Correlating Areas of Radiation Toxicity with Relative Biological Effectiveness-weighted Dose Distributions in Proton Radiotherapy

The relative biological effectiveness (RBE) of protons for radiotherapy is traditionally assigned a constant, average value of 1.1; however, the actual RBE of protons varies over the deposited dose distribution based on various factors, including proton energy, linear energy transfer (LET), dose per treatment fraction, number of treatment fractions, tissue and cell type specific factors, and biological and clinical endpoints. It is plausible that uncertainties in biologically effective calculated proton dose resulting from the use of an average RBE value may lead to unexpected areas of higher effective dose and subsequent normal tissue toxicity. Such effects may be accounted for by incorporating a model, typically referred to as a variable RBE model, which applies an RBE value determined based on the factors specific to each point in the patient dose calculation grid.

In order to apply a variable RBE model to dose calculated by the treatment planning system (TPS), treatment plan information must first be extracted from the TPS. This information is then used to create input files for Monte Carlo calculation of dose. The variable RBE model developed by Wilkens and Oelfke (1) of the form

$$\text{RBE}(D_p, L, \alpha, \beta, \lambda, \alpha_x, \beta_x) = \frac{\sqrt{\alpha^2 + 4\beta_x D_p (\alpha_0 + \lambda L + \beta_x D_p) - \alpha_x}}{2\beta_x D_p}$$

which is based on the linear quadratic model (2) was then applied to the Monte Carlo dose to obtain a biological effective dose distribution. In this model, $D_p$ is the proton dose per fraction, $L$ is the LET, $\alpha$ and $\beta$ are radiobiological parameters of a reference radiation, and $\lambda$ is a scaling factor used to parameterize a linear dependence of $\alpha$ on LET for protons. For our study, values for these parameters are the same as those used by Frese et al in a study comparing constant and variable RBE dose (3) with the tissue/endpoint specific parameters for brain necrosis employed.

This method was used to recalculate proton dose for a patient treated for malignant meningioma with postoperative intensity modulated proton therapy who subsequently presented with unexpected radiation necrosis of the left temporal lobe. The recalculated variable RBE proton dose was compared to the dose calculated by the TPS (with constant RBE of 1.1 applied), and dose differences were calculated for the treated volume.
Figure 1 displays dose profiles along the central treatment axis for one beam of the treatment plan. TPS and Monte Carlo dose are found to agree reasonably well; however, the variable RBE dose increases by several Gray near the end of the profile corresponding to the end of range for the protons. Such an effect is largely determined by the increased LET of the protons in this region.

Both Figure 2 and Figure 3 contain a contour which corresponds to an area of radiation necrosis identified by a physician on an MRI study fused to the treatment planning CT. Figure 2 displays the region of greatest difference in dose between the two distributions while Figure 3 displays a CT slice where the region of increased biological dose overlaps clearly with the necrosis contour. It was indicated by the physician that the patient exhibited considerable post-surgery swelling at the time the planning CT was acquired and thus the brain tissue presenting necrosis may have shifted from its position during radiation treatment. This provides a possible explanation for the nature of the overlap of the dose differences and necrosis contour. Large dose differences outside of the patient were present as this dose was calculated by Monte Carlo but not by the TPS. This portion of the dose difference was removed by airbrushing for clarity in the Figures 2 and 3. Negative dose differences have also been suppressed to highlight the region of interest.

The largest differences in dose were on the order of 5 Gy, which was approximately 8% of the prescribed dose of 60 CGE. More common dose differences were approximately 3 Gy, which was 5% of the prescription. Dose uncertainties of this magnitude are generally considered significant in clinical practice.

Overlap of the high effective dose region with the contoured area of necrosis is suggestive of a causal relationship and warrants further investigation.

References: