On the dose to a moving target in stereotactic ablative body radiotherapy to lung tumors

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Abstract. This review summarizes the hierarchy of potential dose inaccuracies in lung SABR in terms of their expected clinical impact. The two main terms are targeting accuracy and adequacy of the dose calculation algorithm. One can associate dose-errors at the 50-100% (zero order) and 10-20% (first order) levels with the former and the latter, respectively. At the first order level, strong evidence exists that using dose algorithms which do not account for 3D density scaling is associated with diminished local control. On the other hand, the second-order target dose-errors due to either static approximations to full 4D calculations, or interplay during modulated delivery, are rather unlikely to rise above 5% (conservatively, $\leq$ 1% tumor control probability change).

1. Introduction

To be effective, precision radiotherapy must take target motion into account. Motion management is even more important in stereotactic ablative body radiotherapy (SABR), where hypofractionated high dose is delivered with tight margins to small targets [1]. The SABR in lung poses particular dosimetric challenges because of the often substantial differences in density between the tumor and surrounding normal lung tissue. This leads to the loss of commutative invariance between the fluence/motion and fluence/dose convolution steps [2], thus requiring, at least in theory, full four-dimensional (4D) dose calculations with deformable image registration (DIR) [3]. In this review, we attempt to systematically quantify the effects of various simplifications and approximations to this ideal 4D dose calculation, and correlate them with clinical outcomes.

2. Dose-errors hierarchy

2.1. Geographical miss

The first and obvious effect of the patient or target motion is the possibility of a blatant geographical miss. We will consider it self-evident that poor targeting (>50% dose-error to at least a portion of the tumor) would lead to inferior clinical outcomes. Listed in the order of sophistication, which also roughly corresponds to the chronological order of introduction, the motion management methods include: external immobilization and patient position monitoring; tumor motion assessment at simulation (fluoroscopy or 4D CT) and its incorporation into the internal and planning target volumes (ITV and PTV); daily image

guidance (IGRT); surrogate-based gating; and real-time direct image-guidance / tumour tracking [4, 5]. We will consider adequate targeting the zero-order term of the dosimetric accuracy hierarchy, similarly to an expansion series.

2.2. Calculation algorithms: correlation with SABR outcomes

The next (first-order) term in our accuracy construct is the fidelity of the calculation algorithm. The challenges of dose calculations in low-density tissue such as lung are well documented [6]. It is furthermore established that the only algorithms producing reasonably accurate results in lung are those explicitly taking the lateral change in tissue density (and resulting changes in the dose-deposition kernel) into account ("type b" models by Knöös et al [7]). While it was clear that without the inhomogeneity corrections, or with only 1D correction, the planned dose was misleading, in the pre-SABR era direct clinical correlation between the accuracy of the TPS algorithm and local control was not particularly easy to establish. It was due partly to the generally poor tumor control, and partly to the fact that the cooperative groups were using dose metrics and monitor unit settings based on the homogeneous datasets, extending this practice even into the earlier SABR studies [8]. In retrospective analysis by Xiao et al [8], after recalculating the unit-density plans with the heterogeneity-corrected convolution/superposition algorithms for the RTOG 0236 SABR protocol, the PTV volume receiving the prescription dose decreased on average by 10%.

The advent of SABR allowed for better direct correlation of the TPS accuracy with local control. A confluence of several factors is responsible for that. Local control rates are generally high (i.e. weighted average of 90% for Stage I from the review by Solda et al [9]), and failures were therefore visible and piqued the researchers' interest. As growing evidence of the dose-response relationship was being reported, it was not lost on the interested physicists that a small near-unit density tumor in the middle of the low density lung tissue was an ideal setup for the 1D density-correction algorithms to fail rather dramatically ([10] is just one of many examples). In addition, it was reasonably easy to geographically correlate local failures with dosimetric deficiencies [11, 12].

