



## Review paper

## Second re-irradiation: A delicate balance between safety and efficacy

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## ABSTRACT

Except for straightforward palliative indications such as painful bone metastases, re-irradiation is often characterized by a narrow therapeutic window and the potential for decreased efficacy and increased toxicity, especially if the cumulative total dose from both courses is high. Second re-irradiations tend to pose even bigger challenges and are thus offered in a restrictive manner to highly selected patients on a case-by-case basis. Normal tissue dose constraints are still an area of active investigation. Nevertheless, examples of potentially useful indications have been published. The present review briefly summarizes areas of uncertainty and opportunities for future research. If evidence-based concepts with acceptable side effect profiles can be developed, an increasing number of patients may benefit from additional radiotherapy to previously exposed target volumes.

## 1. Introduction

Radiation oncologists involved in palliative treatment scenarios frequently prescribe repeated courses of radiotherapy to anatomically distinct parts of the body, e.g., because of newly arising painful bone metastases. Due to non-overlapping dose distributions and moderate biologically equivalent doses, this type of retreatment is not particularly challenging. The complexity of decision-making and treatment planning increases when the new lesion is located close to the previous target volume, even in the absence of direct re-irradiation of an already treated lesion. For example, repeat radiosurgery (SRS) for new distant brain metastases or repeat stereotactic body radiotherapy (SBRT) for new lung lesions poses challenges regarding the cumulative dose to critical organs at risk, in case of lung SBRT mainly lung, esophagus, trachea, heart and large blood vessels [1,2]. Re-irradiation of the same target lesion is the most complex situation, however, some guidance from previous prospective studies and expert recommendations is available [3–6]. In contrast, very limited data exists to guide treatment planning for a second re-irradiation of the same target lesion [7]. These highly individualized treatments are uncommon, even in large institutions, thus rendering prospective studies very difficult to conduct. As recently reviewed, the literature is dominated by small retrospective studies that included heterogeneous patient populations, e.g. with brain metastases, spinal metastases, pelvic and thoracic targets. In the absence of widely agreed dose constraints, many assumptions have to be made when reviewing the dose distribution and signing the final plan. Therefore, the present review aims at proposing a strategy for collection

of further clinical, and ideally also experimental, data, which may contribute to the development of evidence-based, safe dose/fractionation regimens.

## 2. The clinical landscape

Second re-irradiation comprises less than 1% of the workload in the author's current and former departments. The vast majority of these carefully selected patients receive treatment for metastatic bone lesions. However, we have recently also provided other examples of worthwhile re-re-irradiation to pelvic target volumes [8]. No serious toxicity was observed. One patient had sacral bone infiltration from rectal cancer and another patient lymph node and soft tissue recurrence from bladder cancer. In addition, patients with brain metastases may derive benefit from this approach, although the risk of radiation necrosis must be factored in [9,10]. We have previously reported a case of metastatic malignant melanoma initially treated with whole-brain radiotherapy (WBRT) in 2004, which was followed by SRS and repeated SRS to the same lesion in 2005 [11]. This patient is still alive as of summer 2018, free from radionecrosis and recurrence. Historically, re-re-irradiation has been employed with variable success in the era before effective systemic therapy became available and with now outdated equipment, e.g., for hematological and solid malignancies [12]. However, the available modern literature is still limited and definitive recommendations are difficult to develop [13–17]. Often, re-irradiation studies included a limited number of patients who were re-irradiated twice [18]. Since this subgroup was not the primary focus of the

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publication, not all relevant data can be extracted, as already acknowledged in a previous review [7].

