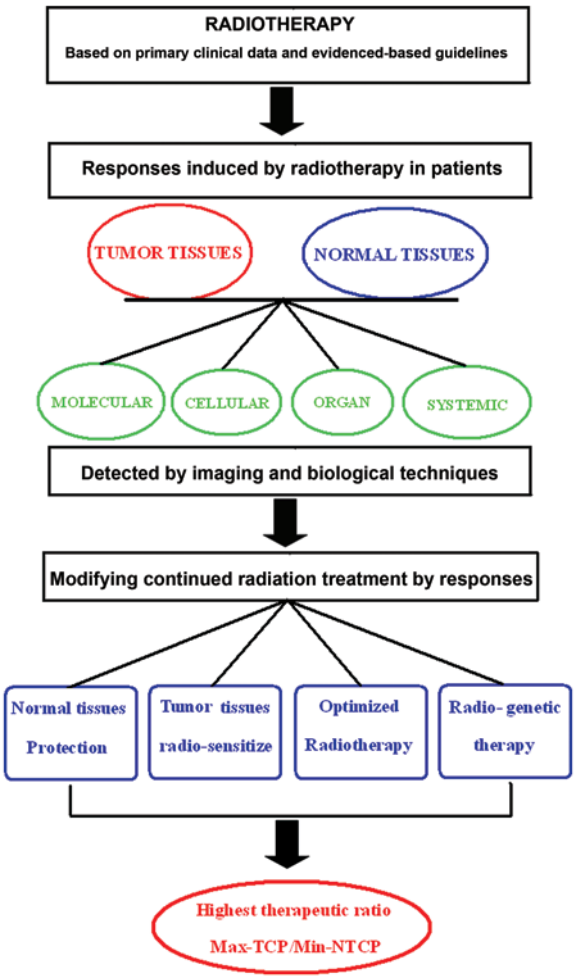

Figure 1. Flowchart illustrating the basic steps of one cycle of RGRT, which mainly includes the detection of various responses in normal and tumor tissues caused by primary radiotherapy, the modifications of continued radiotherapy based on detected responses. Practically, a complete radiation treatment course usually contains several RGRT cycles. Radio-genetic therapy mentioned herein represents a novel treatment strategy in which gene therapy is controlled by radiation via radiation inducible gene promoters such as Egr-1. RGRT, response-guided radiotherapy; TCP, tumor control probability; NTCP, normal tissue complication probability.

and ii) the tumor tissue radiosensitizer (37) and radiation protection of the normal tissue (50). For example, based on the close relationship between TGFβ and pulmonary fibrosis, if high levels of TGFβ in peripheral blood of patients undergoing chest radiotherapy are detected, appropriate measures should be taken to block radiation-induced pulmonary fibrosis. Thus, radiotherapy may be modified along the entire process.

Response-modified radiotherapy is not only a new modality of treatment, but also a novel radiotherapy philosophy. A variety of optimization methods can be inserted at specific stages of radiotherapy. Every fractionation in the whole process of radiotherapy should be unique and should be dynamically optimized according to specific tumor and normal tissue responses.

Response-modified radiotherapy is a new treatment modality developed from adaptive radiation therapy (ART) (51,52), however, it places more emphasis on the comprehensive information from multiple stages and across disciplines, such as molecular biology, physiology and

Table I. Responses of tumor and normal tissues in patients treated by radiotherapy and techniques to modify the radiotherapy.

Level	Response	Detection methods	How to modify radiotherapy
Molecular	DSB, ATM, ATR, NBS1, BRCA1, DNA-PK, HIF-1a, γ-H2AX, Egr-1, c-fos	Molecular imaging, molecular biological methods	Enhance radiosensitivity, radiogenetic therapy
Cellular	Apoptosis, autophagy, cell cycle arrest, proliferation rate	Biological imaging Functional MRI	Biological target definition, dose painting, optimal fractionation
Organ	Volume changes, inflammation, fibrosis	CT, Functional MRI	Target modification, normal tissue protection
Systemic	IL-1, IL-6, FGF2, TNFα, TGFβ	Biological assays, biochemistry assays	Normal tissue protection, NTCP modelling

NTCP, normal tissue complication probability.

