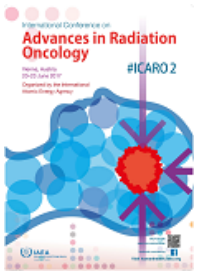

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Radiobiological modeling and treatment planning for sequential and concurrent combination of internal and external radiotherapy modalities

Thursday, June 22, 2017 10:40 AM (5 minutes)

The use of therapeutic schemes combining external beams radiotherapy (ERT) with internal radiotherapy (IRT) using radiopharmaceuticals could be a promising alternative for patients with multiple lesions or those where treatment planning maybe difficult to fulfill the organ(s)-at-risk (OARs) dose constraints. Since the temporal and spatial patterns and levels of dose delivering are different, these issues should be regarded for any formulation developed with the goal of biological evaluation or ranking in the treatment effectiveness. It has been further recommended the use of dose-response magnitude like Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) for biological treatment planning or for evaluation of prescriptions. In this work is evaluated an extension of LQ model for radiobiological evaluation of CIERT treatments through the calculation of TCP and NTCP. On the other hand, it was studied how this formulation could be used to determine the CIERT conditions: administered activity, number of administrations for IRT as well as the dose per session and number of session for ERT that produce an iso-effective response. The results of calculations for several simulated clinical situations are also shown.
The synergistic effects of combined irradiation were studied through the calculation of the Biologically Effective Dose (BED) adapting the LQ model for CIERT schemes. For IRT the dose rate was considered as multi-exponentially variable in time. For external radiotherapy was considered the standard fractioning of 2Gy per session with complete repair between fractions. Two conditions were regarded: (a) *sequential CIERT* (sCIERT): each irradiation is carried out one after the other one regardless the order and both separated by an interval t and (b) *concurrent CIERT* (cCIERT): both irradiations will be given at the same time. It was considered that external irradiation is delivered in the course of a single administration of radiopharmaceutical. The calculation considered the probability of lethal damage produced due to cross-interaction of sub-lethal damages produced by IRT and ERT.

Dose spatial distributions in tumor (PTV) and OARs with different heterogeneity degree were considered. For three-dimensional dose distributions the calculations must be done for each voxel in the Volume of Interest (VoI). For IRT was considered that all voxels, either PTVs or OARs have the same rate constants (uptake and elimination). The biological effect of the heterogeneity in the dose distribution into the VoI was evaluated by the calculation of the Uniform Dose Equivalent Biologically Effective (EUBED).
The formulation was extended to the case of IRT with multiple administrations of the therapeutic radiopharmaceutical considering the interval between two successive administrations is such that accumulation is not observed. However, it should be noted that in case of cCIERT the combination must happen in the course of a single administration like it was previously supposed in the BED calculations. It was supposed that the same administered activity in each IRT session and no further changes will occurs in the radiopharmaceutical biodistribution (the uptake fractions will remained almost constant).

Iso-effective figures were calculated for the different conditions tested like comparing the feasibility of therapy schemes with IRT or ERT alone and CIERT (sequential or concurrent). The input variables are: administered activity per session and number of administrations for IRT and dose per session and number of sessions for external radiotherapy.

The TCP(D) (Poisson) and NTCP(D) (LKB) profiles were built considering the effects due to the heterogeneity in dose distribution, the radiosensitivity in the tumor irradiated volume and the OAR´s volume irradiation fraction.

The synergetic effects of CIERT schemes were more observable in normal tissue (alpha/beta=3Gy) than tumors (alpha/beta =10Gy). It was also dependent of radiobiological parameters and its heterogeneity degree. This could be important if hypo-fractionated ERT is planned to be used as part of combination. The radiopharmaceutical biokinetics was also relevant. Special care should be taken if high uptake of radiopharmaceutical is observed in critical tissues near to the irradiated target. This situation must be carefully evaluated for those cases where the CIERT schemes might be a feasible alternative when the tolerance level constraints in all OARs involved are not fulfilled during the treatment planning using ERT alone.

Conclusions
The formulation developed could be used for the validation of treatment prescription in case of CIERT for sequential and concurrent scenarios. The inclusion of variability of LQ parameters in the calculation of TCP and NTCP must be taken into account because the curves will changes. It must be noted that in the case of cCIERT, the time interval between administrations should be chosen so that the combination of treatments occurs only in one IRT session what is dependent of biokinetics parameters of radiopharmaceutical. The formulation will allows also the planning and may be useful for optimization when conformal boosting using targeted molecular radiotherapy with radiopharmaceuticals might be a good alternative.

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