Commentary: The Impact of Insulin-Like Growth Factor Index and Biologically Effective Dose on Outcomes After Stereotactic Radiosurgery for Acromegaly: Cohort Study

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The study by Graffeo et al[1] reports on the efficacy of Gamma Knife radiosurgery (GKRS; Elekta Instrument AB, Stockholm, Sweden) in the treatment of a cohort of 102 patients for acromegaly. This approach has been now well established for many years, but the authors' novel approach was to assess the impact of two specific parameters. The first was to access the role of initial IGF-1 levels as a predictor of the long-term anti-secretory efficacy of GKRS. This has been a controversial issue for many years, as about half of the studies published on the use of GKRS for acromegaly suggested that the lower the initial IGF-1 level, the higher the chance of control/remission. For example, it has been reported, based on long-term follow-up data,[2,3] that there was a significant difference between the initial IGF-1 level between patients cured or not cured by GKRS and that this might be taken into account in the therapeutic decision-making process in the treatment of acromegaly. However, this has not been confirmed by others.[3] These authors report here that this discrepancy might be explained by the use of age- and sex-adjusted IGF-1 values in order to make comparisons, rather than unadjusted IGF-1 values (taken as a whole set of IGF-1 measurements). IGF-1 measurements have been a matter of controversy for years, in terms of methodology, as recently emphasized by Chanson et al.[4] However, it appears reasonable to assume that the initial hormone level could be predictive of the efficacy of GKRS, as the progression of anti-secretory efficacy appears to develop progressively, usually reaching a plateau phase after 2 to 5 yr. Interestingly, in the series reported by Graffeo et al,[1] showing 57% remission, sex- and age-adjusted IGF-1 values were the only predictive factor associated with remission (after adjustment for the margin prescription dose, a parameter that has been reported as predictive in other studies).[5-7]

The second important aspect of the study by Graffeo et al[1] is the use of the concept of biological effective dose (BED) to assess efficacy. Due to the natural decay of Cobalt-60 and the variable complexity of treatment, in terms of the use of the number of iso-centers to adequately cover the target volume for a given prescription dose, the total treatment time (inclusive of the gaps between iso-centers and any unscheduled gaps) of the radiosurgical intervention with the Gamma Knife varies considerably. A spreading of the total treatment time for a given dose delivery is known to dramatically influence the biological effect of radiation on tissue due to the repair of sublethal radiation damage over the total period of exposure; the longer the exposure time, the lower the biological effect of a given dose. For example, an increase in the total treatment time from 30 to 120 min was shown to have a marked effect in cell survival studies.[8] This level of variation in treatment time would not be considered unusual in routine radiosurgical practice. Although it had long been a common assumption by the GKRS community that the range of variation is too narrow to make a difference in terms of biological effect, the validity of this dogma is now rightly being questioned. A recent study has explored this in depth; looking at the influence of changes in both the prescription dose and overall treatment time on the BED for radiosurgery for a functional indication, using single iso-center irradiation for the treatment of trigeminal neuralgia.[9]

The study by Graffeo et al[1] assesses the influence of BED in the case of complex multi iso-center treatment plans. As indicated, a difficulty in assessing the biological effectiveness of radiation dose(s) in radiosurgery is the large variation in treatment times associated with the delivery of any given dose(s). Repair of sublethal radiation damage begins at the start of irradiation and thus the longer the treatment time, inclusive of both scheduled and unscheduled

gaps, when repair of sublethal damage continues to occur but when no additional damage is produced, the lower the biological effectiveness of any given dose. Previously, investigators[10] have tried to account for the different variables in multi iso-center treatments that can influence the total dose delivery time, by only considering the impact of the change in the activity of the Cobalt-60 sources; as measured in a calibration phantom, in effect of the reference dose-rate. However, this approach is totally flawed[11] because it does not take account of the variable dose rate in tissues where the damage is actually produced. This is influenced by the different collimator factors for the different iso-centers used in any particular treatment, the impact of sector blocking (this will always increase treatment times) and individual patient geometry, plus scheduled and any unscheduled gaps in treatment. These factors, plus changes to the prescription dose, can only be taken into account using the concept of BED.

Graffeo et al[1] are perfectly correct; the calculation of BED values for a multi iso-center treatment is a daunting process. It requires knowledge of the dose contribution from each iso-center, in each voxel in the region of interest in a given treatment plan, information that is not currently available from commercial versions of GammaPlan®. However, Elekta Instrument AB has produced a limited research version (GammaPlan® version 10 and lower) that provides these values.[12,13] In order to overcome some of these difficulties associated with this for the more general user, Jones and Hopewell[14] have developed a simplified approach, specifically for use in the analysis of retrospective data, and this approach has been exploited for the evaluation of the efficacy of radiosurgery in the management of acromegaly by Graffeo et al.[1]

The BED values calculated using the simplified model are an approximation for each patient, when compared with those obtained using the more precise voxel by voxel calculations for each patient[12,13] that would be needed if BED treatment planning were adopted. The original analysis by Jones and Hopewell[14] compared multi iso-center treatments for vestibular schwannomas and found that the simple model produced a BED value that was 3% less than the mean BED value produced by the voxel by voxel approach[12,13] for treatment times that varied from 25 to 130 min. The variation in total treatment time was significantly less in the study by Graffeo et al,[1] namely, 73.3 and 126.0 min.

If an actual clinical effect of the changes in total treatment time in the clinical practice of GKRS was demonstrated, this could lead neurosurgeons practicing GKRS to modify the dose prescription, according to the predicted total treatment delivery time, or performed dose planning no longer in displaying physical gray iso-doses but BED iso-doses. Indeed, this was proposed as a result of the conclusions obtained from the investigation based on the treatment of trigeminal neuralgia; treatment time/dose combinations were suggested for BED values associated with either a 5% or 10% incidence of hypoesthesia.[9]

To conclude, the study by Graffeo et al[1] confirms the efficacy of GKRS in the treatment of acromegaly. Most interestingly, it indicates an ideal profile for patients to be treated successfully with this technique. Given the lack of success of medical treatments and their cost, which are only able to control the secretion, GKRS should still be considered as an interesting therapeutic option in patients unsuccessfully treated by transsphenoidal surgery.

Disclosures

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