



# Doses, fractionations, constraints for stereotactic radiotherapy

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## ABSTRACT

This paper describes how to select the most appropriate stereotactic radiotherapy (SRT) dose and fractionation scheme according to lesion size and site, organs at risk (OARs) proximity and the biological effective dose. In single-dose SRT, 15–34 Gy are generally used while in fractionated SRT 30 and 75 Gy in 2–5 fractions are administered.

The ICRU Report No. 91, which is specifically dedicated to SRT treatments, provided indications for dose prescription (with its definition and essential steps), dose delivery and optimal coverage which was defined as the best planning target volume coverage that can be obtained in the irradiated district. Calculation algorithms and OARs dose constraints are provided as well as treatment planning system characteristics, suggested beam energy and multileaf collimator leaf size. Finally, parameters for irradiation geometry and plan quality are also reported.

**Key words:** stereotactic radiotherapy; hypofractionation; dose prescription; dose delivery; target coverage; calculation algorithms; dose constraints; radiosurgery

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## Introduction

Stereotactic radiotherapy (SRT) is a therapeutic option with potential long term disease control and low toxicity profile: the most appropriate indications are rapidly expanding and included oligometastatic disease, recently classified in different clinical scenarios, i.e. oligo-recurrence, oligo-progression and oligo-persistence, depending on whether it was diagnosed during a treatment-free interval or active systemic therapy or whether it progressed on current imaging [1]. In order to achieve the disease control, while reducing the risk of toxicity and complications, SRT dose and fractionation schemes vary according to lesion size and site, organs at

risk (OARs) proximity and the biological effective dose of each treatment schedule. Furthermore, SRT requires special care in prescribing, recording and reporting. All these aspects are analyzed in the present paper.

## State of the Art

Aim of SRT is to ensure highly conformal dose distributions in the target volume and a minimal normal-tissue irradiation [2]. The most appropriate dose and fractionation in SRT are selected by considering lesion size and site, OARs proximity and the biological effective dose. In single-dose SRT, 15–34 Gy are generally used, while in fractionated

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SRT 30 and 75 Gy in 2–5 fractions are administered [3]. To identify the maximum tolerated dose and achieve at least 90% probability of tumor control, dose escalation studies were conducted on different primary tumors and diverse metastatic sites [4–9]. The dose was prescribed at  $\leq 80\%$  isodoses, with hot spots of up to 150% of the prescription dose within the target to improve the dose gradient immediately outside the target and spare OARs [10, 11]. Target dose heterogeneity and hot spots aid in eradicating hypoxic cells which are more likely to be found in the central part of the tumor [12].

ICRU Report No. 91 defined dose prescription for SRT as “the dose delivered to the outer edge of the planning target volume (PTV) or the surface isodose that is more conformed to the PTV surface as a percentage of the maximum dose, sparing adjacent OARs” [13] and stated it must include the following steps:

1. Definition of planning objectives: OARs dose limits should be well defined for each Center and complied with.
2. Planning and optimization: planning objectives should be prioritized.
3. Final prescription with treatment plan approval: the absorbed dose must be prescribed to the isodose surface ( $D_v$ ) that covers an optimal percentage volume of the PTV, while optimally saving the planning organ at risk volume (PRV).

Optimal coverage means the best PTV coverage that can be obtained in the irradiated district. For example, the prescription may be close to 100% for a 1.5 cm<sup>3</sup> brain metastasis but above 85% for a vertebral metastasis may not comply with spinal cord limits [13].

The treatment planning system (TPS) should include at least one calculation algorithm such as the superposition/convolution, the analytical anisotropic (AAA) or the Monte Carlo which is particularly useful when the beams cross an interface between tissues like the lung and bone that have significant electronic density differences. Using multiple fields provides a high dose gradient with a dose drop and isotropic, uniform distribution which is essential, for example, with adjacent OARs in series [14]. The TPS should be able to process intensity modulated radiotherapy (IMRT) plans with static or dynamic fields, or with arc or volumetric techniques.

