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Radiobiological concepts for treatment planning of schemes that combines external beam radiotherapy and systemic targeted radiotherapy

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ABSTRACT

The combination of radiotherapy modalities with external bundles and systemic radiotherapy (CIERT) could be a reliable alternative for patients with multiple lesions or those where treatment planning maybe difficult because organ(s)-at-risk (OARs) constraints. Radiobiological models should have the capacity for predicting the biological irradiation response considering the differences in the temporal pattern of dose delivering in both modalities. Two CIERT scenarios were studied: *sequential combination* in which one modality is executed following the other one and *concurrent combination* when both modalities are running simultaneously. Expressions are provided for calculation of the dose-response magnitudes Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). General results on radiobiological modeling using the linear-quadratic (LQ) model are also discussed. Inter-subject variation of radiosensitivity and volume irradiation effect in CIERT are studied. OARs should be under control during the planning in concurrent CIERT treatment as the administered activity is increased. The formulation presented here may be used for biological evaluation of prescriptions and biological treatment planning of CIERT schemes in clinical situation.

1. Introduction

The combination of different therapy modalities like surgery, internal and external radiotherapy and chemotherapy has been frequently used in order to enhance the cancer treatments outcomes. The therapeutic schemes which combine the external beams radiotherapy (EBRT) with the systemic targeted radiotherapy (STRT) is often denominated as CIERT. This therapeutic scheme could be an alternative for patients with multiple lesions or those cases where treatment planning might be difficult due to the constraints imposed by the organ(s)-at-risk (OARs). The EBRT is performed by local external irradiation using photon or charged particle beams. Complex irradiation techniques like stereotactic body radiotherapy (SBRT) or intensity modulated radiation therapy (IMRT) could be used. The STRT is done using radiolabeled monoclonal antibodies like radioimmunotherapy (RIT) or peptide receptor radionuclide therapy (PRRT). Some papers have been published on applications of CIERT either in clinical trials [1–3] or pre-clinical researches [4,5]. The helpfulness of biological planning methods in radiotherapy has been mentioned in AAPM task group 166 report [6]. The calculation of Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) is one of way used when biological treatment planning methods are applied. Since the temporal, spatial patterns and levels of dose delivery for both modalities are different these issues should be regarded for any formulation developed for biological evaluation of CIERT effectiveness. The concept of the biologically effective dose (BED) through the formulation of linear-quadratic model (LQ) have been widely used for the comparison of different irradiation schemes that produce iso-effective responses [7]. A formulation for the calculation of TCP and NTCP based on the use of LQ model for CIERT treatment schemes is presented. The possible synergistic effects of the EBRT - STRT combinations given sequentially or simultaneously considering the influence of the heterogeneity of the spatial distributions of the absorbed dose, the type of tissue irradiation response and treatment parameters such as the activity injected in STRT and the number of sessions in EBRT.

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2. Material and methods

2.1. Adapting the linear-quadratic (LQ) model for calculation of the biologically effective dose (BED) for CIERT

The BED distribution at voxel level for each modality must be calculated in the volume of interest (VoI) either for the OARs and tumors. In accordance with the LQ model, the BED at the ijk-th voxel could be calculated by:

$$BED_{ijk}=\mathrm{D}_{ijk}\left[1+g_{ijk}(\mu,\dot{D}_{ijk}(t))\frac{D_{ijk}}{\alpha/\beta}\right] \tag{1.1}$$

$$g_{ijk}(\mu,\dot{D}_{ijk}(t))=\frac{2}{D_{ijk}^2}\left\{\int_0^{\infty}\dot{D}_{ijk}(t)\int_0^{t}\dot{D}_{ijk}(\tau)e^{-\mu(t-\tau)}d\tau dt\right\} \tag{1.2}$$

where μ (h^{-1}) is the damage repair rate which is related to the damage repair time by $\mu = 0.693/T_{repair}$; (T_{repair}=1.5h), $\dot{D}_{ijk}(t)$ (cG/h) is the dose rate function for the ijk-th voxel. Two conditions have been regarded: (a) *sequential combination* (sCIERT) and (b) *concurrent combination* (cCIERT). The sCIERT will represent the scheme where one irradiation modality is carried out after the other one, both separated by an interval Δt (h). It should be noted that the interval between STRT and EBRT is large, such that there is no interaction between sub-lethal damages produced by each modality. The cCIERT consider the irradiation scheme where the two modalities are performed simultaneously. The Fig. 1 graphs an example of dose rate time profiles for each CIERT scheme considered.

In the case of cCIERT the dose rate function can be represented by the sum of contribution from each modality:

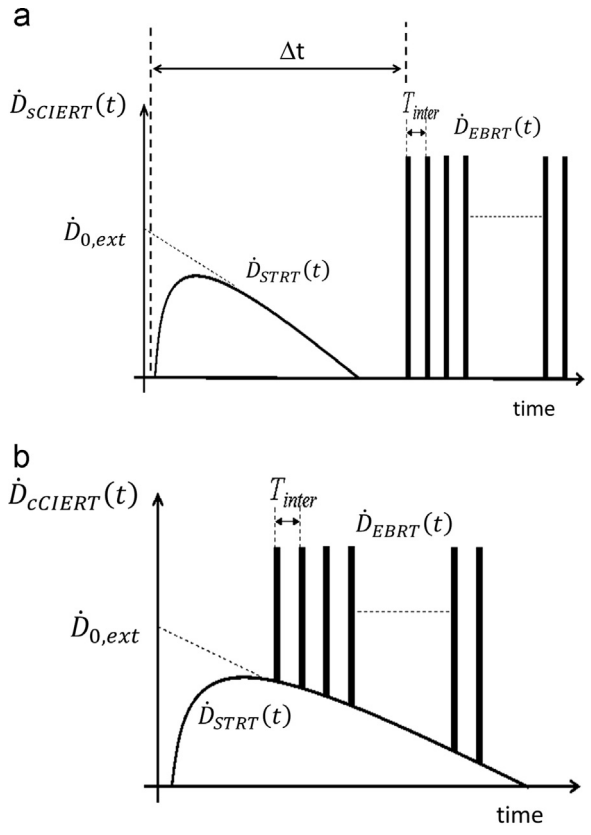

Fig. 1. Dose rate functions for CIERT: (a) sequential CIERT (sCIERT): one irradiation modality is carried out after the other one both separated by an interval Δt large enough that there is no interaction between sublethal damages produced by each modality; and (b) concurrent CIERT (cCIERT): both irradiation modalities are given at the same time. In both panels $\dot{D}_{EBRT}(t)$ and $\dot{D}_{STRT}(t)$ are the dose rate functions for EBRT and STRT respectively.

$$\dot{D}_{ijk,cCIERT}(t)=\dot{D}_{ijk,EBRT}(t)+\dot{D}_{ijk,STRT}(t) \tag{2.1}$$

where:

$$\dot{D}_{EBRT,ijk}(t)=d_{ijk}\sum_{z=1}^{N}\delta(t-zT_{inter}) \tag{2.2}$$

d_{ijk} is the dose (Gy) per session received by the voxel in EBRT, $\delta(t-zT_{inter})$ is the Dirac delta function, T_{inter} (hours) is the time interval between consecutive sessions, z is an integer number which varies from 1 to N which is the total number of sessions in EBRT, and

$$\dot{D}_{ijk,STRT}(t)=A_{inj}\dot{D}_{0ext,ijk}(t)\sum_{m=1}^{M}f_m exp[-k_{e,m}t] \tag{2.3}$$

where f_m is the fraction of uptake or elimination m-th phase, which satisfying $\sum_{m=1}^{M}f_m=1$, $k_{e,m}$ (h^{-1}) is the effective rate constant of m-th phase in dose rate function for the VoI, A_{inj} (GBq) is the injected activity to patient, $\dot{D}_{0,ext,ijk}$ (Gy/h/GBq) is the extrapolated initial dose rate per GBq of injected activity in the ijk–th voxel (see Fig. 1). The effective rate constants were considered as constant over all voxels in the VoI.

The total dose delivered (cGy) in EBRT to the ijk-th voxel is $D_{EBRT,ijk}=Nd_{ijk}$. For STRT the total dose delivered (cGy) to the ijk-th voxel on VoI is $D_{STRT,ijk}=A_{inj}\dot{D}_{0ext,ijk}\sum_{m=1}^{M}\frac{f_m}{k_{e,m}}$.

Several dose spatial distributions in tumors and OARs with different heterogeneity degree were simulated. A cubic voxel of 27 mm^3 were considered during the calculations. The biological effect of the heterogeneity in the dose distribution into the VoI was evaluated by the calculation of the equivalent uniform biologically effective dose (EUBED) from the differential BED-volume histogram (BVH) [8,9]:

$$EUBED_{CIERT,VoI}=-\frac{1}{\alpha}ln\left[\sum_{j}v_j exp(-\alpha BED_{CIERT,j})\right] \tag{3}$$

where α is the intrinsic radiosensitivity(Gy^{-1}), v_j is the volume fraction of the VoI which receive a biologically effective dose equal to $BED_{CIERT,j}$.

2.2. Calculating TCP and NTCP for CIERT approach

The Tumor Control Probability (TCP) in the VoI which define the tumor was calculated by the Poisson´s model:

$$TCP_{VoI}=\prod_{ijk}exp[-\psi\rho_{cell}V_{voxel}exp(-\alpha BED_{CIERT,ijk})] \tag{4}$$

where ψ is the tumor clonogenic cell fraction (40–60%), ρ_{cell} (cells/cm^3) is the cell density in the VoI (10^8–10^9 cells/cm^3), V_{voxel} [cm^3] is the voxel volume, α(Gy^{-1}) is the intrinsic radiosensitivity and $BED_{CIERT,ijk}$ [$Gy_{\alpha/\beta}$] is the BED for the combination modality, either sCRT or cCRT. The influence of inter-patient variability in the radiosensitivity was also included in the calculation. Briefly, a sequence (2000–3000) of α_j values normal-distributed in the interval $[\bar{\alpha}\pm\sigma_\alpha]$ was generated and a $TCP_{VoI,j}$ value was calculated for each one. The set of α_i was generated using the Box-Müller polar method [10]. The mean TCP for the VoI in question was then calculated by averaging overall $TCP_{VoI,j}$ values.

The Normal Tissue Complication Probability (NTCP) for the VoI which defines an organ-at-risk (OAR) was made by the Lyman-Kutcher-Burman´s (LKB) model [11,12]:

$$NTCP_{VoI}=\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{x}exp\left(-\frac{t^2}{2}\right)dt=\frac{1}{2}\left[1-erf\left(\frac{x_{VoI}}{\sqrt{2}}\right)\right] \tag{5.1}$$

$$x_{VoI}=\frac{SED_{2Gy,VoI}-TD_{5/5,VoI}(\vartheta_{VoI})}{\xi_{VoI}TD_{5/5,VoI}(\vartheta_{VoI})} \tag{5.2}$$

where $SED_{2Gy,VoI}=\frac{EUBED_{CIERT,VoI}}{\left(1+\frac{2}{\alpha/\beta_{VoI}}\right)}$ and $TD_{5/5,Vol}(\vartheta_{VoI})=\vartheta_{VoI}^{-\eta_{VoI}}TD_{5/5,Vol}(1)$, ξ_{VoI}