Margins Matter: current radiation therapy practice and future directions

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This issue of the Journal of Medical Radiation Sciences includes two studies where radiation therapy clinical tumour volume (CTV)-to-planning tumour volume (PTV) margins have been evaluated or calculated. Oates et al.1 evaluated the adequacy of CTV-PTV margins used for prostate cancer patients treated with image-guided radiation therapy (IGRT) by assessing geographical miss on post-treatment cone-beam computed tomography (CBCT) images. Lin et al.2 evaluated the efficacy of three head and neck (HN) stabilisation systems using CBCT-planning CT image registrations to determine setup displacements and calculate device-specific margins. Both studies demonstrate the use of CBCT images for purposes other than the correction of daily setup errors during online IGRT. Both studies exploit CBCT’s ability to more completely assess tumour and organ at risk (OAR) inter-fraction volume variation, in order to retrospectively calculate or assess a radiation therapy margin.

The International Commission on Radiation Units and Measurements (ICRU) Report 833 was published in 2010 in response to the advent of and wider clinical implementation of intensity modulated radiation therapy. It provides an excellent discussion on the evolution of PTV and planning risk volume (PRV) margins, including how ICRU Report 50 first described and defined various volumes that were necessary to create a PTV for 3D conformal radiation therapy. Most importantly, ICRU Report 83 reiterates the concept that the many factors contributing to overall geometric uncertainty should be reflected in the final PTV or PRV margin used, and that these should be cancer site and equipment specific. The PTV margin expansion on the CTV, or the internal target volume (ITV) where relevant, should include all sources of systematic and random setup errors. PRV margin expansions on OARs are specifically recommended for serial structures such as the spinal cord, to account for variation in position and size and are typically applied to OARs in HN treatments.4 The consequence of inadequate PTV margins is the increased risk of treatment failure due to insufficient dose to the tumour when it is not encompassed by the treatment fields, while excessive PTV or inadequate PRV margins risk increasing treatment toxicity.

Various formulae have been proposed for calculating population-based expansion margins,3 with van Herk’s5 margin formula widely adopted to calculate PTV margins. Van Herk’s formula is expressed as a weighted function of the total systematic ($\Sigma$) and random errors ($\sigma$) where the calculated margin will deliver 95% of the prescribed dose to the CTV for 90% of patients (eq. 1).

$$\text{PTV margin} = 2.5\Sigma + 0.7\sigma \quad (1)$$

$\Sigma$ and $\sigma$ are determined by combining the standard deviations of all the systematic and random errors respectively. Van Herk’s formula reflects the significant impact of systematic (or treatment preparation) errors as they will result in a geometric miss of the CTV that will occur for all treatment fractions. Random (or treatment execution) errors will vary in magnitude and direction for each treatment fraction, lowering or ‘blurring’ the dose at the outside edges of the PTV. The sources of geometric uncertainty contributing to systematic errors include GTV localisation errors during treatment planning associated with organ motion, image quality, image registration, and observer contouring variation. Tumour volume (TV) inter-fraction variation, intra-fraction organ motion and the precision of the technology used during treatment delivery contribute to random errors. IGRT has facilitated the reduction in PTV and PRV margins as fractional variation in the TV and OARs is able to be corrected for via pre-treatment imaging, which was not possible when the alignment of the isocentre lasers with external skin marks was the sole means of targeting treatment fields.
Lin et al² used van Herk’s formula to calculate margins based on setup errors derived from registration of structures proximal to the nasopharyngeal region, as well as margins derived from the registration of the cervical spine. Based on their results, they propose the use of non-uniform (or anisotropic margins) as well as the use of a larger margin in the cervical region, due to a small but significant difference in stability between the cervical spine and the nasopharynx. They demonstrate how easily van Herk’s formula facilitates the calculation of anisotropic margins where setup uncertainties of anatomical sub-regions is variable. Lin et al² state that the margins calculated in their study would be the basis for the creation of device-specific margins. This reflects the fact that IGRT derived setup error calculations do not compensate for all of the possible sources of geometric uncertainty that must be considered when deriving a PTV margin. Lin et al’s² study also emphasises the importance for individual departments to be aware of site-specific and immobilisation device-specific set up variations when generating CTV-PTV expansions for their patients. This of course is paramount when moving toward extreme hypofractionation protocols. Lin et al² made no comment on the temporal change in stability of the cervical spine, difficult due to their use of weekly rather than daily CBCTs. Many nasopharynx patients and indeed other HN cancer patients have bulky nodal disease at presentation. This often responds to treatment resulting in changes to CTV volume and shape which in turn, may result in changes to cervical stability within the immobilisation device. Adaptive treatment planning in this situation has been shown to have dosimetric benefit and may impact on tumour control and toxicity.