### 3. The preclinical basis

The re-irradiation tolerance or residual injury of different organs has been studied in animal models [19–21], as summarized in a comprehensive review [22]. However, a second re-irradiation has rarely been performed by these research groups. Chen and Hendry studied mouse skin injury after irradiation of the middle 3 cm of the tail [23]. They administered 25, 22.5, and 20 Gy with a time interval of 9 weeks (time required for skin healing) between these priming tolerance doses. Nine weeks after the third priming dose an additional test single dose was given. Among other endpoints, dose-response curves for healing were evaluated. Summarized briefly, residual injury was characterized by a 35% reduction in the iso-effective dose after three priming doses. This animal model does not closely resemble the clinical scenarios of re-irradiation and is limited to skin only. Therefore, decisions have to be based on the magnitude of tissue recovery between the first and second course, and the assumption that the fundamental principles of radiobiology and damage repair in cells and tissues remain valid also after the second course. Ideally, additional experiments, e.g. for spinal cord, lung and bowel tolerance, would be performed to confirm the “disappearance” of large parts of the subclinical damage induced by both previous treatment courses, even if such experiments are time and resource consuming. Since kidney, heart and bladder have been shown to tolerate re-irradiation poorly (no recovery; in case of bladder for whole-organ irradiation, which is uncommon in the clinic) these organs should be considered critical organs at risk during treatment planning in patients.

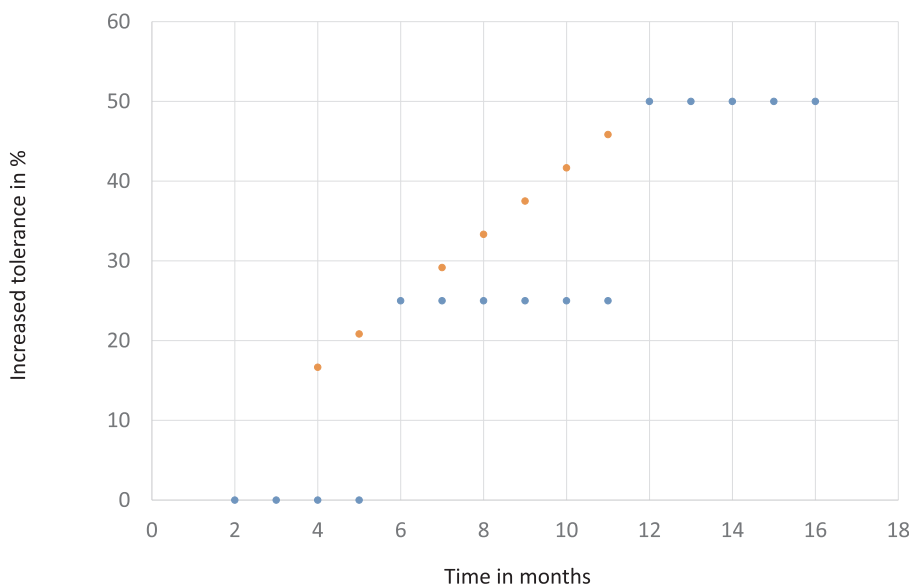
### 4. The magnitude of recovery from initial subclinical radiation effects

The spinal cord data published by Ang et al. suggest that for a time interval of 1, 2, and 3 years between the treatment courses, cumulative doses of 150%, 156%, and 167% of the first-line setting's tolerance dose appear possible [19]. Clinical data from patients who received two and even three courses of radiotherapy to the spine confirm the feasibility of re-irradiation with cumulative doses higher than first-line tolerance, albeit with limited follow-up due to the palliative nature of treatment [24,25]. Many clinicians have adopted the tolerance doses derived from the Ang et al. data. For example, Abusaris et al. set the maximum re-irradiation dose as 50% more than the normal constraint if the interval was at least 12 months, also for re-re-irradiation [26]. For spinal cord, this resulted in an equivalent dose in 2-Gy fractions (EQD2) of 75 Gy for the second course. A dose adjustment of 25% was made for intervals between 6 and 12 months. Fig. 1 illustrates this approach (blue data points). Given that biological processes tend to proceed in a more continuous way, it appears possible that the orange data points may better describe the increase of tolerance doses over time. This hypothesis is accessible for testing in experimental and clinical settings. So far, the clinical toxicity data [7,8,24,25,26] is fully compatible with the proposed 50% increase for time intervals  $\geq 12$  months. It is not recommended to assume 100% recovery at any longer interval. It can not be advocated to adopt a time-dependent 25–50% dose increase to the heart [21]. Compared to simple models the clinical situation is complicated by additional risk factors for toxicity, e.g., comorbidity and different other oncological treatments. It is recommended to refrain from re-irradiation if prior radiotherapy was poorly tolerated and/or late tissue damage has been detected. This policy introduces an additional safety margin, because the population-based tolerance dose recommendations (TD<sub>5/5</sub> etc.) capture many events that occur in the part of the population that tolerated treatment less well than the majority. Excluding these patients, e.g. with severe skin and mucosal changes, from re-irradiation allows for prescribing higher doses with higher

