

Motivation for the inclusion of genetic risk factors of radiosensitivity alongside dosimetric and clinical parameters in predicting normal tissue effects

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To the Editor,

Two recent original research articles appearing in *Acta Oncologica* have further explored the correlation of dosimetric parameters with normal tissue toxicities [1,2]. Notably, considering the increase in the number of proton therapy centres worldwide, the comprehensive report by Indelicato et al. on proton therapy-induced brain stem necrosis in paediatric patients provides valuable clinician relevant insight for the treatment of such cases [1].

As discussed in both articles, the need to understand which parameters for a given treatment regimen contribute to radiation-induced normal tissue toxicities is an important task in attempting to prevent aberrant radiation-induced toxicities. The clinical significance of being able to identify and estimate patient-specific normal tissue damage risk will, in theory, allow for safer dose escalation in low-risk patient groups and dose reduction in higher risk groups.

Although dosimetric parameters have, in these instances, resulted in clinically meaningful guidelines, neither study has considered the confounding effects of clinical, dosimetric and biological parameters combined together into a single model. Without considering such effects, these studies have likely been unable to fully account for or identify the confounding biophysical effects which are induced by radiation therapy [3]. This is especially true in cases, such as brain or head and neck, where target volumes are surrounded by heterogeneous tissues or organs at risk which may have differing intrinsic radiosensitivities. These factors have likely contributed to the limited usefulness and predictive power of normal tissue complication probability (NTCP) models to date.

Several well-studied and robust modelling approaches exist to combine different types of relevant patient-specific data (namely, clinical and biological variables alongside standard QUANTEC recommended dosimetric parameters [4]). Examples

of such frameworks include the well-studied regression-based data-mining approach [5] or generalised versions of canonical analytical models [6]. These modelling frameworks are based on multi-metric analyses but do not necessarily exclude univariate parameters if found to correlate well with outcomes. As such, the frameworks serve as extensions of univariate statistics rather than substitutes.

Institutional works have previously reported increased performance by combining either clinical variables with dosimetry [7] or biological variables, such as polymorphisms, with dosimetry (radiogenomics) [8]. However, their sample sizes were modest and none were cross-validated. The former can likely be attributed to the cost associated with genotyping or sequencing for particular mutations in a large number of patients although this is expected to become less of an issue as more cost-effective alternatives are proposed [3].

Whilst more studies are required to corroborate the increased predictive performance of these mixed (clinical, biological and dosimetric) data-type models, their impact in the clinic could be substantial. Furthermore, proposed models for clinical implementation need to be rigorously cross-validated as they may eventually contribute to improved outcomes and higher quality of lives for patients.

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References

- [1] Indelicato DJ, Flampouri S, Rotondo RL, Bradley JA, Morris CG, Aldana PR, et al. Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. *Acta Oncol* 2014;53:1298–304.
- [2] Anderson NJ, Wada M, Schneider-Kolsky M, Rolfo M, Joon DL, Khoo V. Dose-volume response in acute dysphagia toxicity:

- Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy. *Acta Oncol* 2014;53:1305–11.
- [3] Kerns SL, Ostrer H, Rosenstein BS. Radiogenomics: Using genetics to identify cancer patients at risk for development of adverse effects following radiotherapy. *Cancer Discov* 2014; 4:155–65.
- [4] Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010;76(3 Suppl):S3–9.
- [5] Naqa IE, Deasy JO, Mu Y, Huang E, Hope AJ, Lindsay PE, et al. Datamining approaches for modeling tumor control probability. *Acta Oncol* 2010;49:1363–73.
- [6] Tucker SL, Dong L, Bosch WR, Michalski J, Winter K, Mohan R, et al. Late rectal toxicity on RTOG 94-06: Analysis using a mixture Lyman model. *Int J Radiat Oncol Biol Phys* 2010;78:1253–60.
- [7] Defraene G, Van den Bergh L, Al-Mamgani A, Haustermans K, Heemsbergen W, Van den Heuvel F, et al. The benefits of including clinical factors in rectal normal tissue complication probability modeling after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;82:1233–42.
- [8] Tucker SL, Li M, Xu T, Gomez D, Yuan X, Yu J, et al. Incorporating single-nucleotide polymorphisms into the Lyman model to improve prediction of radiation pneumonitis. *Int J Radiat Oncol Biol Phys* 2013;85:251–7.
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