Beam energy and multileaf collimator (MLC) leaf size influence the dose gradient. For small

beams, as used in SRT, the greater the energy, the greater the penumbra. 6 MV photon beams offer a reasonable compromise between penetration capacity and penumbra. Although 5 mm leaves are adequate for most treatments, 3 mm leaves are better when lesions are under 3 mm [15–19]. Essential for defining irradiation geometry are dose distribution, OARs sparing, mechanical constraints and incoming beam path. In general, the more beams, the better compliance and the greater the dose gradient [20–25].

Plan quality is assessed by means of parameters related to target dose distribution, dose homogeneity, dose limits for OARs, dose outside the target and the healthy tissue volume that is exposed to low doses. Dose limits for healthy tissues are significantly different in SRT and conventional radiotherapy [26]. Healthy tissue tolerance of radiotherapy and, therefore, the risk of toxicity, depends on many factors, principally:

- total dose and dose per fraction;
- fractionation;
- volume;
- type of expected complications;
- expected follow-up time;
- estimated risk of complication.

Emami et al. [27] reported the minimum and maximum tolerance doses for 5-year toxicity risks not exceeding 5% and 50% for twenty-five OARs. Their findings were updated in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [28]. Unfortunately, few data are available on sequelae with such a long follow-up after SRT treatments. Several publications, including RTOG studies, reported different constraints for OARs [29–34] and those in the Report 101 of the American Association of Physicists in Medicine (AAPM) were most adopted [19], as they indicated the maximum dose and threshold limits for various OARs in a single or multiple fraction (3 or 5) SRT. For example, in single dose SRT to the spinal cord, the maximum dose is 14 Gy, the threshold dose is 10 Gy at under 0.35 cm<sup>3</sup> and 7 Gy at under 1.2 cm<sup>3</sup>.

Risk maps of DVH, containing a subplot for each specific OARs volume [26], assembled and summarized all data on constraints to enable stratified risk comparisons as a function of dose, fractionation and volume [6, 35–48]. They integrated and updated the Report AAPM 101 constraints. For

example, when central pulmonary lesions were irradiated with 50 Gy in 5-fractions, about 50% risk of radiological occlusion was reported with 0.5 cm<sup>3</sup> segmental bronchus volume. With maximum doses of 55 Gy to intermediate bronchi and 65 Gy to the main bronchi, there was a 50% risk of developing a grade 1 radiological stenosis [42].

The British consensus on SRT constraints partly adopted the AAPM 101 dose limits, integrating them with more recent data [49].

ICRU report No. 91 suggested the following parameters for plan reporting:

- PTV: D50% (median absorbed dose), Dnear-max (which for a PTV = 2 cm<sup>3</sup> corresponds to D2%), Dnear-min (which for a PTV = 2 cm<sup>3</sup> corresponds to D98%);
- clinical target volume (CTV): D50%;
- OARs: maximum, average and minimum dose.

In addition to the prescription dose, ICRU reference point, number of sessions and total treatment time, some RT centers also report:

- target coverage;
- conformity index;
- drop in dose outside the target, e.g. the ratio between 50% volume of the prescription isodose divided by the PTV;
- heterogeneity index: the ratio between the highest dose received by 5% of the PTV and the lowest one received by 95% of the PTV;
- high dose areas outside the PTV;
- dose to OARs: 1% and 5% of the volume and average dose [19, 50, 51].

## Conclusions

As radiation oncologists are adopting SRT more and more often in their daily clinical practice, this non-systematic review aims at giving instruments for its use and administration, considering the risks of toxicity. Dose prescription and delivery are described with indications for reference reports, such as calculation algorithms, and OARs dose constraints. As the latter topic is a critical issue, it was recently explored in depth in two excellent review articles [52, 53], the first one focusing on lung SRT [52] and the other one in OARs dose constraints adopted in 53 ongoing clinical trials of SRT in different body areas. A variability in OARs dose constraints emerged, which suggested future research in order to reach a standardization.

## Conflicts of interest

The authors have no conflict of interest to declare.

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