tumor control probability. Recently, retrospective efforts were made to decipher the tolerance of the brachial plexus and aorta to re-irradiation [27,28]. These clinical data (n = 43 patients) suggested that cumulative maximum dose to the plexus should be lower than the median (95 Gy) and that re-irradiation within two years increased the risk of neuropathy. Based on time interval and cumulative dose, three risk groups were proposed [27]. For the thoracic aorta, maximum dose to 1 ml should be lower than 120 Gy [28]. Independent validation of these predictive models is urgently awaited. In this context one has to be aware of the uncertainty around true cumulative dose assessment. Even with co-registration of different plans and deformable image registration the treatment planning scans only represent a snap-shot, which does not account for patient movement and organ movement during a course of fractionated radiotherapy. This uncertainty and “geographical miss” of organs at risk might be disadvantageous if the high-dose region unintentionally moves towards a dose-limiting structure. However, it might also protect such structures because of a blurring of the high-dose region over a larger area than visible on the snap-shot scan. Daily registration of the actually delivered dose would be required to definitely establish tolerance doses. For organs where parameters other than maximum dose are important (mean dose, V30, V50, or combinations of different dose-volume histogram metrics) a clarification is needed as to whether the same policy (50% more dose after  $\geq 12$  months) should be recommended. It also appears relevant to study the influence of target volume size on development of toxicity. For example, if pelvic re-irradiation involves one course with a large target volume, such as bilateral elective lymph node regions, the inclusion of the vasculature might result in a higher risk of reduced blood perfusion and tissue necrosis compared to three courses to small target volumes, especially if full overlap can be avoided. In head and neck cancer re-irradiation, published studies often contained some patients with recurrent tumors and others with second malignancies. The sparse literature about second re-irradiation so far does not contain sufficiently many patients with second malignancies to allow for meaningful analysis. In the uncommon situation of potential long-term survival one may consider efforts that limit the second cancer risk from re-irradiation [29–31].

### 5. Perspective

Even if second re-irradiation is a challenging topic that receives less attention than other recent developments, the available evidence and the experience at the author's department suggest that this strategy, which is inexpensive compared to other oncological treatments [32], may be effective in terms of symptom palliation, e.g. pain from bone metastases or soft tissue/lymph node tumors [8–10,24–26]. However, the therapeutic window is narrow and several studies have reported clinically relevant, sometimes fatal side effects such as soft tissue necrosis and fistula [33,34]. In order to improve the safety and reduce barriers for routine clinical administration (including legal aspects) a well-defined strategy is needed. The existing literature is difficult to put in context due to lack of comprehensive dosimetric and volumetric information. Only if individual institutions collaborate will we be able to establish sufficiently large databases and to recruit patients into prospective trials that can pave the way towards evidence-based treatment regimens, as already demonstrated for the first re-irradiation setting [35–37]. Both, clinical and experimental research should be conducted to deepen our understanding of tissue recovery and dose-volume effects. In the future, population-based dose constraints might be replaced or supplemented by personalized information based on innovative prediction models [38,39]. Cooperative groups should consider establishing expert panels, which review and modify the re-irradiation concepts and plans of participating institutions comparable to pre-treatment quality assurance in large, landmark clinical trials. Outcomes of these “consensus” treatments should then be registered and monitored to increase the knowledge base and bridge the gap until formal prospective trials can be completed.



**Fig. 1.** Recovery and increased tolerance during the time interval after previous radiotherapy. The blue bullets illustrate the strategy published in [26]. If recovery is a continuous biological process, tolerance might increase in the manner illustrated by the orange bullets. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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## 6. Declarations of interest

None.

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