A study by Liu et al [12] of 77 patients with median follow-up of 13.4 mo found that with all other parameters being equal, the patients treated with the CyberKnife based on the equivalent path length calculations had diminished local control compared to the Monte Carlo-calculated cohort treated to the same nominal biologically equivalent doses (BEDs). A larger study by Latifi et al [10] involved 201 patients (23 mo median follow-up) whose plans were calculated with either Pencil Beam (PB) or Collapsed Cone Convolution (CCC) algorithms to the same nominal physical dose (10 Gy×5). Crude local recurrence rates were 21.5% vs. 4.7% in the PB and CCC cohorts, respectively, and the hazard ratio difference was statistically significant by Gray's competing risks analysis. The PB cohort was treated very similarly to the prior smaller study by Videtic et al [13], yet demonstrated diminished local control (78 vs. >93%). While not definitively explained, the comparison results are consistent with the idea that a dose regimen of 50 Gy in 5 fractions to 95% of the PTV is right at the cusp of the BED adequate for local control (100 Gy, [14, 15]).

Based on the combination of dosimetric correlations in the cited papers, we will conservatively assume that the suboptimal planning algorithm introduces a clinically significant dosimetric error of ≥10%, and that will quantify the first-order term in the error hierarchy.

2.3. Second-order effects

The remaining task is to establish the clinical significance of the second-order terms in our dose-error expansion series. The most straightforward approach is to find the gradient of the tumor control probability (TCP) curve, and compare it to the magnitude of dose-errors characteristic of the second-order effects. To that end, we numerically differentiated three original and compiled [12, 16] TCP vs. BED ($\alpha/\beta = 10$) curves. The steepest derivative at 100 Gy BED showed a ~0.2% change in TCP per 1 Gy (1%). Therefore a

5% target underdosage corresponds to 1% TCP loss, which we will conservatively consider the threshold of clinical significance around 100 Gy BED. The threshold will be even higher for the more robust dose-fractionation schemes [17]. The question then becomes if the effects of various approximations to the full 4D calculations, and/or possible interplay consequences, could rise above the threshold of clinical importance.

2.3.1. Approximations to full 4D calculations. The first step is elimination of the dose calculation on every phase, which could be time-consuming, particularly for VMAT treatments. Glide-Hurst et al [18] established feasibility of this approach by performing the dose calculation on an average CT, while still using DIR for target dose accumulation throughout the breathing cycle. The largest singular discrepancy between the simplified and full 4D calculations in the relevant gross tumor volume (GTV) dosimetric indices was -2.4% (D_1 in one plan), with the vast majority well under 1%. While DIR software packages are relatively widely available by now, the method introduces additional steps and its own uncertainties [19]. The next step, elimination of DIR, was explored by Rao et al [20]. With a simple 3D calculation on a single respiratory phase, the average and maximum differences from a full 4D approach for the GTV D_{99} did not exceed 1.2 and 2.4%, respectively. Similar conclusions were reached by Admiraal et al [21]. Both the 3D and 4D dose calculations on a deformable phantom agreed with measurements in the GTV, and the differences were observed primarily at the edges of the PTV [22]. That error can be further remedied by intelligent CT density overrides [23]. A somewhat different approach to circumventing the need for DIR in lung was examined by Zhang et al [24]. It relies on the concept of motion-weighted clinical target volume (mwCTV), which carries more 4D information into planning than the 3D internal target volume (ITV) method. This solution allows, in principle, plan optimization based on occupancy weighting of the CTV, and generation of motion-weighted DVHs (mwDVH) that approximate the DVHs (but not the dose distribution) of the full 4D dose accumulation. The percentage of the CTV volume covered by the prescription dose differed on average by only 0.3±0.7% between the mwDVH and full 4D calculations, which was statistically less than for 3D/ITV calculations.

2.3.2. Interplay. In brief, point dose measurements [25] tend to over-emphasize the importance of the interplay between target motion and radiation fluence modulated in space and time, while full 3D calculations [20] or measurement-guided reconstruction [26] indicate that the important target DVH parameters are not substantially affected. Overall, the magnitudes of target dose-errors due to either 3D calculation approximations or interplay during delivery are rather unlikely to rise above 5% (1% TCP change).

3. Conclusions
Clinical evidence exists that using less accurate, 1D heterogeneity corrections is associated with diminished local control in lung SABR. The second order effects, such as static approximations to 4D dose calculations and potential interplay during modulated deliveries, do not appear likely to affect local control.

4. References
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