Editorial

Uncertainties of cumulative dose assessment for prostate IMRT

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Intensity-modulated radiation therapy (IMRT) is capable of providing conformal doses to the target volume while minimizing doses to nearby normal tissue for radiotherapy of localized prostate cancer (1). However, the clinical gains of prostate IMRT may be limited by geometric uncertainties of a patient. The prostate movement between fractions, i.e., inter-fractional motion, is associated with patient setup uncertainty as well as internal organ displacement between fractions. The inter-fractional motion contributes to the deviation in the delivered doses to the target volume and organs at risk (OARs) (2). Depending on the filling state of the rectum and bladder, the prostate can move by more than 1 cm (3,4). Image guidance before each fraction can reduce these errors and deliver a precise prescription dose to the target volume while sparing doses to OARs. On the other hand, intra-fractional motion refers to the external patient movement as well as internal organ motion during the actual treatment. The major intra-fractional motion of the prostate gland is generally due to changes of gas in the rectum and surrounding digestive track (5). This temporal behavior of prostate motion can vary rapidly and substantially, which could result in large discrepancies between planned doses and actually delivered doses to a patient.

Inter- and intra-fractional variations of the prostate position, shape, and size have been traditionally compensated for by adding margins to the clinical target volume (CTV), generating the planning target volume (PTV). However, this compensation method increases the treatment volume and consequently increases normal tissue toxicity while limiting the tumor dose. Adaptive radiation therapy (ART) based on image guidance could compensate for the effect of patient-specific variation during the entire treatment process without increasing radiotherapy toxicity (6). Therefore, numerous studies on ART have been performed up to date (7-9). ART is the incorporation of daily images in the treatment process so that the treatment plan can be evaluated and modified to improve the precision of treatment. Clinical implementations of ART for prostate cancer have been greatly promoted by image guidance with on-board cone beam computed tomography (CBCT) (10-13). On-board CBCT allows the target volume and adjacent anatomies to be localized before treatment for a patient in treatment position. However, the image quality of CBCT in comparison to that of planning CT is insufficient to provide highly accurate delineation of structures and dose calculation due to higher scatter and lower mechanical stability (14,15). Furthermore, in the inhomogeneous regions, the inconsistency in the CT number to electron density curves between CT and CBCT images could result in a discrepancy in dose calculations (16). Nevertheless, dosimetric changes by inter-fractional errors were often evaluated by the deformable image registration (DIR) of CBCT to the planning CT. DIR is employed to establish a spatial correlation between images for contour propagation as well as dose accumulation. High soft-tissue

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contrast and low artifacts from the image are important aspects for providing accurate deformation registration (17). The accuracy of the DIR also affects the calculation of accumulated doses. Besides the DIR algorithm accuracy, there are inherent uncertainties related to the dose accumulation process of DIR since the DIR process is not one to one mapping of voxels between images. Although the issue on the dose accumulation uncertainty of DIR was recognized in the society of radiation therapy, no clear solution for the issue has been suggested.

Nassef *et al.* recently published results on the dosimetric uncertainty of dose accumulation in prostate IMRT using CBCT images, particularly for the bladder and rectum, which is the first report revealing dose accumulation uncertainty by eliminating the DIR uncertainty (18). They eliminate the DIR uncertainty using finite element method (FEM)-based numerical phantoms in order to analyze the dose accumulation uncertainty. A total of 16 phantom sets simulating plausible organ deformations during prostate IMRT were generated to calculate reference cumulated doses. They also acquired estimated cumulated doses with 24 patient cases with a conventional DIR-based method, which contained both the DIR uncertainty and the dose accumulation uncertainty. They found large differences between the planned and delivered doses as well as considerable dose accumulation uncertainty for the bladder during prostate IMRT. In the case of rectum, the differences between treatment plan and delivery as well as dose accumulation uncertainties were smaller than those of bladder. Moreover, they found high cumulated dose errors were localized in high dose gradient regions not in regions of high registration errors. Nassef *et al.* provided solid evidence that the inter-fractional variation in OARs is significant and causes considerable dose discrepancy for prostate IMRT. Assessment of dose accumulation uncertainty of DIR is not a total solution to perform successful ART. As mentioned above, a lot of issues should be solved for successful ART such as improvement of the CBCT image quality, more accurate DIR algorithm, consideration on the intra-fractional organ movements and so on. However, an evaluation of dose accumulation uncertainty of DIR is an important issue to be solved in order to achieve successful ART. Although these findings could not be directly applied to the current clinical practice of IMRT for prostate cancer, this study provides valuable information to the society. The methodology of this study could be extended to studies on the intra-fractional errors using 4D CT. Since intra-fractional dose accumulation could be achieved by DIR of each phase of 4D CT, the methodology by Nassef *et al.* to assess the dose accumulation uncertainty could also be applied to analyze intra-fractional dosimetric errors, which is more crucial for stereotactic ablative radiotherapy (SABR) or hypofractionated radiation therapy (19).

Currently, numerous studies explore real-time image guidance combined with gating or tracking techniques in order to compensate for the intra-fractional motions during treatment without adding margins. Similar to the approaches for ART, gating or tracking techniques also have inherent technical uncertainties, therefore, specific recommendations on those uncertainties should be established by further research. Ideally, every institution should establish its own uncertainty estimation for the treatment on the available imaging and treatment technologies as well as treatment strategies of the institution.

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