Biological Effective Dose Varies by Treatment Platform and Duration: A Multi-Institution Review For Vestibular Schwannoma

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Objectives: Treatment delivery time in stereotactic radiosurgery (SRS) affects the biological effect for a given physical dose due to sub-lethal DNA damage repair (SLDR) processes described by biphasic repair kinetics. The linear-quadratic (LQ) model cannot account for SLDR as it assumes instantaneous dose delivery, thus overestimating the biologically effective dose (BED) delivered. In recent years there has been mounting evidence that BED may be a better predictor for some outcomes and toxicities than physical dose in a variety of clinical sites treated with SRS. As SRS treatments are increasingly performed on faster delivery systems, the impact of treatment duration on the BED may be important when translating historical fractionation schemes to modern systems. We applied Jones' BED formalism, a simplification of the Millar BED model, to explore the impact of variable treatment times on the BED delivered across multiple SRS treatment platforms for a cohort of vestibular schwannoma (VS) patients. For a range of physical doses, we illustrate the critical need to consider they typical treatment duration of a given platform when selecting the appropriate physical dose to prescribe.

Methods: Prescription dose and treatment data were reviewed for 753 VS patients treated between 2001 and 2024. Patients received treatment with either Gamma Knife (GK) Model B (76), Perfexion (344), Truebeam (TB) (216) or Cyberknife (CK) VSI (117). 594 single fractions of 11, 12, 12.5, 13 or 14 Gy and 159 multi-fraction treatments of 5, 5.5 or 6 Gy were included. In the TB patient cohort, 130 patients were planned with volumetric modulated arc therapy (VMAT) (Brainlab Cranial SRS Element) and 97 patients with dynamic conformal arc (DCA) (Brainlab Multiple Metastases Element). 156 of 216 TB patients were treated with no GTV-to-PTV margin, 45 with 0.5 mm margin and 28 with a 1 mm margin. No margins were used for any GK or CK patients. Equation A9 from Jones was used to calculate the BED based on the input parameters that included treatment time from first beam-on to final beam-on, average interval between isocenters, beamlets or arcs and the average beam-on time. The physical dose, number of fractions, number of isocenters, beamlets, or arcs, and the dose received by 95% of the GTV were also used. Radiobiological parameters used included an alpha/beta ratio of 2.47 Gy, fast and slow repair half-times of 11.4 minutes and 129.6 minutes, respectively and a partition coefficient of 0.98. For each patient plan, the BED from the conventional LQ model was also calculated for comparison.

Results: It was observed that TB delivery times were significantly faster than the CK or either of the GK platforms. TB delivery times (mean 8.3 min, 4 - 19 min) resulted in higher BEDs for the same physical dose delivered on either Model B (mean 55.5 min, 17 - 127 min), Perfexion (mean 44.3 min, 18 - 84 min) or CK (mean 31.4 min, 17 - 73 min). Therefore, it can be interpreted that for the same physical dose delivered on the TB, an effectively 'hotter' treatment was delivered. For a physical dose of 12 Gy, the mean BED2.47 calculated for the TB cohort with no margin applied was 25.5% higher compared to the same dose treated on the GK and 22% higher than the same dose delivered on CK. The CK's slower delivery time resulted in mean BED2.47 only 3.1% higher than either the GK Model B or

Perfexion. In the 18 Gy / 3 TB cohort, the mean BED2.47 increased 18.7% compared to CK. The addition of GTV-to-PTV margins, commonly used in linac-based radiosurgery further increased the mean BED differences. For single fraction, 12 Gy treatments, a mere 0.5 mm margin resulted in a mean BED2.47 increase of 41% compared to GK and 38% compared to CK. Compared to 12 Gy GK treatments, the largest increases were observed in 5 Gy x 5 and 5.5 Gy x 5 cases where a 1 mm margin was added to the GTV. Here increase in the mean BED2.47 were observed to be 64% for 5 Gy x 5 and 92% for 5.5 Gy x 5, nearly doubling the BED of the historical GK BED. When the physical dose for TB patients was reduced to 11 Gy from 12 Gy, we found the mean BED2.47 reduced to 59.6 Gy, an increase of 13% compared to the 12 Gy physical dose used with GK or CK.

Conclusion(s): The migration of stereotactic radiosurgery treatments from GK, where many of today's doses were derived from to newer and faster versions GK or from CK to a linac-based system has been shown to warrant a close examination of the physical doses prescribed. The much faster treatment times observed on the TB resulted in significantly higher BED2.47 using Jones' BED formalism, which accounts for the effects of sublethal damage repair on the BED that the conventional LQ model does not, compared to GK or CK. Therefore we conclude that for a given physical dose, delivery on the TB yielded an effectively hotter treatment compared to the other platforms. Addition of even a small PTV margin exaggerated the already significant BED differential further, which may increase the risk of toxicity to adjacent cranial nerves or other normal tissues even when hypofractionated. For the TB it was shown that reducing the historical, 12 Gy single fraction physical dose to 11 Gy, resulted in mean BEDs that were more closely aligned to GK and CK BED values. Thus, clinicians using modern, faster delivery platforms can use the A9 formalism to account for treatment time effects to modify the prescribed physical dose. Accounting for SLDR during treatment in the BED calculation demonstrated the variation in delivered BED and critically, the inadequacy of the basic LQ model in comparing radiosurgical treatment modalities.