biochemistry. Thus, in addition to the features of ART in terms of physics, it also has the following characteristics:

i) Information integration. This model makes full use of multiple levels of information from the human body, that is, different levels of response caused by radiation. The main biological characteristics of tumor and normal tissue, including physiological and biochemical features, are obtained non-invasively from the whole body and the local site, at static and dynamic levels. Biological and physical approaches are then used to translate this information into radiotherapy optimizing strategies.

ii) Evidence-based modification. Generally speaking, the use of molecular markers that 'predict' the radiosensitivity of the tumor is hard to achieve with the desired sensitivity and specificity. Response-modified radiotherapy avoids this problem; it only considers the final outcomes directly caused by radiation therapy, regardless of its mechanisms and biological process. For the treatment modality of response-modified radiotherapy, radiotherapy is optimized based on the integrated information of the final actual outcomes of tumor and normal tissues caused by radiation. For instance, cell apoptosis in tumors is detected using molecular imaging after a fraction of radiotherapy, then the acquired apoptosis information is used to modify further treatment planning.

iii) Technology integration. It is worth noting that the biggest advantage of the modality is that its optimization integrates all aspects of treatment throughout the course of radiotherapy, which include radiotherapy planning optimization, the implementation of radiotherapy quality assurance, sensitivity modification of tumor and surrounding normal tissues to radiation, the use of various physical and biological measures.

This radiotherapy model combines a variety of radiation responses in all the normal tissues and tumor tissues and truly achieves individualized technologies. At the same time, it maximizes the use of the most systematic and comprehensive optimization tools, which bring the greatest benefits to patients with minimal side effects and maximal efficacy.

In recent years, the response-guided radiotherapy modality has gradually been incorporated into daily radiotherapy practice. For instance, for nasopharyngeal carcinoma treatment, in the course of radiotherapy, we dynamically observe the changes in tumor volume to re-delineate the target volume and modify the radiation plan to maximize the protection of at-risk organs without missing the tumor target. Following years of extensive work and systematic research, our centre has reviewed the alterations of nasopharyngeal carcinoma volume in radiation treatment and used this knowledge as a basis to explore the best timeline for replanning. Our results revealed that the revised target volume had 100% coverage, doses on the normal tissue were reduced by 15%; side effects was reduced by 40%, with a local control rate of 92% and 5-year survival rate of 87% (53). Similarly, this treatment model has also been implemented at certain other radiation oncology centres. Wang *et al* investigated the target volume and dose distribution changes during nasopharyngeal carcinoma radiotherapy. CT scans were performed following 18 fractionations of radiotherapy, and doses and target size of the former and new plans were compared. The results revealed that the bilateral parotid gland volume had reduced by 6 cc, and the new plan decreased the parotid gland dose by 2.57-2.97 Gy; similar dose changes were also achieved for other at-risk organs. When compared with the former plan, the new plan decreased the dose in the brain stem from 6.51 Gy to 0.08 Gy and the dose in the spinal cord from 7.8 Gy to 0.05 Gy. Accordingly, they concluded that in the case of nasopharyngeal carcinoma radiotherapy, replanning based on the changes in tumor size may better protect at-risk organs such as the parotid gland, spinal cord and brain stem (54). Wang *et al* reported that in 28 cases of replanning of nasopharyngeal carcinoma IMRT, the dose in high-risk targets increased by 4.9-10.8%, the maximum dose in the spinal cord decreased by 5-9.23 Gy and the average dose in the parotid gland decreased by 4.23-10.03 Gy with replanning following 25 fractionations of radiotherapy followed by CT scan (55).

Hansen *et al* analyzed the replanned target regions and dose changes on the organs at-risk of 13 patients with head and neck cancer by IMRT. The results suggest that replanning could increase the dose for lesions and high-risk clinical volume by 0.8-6.3 Gy dose and 0.2-7.4 Gy, respectively, while decreasing

the doses in the spinal cord and brain stem by 0.2-15.4 Gy and 0.6-8.1 Gy, respectively (56). Mechalakos *et al* used weekly CBCT to observe the effect of volume reduction in a neck mass on the dose to the spinal cord in a case of recurrent nasopharyngeal carcinoma. The results demonstrated that volume reduction of the lesion had little impact on the dose distribution in the spinal cord (57). Zhao *et al* reported that with replanning following 15 fractionations of radiotherapy in 33 patients with nasopharyngeal carcinoma, the 3-year disease-free survival rate was 72.71%, which was higher than that when a single plan was used over the entire course (68.16%) ($P<0.05$). In particular, the advantage was most pronounced in patients with local advanced disease (58). Zhang and Li studied the effects of radiotherapy replanning in non-small-cell lung cancer radiotherapy. The preliminary results indicated that multiple-planning radiation treatment not only greatly increased the dose for the lesions but also maximized the protection of the healthy lung tissue (59).

The above replanning treatments of nasopharyngeal carcinoma and lung cancer essentially used the radiation responses of tumor to modify the radiotherapy. The changes in tumor size during radiotherapy is the main response to radiation. Using this response to re-delineate the tumor target, revise the radiation treatment planning and modify the IMRT of nasopharyngeal carcinoma reflects the core spirit of response-modified radiotherapy. It may be inferred that further advancements in molecular imaging technology would result in biological responses increasingly being used to guide radiotherapy optimization.

Another example of response-modified radiotherapy in practice is that we usually use different doses and fractionations in several lesions of the same patient, observe the changes in lesions and normal tissue response following several fractionations of radiotherapy to identify the best therapeutic dose and then apply this fractionation model in the next step of the treatment. According to our preliminary statistical results, this treatment model not only greatly increases the tumor control rate but also significantly reduces the side effects of radiotherapy and achieves the maximum benefit to patients. These results once again demonstrate the scientific rationale of response-modified radiotherapy.

4. Perspective on response-modified radiotherapy

This new radiotherapy modality considers the individual differences in radiation-induced biological responses and feeds this difference back to the radiation treatment planning and implementation process through repeated revisions to achieve tailor-made radiotherapy. Given the complexity of biological phenomena, it is difficult to find ideal, consistent predictive factors. Radiotherapy response involves complex molecular networks, therefore a single or a small number of molecular markers are hard-pressed to anticipate the actual results of radiotherapy (60-62). However, response-modified radiotherapy is based on the actual responses from the tumor and normal tissue and uses this information to amend and optimize radiotherapy planning. Sidestepping the complexities of biological mechanisms of radiation and using actual response feedback to guide radiation therapy is an efficient and pragmatic way of working and eliminates the need for detailed considerations of complex intermediate mechanisms in treatment.

This real-time response guided radiation therapy approach not only delivers the most effective radiation doses to tumors but also takes into account the dose tolerance of normal tissues. The current standard normal tissue tolerance doses are empirical, rather than the actual tolerance levels of the individual tissues. Perhaps a specific patient is able to tolerate a higher dose than the current standard, and thus we are able to safely increase the therapeutic dose without serious side effects. This radiotherapy model, taking the individual tumor and normal tissue response into account, thus guarantees the most effective dose of radiation to the tumor and achieves the ultimate goal of safety.

Although certain cancer centers have begun to explore response-modified radiotherapy and have achieved encouraging results in cancer treatment, much research is required before we are able to achieve true personalized treatment in clinical practice. As such, a number of important issues still need to be addressed:

Identification of a series of reliable molecular, cellular and systemic markers for radiation responses. This would not only reliably represent the control rate of the tumor and clinical efficacy, but also reflect the sensitivity and dose tolerance of normal tissue. Although a considerable number of molecules have been studied, specific and sensitive markers are rare.

Establishment of a set of technologies for detecting radiation response. To carry out this modality, we must acquire non-invasive, real-time and dynamic information regarding *in vivo* radiobiological responses in tumor and normal tissues. Existing molecular imaging techniques, such as PET, SPECT and fMRI, yet cannot fully satisfy the actual needs of response-modified radiotherapy (63,64).

Exploration of how to integrate the information of radiation responses into radiotherapy optimization. Taking full advantage of the available physical and mathematical tools, it also require interdisciplinary work to integrate a variety of radiation responses into the radiation therapy feedback process.

5. Conclusion

Modern radiotherapy requires advanced equipment and a reasonable treatment strategy to gain the best clinical outcome. Making full use of biological information to generate reliable radiotherapy models needs to be addressed in the near future. Response-modified radiotherapy perhaps may not be the most optimal radiotherapy modality, nevertheless, it will shed new light on the way to personalized radiotherapy.

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