Van Herk’s formula assumes that all errors, systematic and random are distributed normally and that the random error is the same across all patients.⁵ Herschtal et al⁶ have proposed a novel statistical approach to model individualised adaptive PTV margins for prostate cancer patients, building on their previous work demonstrating random errors caused by inter-fraction variations are better modelled using an inverse gamma distribution. Their method for creating individualised adaptive PTV margins uses a Bayesian statistical approach to facilitate the incorporation of accumulated displacement information from treated fractions to predict the magnitude of future displacements. Research using these types of mathematical methods is particularly important if personalised, rather than population based margins, and online adaptive radiation therapy are to be robustly implemented.

Oates et al⁷ discuss the role of individualised adaptive radiation therapy margins for patients with prostate cancer based on assessment of their department’s PTV margin. They used post-treatment CBCT to evaluate if a 6 mm posterior margin used for fiducial marker based IGRT is adequate. The prostate was contoured on the CBCT images, and subtracted from the PTV, to assess if any part of the prostate was not within the PTV, resulting in a geometrical miss. If geometric miss occurred, CTV expansions, increasing in 1 mm increments, were then created to determine the degree and direction of geometric miss. CT-based IGRT imaging allows for direct visualisation of tumours, and the assessment and correction of displacements, rotation and deformation of tumours and OARs. Oates et al¹ concluded that determining the random error component of a margin using applied translation data only, failed to account for the variability of organ rotation and deformation, and as a result the 6 mm posterior margin applied to the prostate was inadequate for some patients and fractions. However, it must be stated that the potential inter-observer variability in contouring the prostatic apex and base on CBCT, the areas most affected by rotation and on which the results are based, may have had a significant impact on results.

Using a post-treatment CBCT as a surrogate for prostate motion does not necessarily account for all intra-fraction movement. In prostate cancer treatment, studies utilising real-time fiducial tracking with either electromagnetic beacons⁷ (Calypso, Varian Medical Systems, Palo Alto, CA), or kilovoltage infra-fraction monitoring⁸ (KIM) of gold fiducials, show two patterns of motion related to changes in bladder and rectal filling; continuous drift and erratic drift. While these drifts do not affect all patients nor all fractions, they certainly impact on margin management. Litzenberg et al⁷ compared margins required for different image-guidance protocols and found PTV margins of 1.8 mm left/right, 5.8 mm anterior/posterior and 7.1 mm superior/inferior were required for pre-treatment setup corrections based on marker alignment compared to margins of 1.3 mm left/right, 1.5 mm anterior/posterior and 1.5 mm superior/inferior when continuous marker tracking with a 3 mm threshold for re-alignment during treatment was used. Oates et al¹ do question if the translational information utilised for beam gating in Calypso and KIM is able in all situations to detect rotational or deformation changes that may in turn compromise CTV coverage.

Volumetric imaging of intra-fraction motion in most departments is currently limited to 4D planning CT images, with limited 4D-CBCT capability. However technology such as the MRIdian System (ViewRay, Oakwood Village, OH), which integrates a 0.35 Tesla magnetic resonance imaging (MRI) scanner with three Cobalt-60 sources, and the hybrid MRI-linac, represents the newest approach to intra-fraction motion monitoring using cine-MRI. Robotic ultrasound image guidance
offers an alternative approach for volumetric intra-fraction monitoring that can be implemented on existing linear accelerator technology. The potential for 3D tracking during treatment, with beam gating and ultimately real-time adaptive re-planning will likely have a significant impact on CTV-PTV margins. As we look to the future, these new technologies, together with the potential for adaptive re-planning based on positron emission tomography (PET) and diffusion weighted MRI imaging of metabolic changes during treatment, will allow us to deliver truly personalised radiation treatment to our patients.

Conflicts of interest

There are no conflicts of interest.

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