Impact of geometrical uncertainties in stereotactic radiation therapy: risk assessment and clinical management

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In radiosurgery or stereotactic radiotherapy geometric inaccuracies are present throughout the treatment chain. Besides setup variability and intrafraction motion, geometric imperfections in treatment preparation, planning and dose delivery become relevant in stereotactic treatment. Their impact depends on the type of error (e.g. grand mean, systematic, random) and on technological treatment characteristics.

Current perspectives on the management of these geometrical uncertainties range between two extremes: the radiosurgery perspective (single fraction, ablative dose, no margins) and the radiotherapy perspective (hypo-fractionated, high dose, PTV/PRV margin). Various combinations of and adaptations on these perspectives are described in the literature. Additional considerations that influence the management of geometric uncertainties include: disease site, tumor type, treatment intent, treatment risk, radiobiology, clinical experience etc. In practice, the ways in which geometric uncertainties are accounted for vary per institute, per tumor (group) and even per patient; partly because of actual differences in geometric treatment characteristics and partly as a result of different views.

Consistent management of geometric uncertainties within and across institutes is important for 1. establishing accurate dose-effect relations, 2. an unambiguous relationship between technology advancement and margin reduction or dose prescription for optimal treatment. Therefore, a unified perspective on geometric accuracy (within) radiosurgery and stereotactic radiotherapy is warranted. By reviewing and comparing the different views, management and nature of geometric uncertainties in the chains of radiosurgery and stereotactic radiotherapy, we aim to contribute to such a unified perspective.

Impact of geometrical uncertainties in extreme hypo with brachytherapy

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This presentation will include an overview of dosimetric uncertainties in interstitial/intracavitary brachytherapy and summarize the current state of our knowledge on the most dominant components for the total dosimetric uncertainties for specific types of BT.

The impact of different systematic and random dosimetric uncertainties, caused by geometrical inter- and intra-fraction variations between BT applicator and organ positions, on the reported total dose (EQD2 for EBRT-HDR brachytherapy) depends on the fractionation schedule applied. Examples for the effect of reported uncertainties on different high dose rate fractionation schedules will include prostate and gynaecological BT.

As the analysis of dose-response relationships depends on the reported total treatment doses, large systematic or random dosimetric uncertainties for BT will have a significant influence on the accuracy of outcome prediction. Based on recent literature, e.g. on inter-fraction variations during BT, and morbidity studies, the effect of uncertainties on the assessment of response probabilities for OARs can be estimated.

Based on this discussion it might be possible to develop strategies for reducing uncertainties for dose planning and delivery in the future and therefore widen the therapeutic window.

Unexpected and under-estimated late toxicities with hypo-fractionation

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New radiobiology for severe/extreme hypo: abandoning the LQ model or integrating it ?

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A massive amount of experimental work in the 1970’s and 80’s on many models of normal-tissue injury in rodents and pigs, showed that “-ln(Surviving Fraction)” is best described by a second-order polynomial in dose, the well-known Linear-Quadratic (LQ) equation. That LQ description has since been thoroughly tested in the clinical domain, but almost always in the ”conventional” range of dose per fraction below 6 Gy. LQ is the simplest mathematical description of a non-linear relationship and though empirical in nature, it has nevertheless been subject to many attempts to connect with our understanding of how radiation injury is produced and repaired at the cell and molecular level. Yet any meaningful and clinically useful link in this respect has remained elusive.

LQ deals specifically with the relationship between total dose and dose per fraction, and with interfraction interval using the Incomplete-Repair derivative model. The relationship between total dose and overall treatment time is an even more complex relationship dependent on the different underlying radiobiology of different tissues even within the apparently same category of early-reacting or late-reacting tissues, distinguished by respectively a “high” or “low” ratio of $\alpha/\beta$ in the LQ equation. Overall time is therefore better handled independently of LQ.

A straightforward but untested hypothesis for the different $\alpha/\beta$ values for early- and late-reacting tissues, is that a naturally low $\alpha/B$ for a target cell population is smoothed out to a higher value as the sum of the responses of different proliferative subpopulations, and different phases of the cell cycle that these are in. This explanation could be applied to the responses of malignancies in the lung and head and neck, also adding in the additional response variation of cells at various levels of hypoxia in these sites. Of note is the connection between outcome of radiotherapy and HPV status in oropharyngeal cancers, which implies a possible difference in treatment strategy between these tumor subtypes and could also explain the high $\alpha/\beta$ of head and neck cancer overall as the sum of the responses of the different cancer subtypes (HPV+ and -) which could both have low $\alpha/\beta$ but different radiosensitivity. In some malignancies, notably prostate and breast, clinical data do indeed indicate a low