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Critical Review

Review of thoracic reirradiation with stereotactic body radiation therapy
A focus on toxicity risks

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Abstract Reirradiation of thoracic malignancies is clinically challenging in balancing the risks and efficacy. Stereotactic body radiation therapy (SBRT) can facilitate ablative dosing of discrete targets while minimizing normal tissue exposure; thus, SBRT is an attractive, minimally invasive option to consider for patients with recurrent or new malignancies within a previously irradiated field. Published data are summarized from 28 studies on the use of SBRT for thoracic reirradiation. We review clinical outcomes with a primary focus on toxicity risks, dosimetric correlates of normal tissue complication probability (NTCP), and other factors that correlate with NTCP. Meaningful compilation of published data on reirradiation with SBRT is limited because of the retrospective nature of published studies, which include mostly small numbers of patients, with various clinical scenarios and SBRT dosing and techniques. Nevertheless, these studies show that thoracic reirradiation with SBRT is feasible, with relatively favorable outcomes. Yet, severe to fatal toxicities do occur, and dosimetric measures to predict severe toxicity are poorly characterized, necessitating further study to better characterize predictive factors for NTCP.

Introduction

The treatment of recurrent or new primary cancers within or in close proximity to previously irradiated tissue is a clinically challenging problem. Balancing the need to optimize tumor control while minimizing adverse effects is more difficult when dealing with prior radiation therapy.

Reirradiation in general

When considering re-irradiation (in general) for new or recurrent malignances, many factors are relevant to normal tissue complication probability (NTCP). These include, for the first and second courses of radiation therapy (Fig 1), the following.

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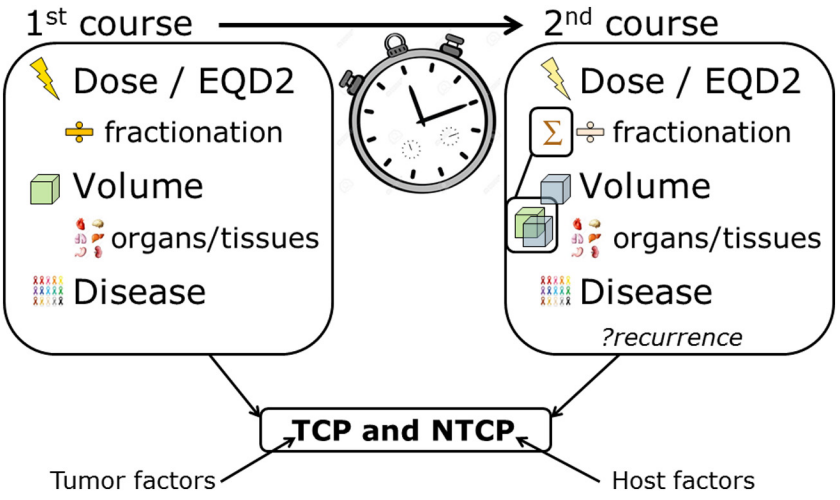

Figure 1 Factors potentially affecting NTCP and TCP in the setting of reirradiation. EQD2, equivalent dose in 2 Gy fractions; NTCP, normal tissue complication probability; TCP, tissue complication probability.

1. Disease treated with radiation therapy (ie, new primary cancer vs recurrence)
2. Total dose, dose fractionation, and biologically effective dose (BED); equivalent dose in 2 Gy fractions (EQD2) is intuitive to most clinicians.
3. Volume exposure to specific organ/tissues at given doses (ie, 3-dimensional dosimetric distribution)
4. Cumulative dose to normal tissue volumes (ie, dose-volume overlap)
5. Functional status of irradiated organ(s)
6. Time interval between radiation therapy courses

In addition to NTCP, tumor control probability (TCP) is also likely affected by items 1 through 3, specifically the retreatment radiation dosimetry, as well as clinical scenario of new versus recurrent disease.

There are many uncertainties in implementing these factors in clinical practice. First, it remains unclear how to add doses from different dose-fractionation schedules. Although the linear-quadratic (LQ) model is used to predict EQD2, its utility in predicting normal tissue response after high fractional doses is unknown. The LQ model was derived from in vitro cell survival assays of cancer cell lines and may not accurately predict in vivo NTCP, for which alteration and/or injury of various cell types is relevant.[1] Even accepting the LQ model, the optimal alpha-beta ratio for each normal tissue is unknown. Also poorly understood are potential tumor and host factors (ie, genomic susceptibility, comorbidities) that could potentially affect NTCP or TCP, particularly in reirradiation settings.

Repair of radiation-induced injury occurs over time; however, the extent and kinetics of repair, and whether such repair saturates after a specific duration (which would likely be organ/tissue dependent), are poorly understood. In a study of rhesus monkeys undergoing 2 radiation courses to the spine (44 Gy followed by 57 Gy at 1-2 years or 66 Gy at 2-3 years), <10% developed paralysis, suggesting repair of occult spinal cord injury in the intervening years.[2,3] Data on spine reirradiation in humans are well-summarized in the Quantitative Analysis of Normal Tissue Effects in the Clinic review,[4] which also described ~25% repair of occult spinal cord injury after 6 months.

SBRT

Stereotactic body radiation therapy (SBRT), also called stereotactic ablative body radiation therapy (SABR), uses novel technologies to more accurately localize radiation therapy targets and deliver ablative radiation therapy doses. Targeting accuracy minimizes setup uncertainty and allows for relatively tighter planning target volume (PTV) margins (vs what one would potentially use without stereotactic/image guided techniques). By reducing volumes of high-dose exposure to normal tissues, NTCP can potentially be reduced, despite high fractional dose delivery (which is classically associated with late effects).

SBRT planning and delivery generally use multiple noncoplanar and/or arcing fields. As a result, dose gradients are steeper than with conventional radiation therapy; maximum doses are appreciably greater than peripheral target doses. This dose gradient also reduces volumes of normal tissue receiving excessive toxic doses. This combination of targeting accuracy and steep dose gradients facilitates ablative radiation therapy dose delivery.

SBRT is an effective, minimally invasive therapy that, for previously unirradiated early-stage non-small cell lung cancer (NSCLC) and lung oligometastases, is associated with relatively high tumor control rates and low toxicity risks. SBRT is also well suited for reirradiation. With tighter PTV margins, the overlap with prior radiation therapy fields can be minimized, thus diminishing NTCP. SBRT also enables relatively high BED delivery, potentially augmenting TCP. Furthermore, SBRT might elicit different