swiss medical weekly

**Technical comment** | Published 30 March 2023 | doi:https://doi.org/10.57187/smw.2023.40070
**Cite this as:** Swiss Med Wkly. 2023;153:40070

# Technical comment on: Balossier A, et al. Gamma Knife surgery for recurrent or persistent Cushing disease

**John W. Hopewell[ab], Ian Paddick[c], Bleddyn Jones[ab]**

[a] Green Templeton College, University of Oxford, Oxford, United Kingdom
[b] CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Oxford, United Kingdom
[c] Queens Square Radiosurgery Centre, National Hospital for Neurology and Neurosurgery, London, United Kingdom

The publication by Balossier et al. [1] is of interest because it proposes to evaluate the long-term results of the radiosurgery treatment of Cushing disease, using a Model C Gamma Knife, in terms of the biological effective dose (BED) associated with each specific treatment. BED is a radiobiological concept that is adapted to take account of changes in "overall exposure time" in respect of the enzymatic DNA repair that takes place over the "entire" time period taken to deliver a given radiation dose. As a consequence, the greater the overall treatment time (the total time from the first beam on to the last beam off) the lower the BED value for a given radiation dose.

A careful reading of the methods used in the publication by Balossier et al. [1] gives cause for concern. The pertinent advice given in the publication by Jones and Hopewell [2], with explicit equations, does not appear to have been followed. This will result in incorrect BED estimates. In this original publication describing the methods [2] two approaches are described, for both, it was stated that "overall treatment time" was used to take account of the enzymatic repair of DNA that continues to take place in the gaps between iso-centres even though in these gaps no further radiation damage is being produced. Indeed, a comparable statement to this, relating to continuing repair over the period of the gaps between iso-centres was made in correspondence in relation to a paper on the treatment of Acromegaly with the model C Gamma Knife [3]. In that acromegaly study, an appropriate allowance for gaps was made in the calculation of BED values, hence imputing the "overall treatment time" in the equations used. The present reference to the use of 'beam-on-time' only, is a total contradiction with the description of the methodology [2] and that subsequent comparable statement [3] and thus, the following questions need to be addressed:

Doses in the range 24–35 Gy were used, with a mean prescribed dose of 28.5 Gy (median 27. 5 Gy). It is stated that the BED was calculated using a simplified approach, *similar* to that described by Jones and Hopewell [2]. However, this statement does not make it clear to the reader which of the two approaches described in that publication was actually used. The publication states that the BED was calculated using a simplified approach, taking into account the "beam-on-time" and the prescribed dose. This would imply that the individual equations for each physical dose were used as listed in Table 1 of Jones and Hopewell [2], since radiation dose and "total treatment time" are the only inputs required using this approach. The more complex approach, referred to as equation A9, requires the input of additional factors, including the average "beam-off-time" between iso-centres, inclusive of any time related to any unscheduled gaps. The simplistic table 1 equations are specific to radiation doses up to 25 Gy. If used, no indication is given as to the modification of equation parameters used for higher doses, or at least the method used to calculate the appropriate equation for these higher doses.

The use of "beam-on-time", instead of "total treatment time" (inclusive of the gaps between iso-centres) is a major shortcoming of the study, since this change will result in a variable and significant overestimate of BED values.

Unless these two fundamental issues are clarified in this limited study, the present findings are questionable, but can be improved by using the above advice, based on standard radiobiological principles. In particular, the data from the cases treated with the Model C Gamma Knife, where the contribution of the "beam-off time" to the "total treatment time" may even exceed the "beam-on-time", will result in variable overestimates of the BED that could even be ≥30%.

**Potential competing interests**

Ian Paddick acts as an intermittent consultant to Elekta AB. John W Hopewell, prior to 2020, was in receipt of a grant from Elekta to investigate the prospect of calculating BED values using specific software in conjunction with GammaPlan and to display BED treatment plans. Work related to the methods described in Jones and Hopewell are totally independent of Elekta and does not require the use of their software.

**References**

1. Balossier A, Tuleasca C, Cortet-Rudelli C, Soto-Ares G, Levivier M, Assaker R, et al. Gamma Knife surgery for recurrent or persistent Cushing disease: long-term results and evaluation of biological effective dose in a series of 26 patients. Swiss Med Wkly. 2021 Jun;151(2526):w20520. http://dx.doi.org/10.4414/smw.2021.20520. PubMed. 1424-3997
2. Jones B, Dale RG, Deehan C, Hopkins KI, Morgan DA. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol (R Coll Radiol). 2001;13(2):71–81. PubMed. 0936-6555
3. Régis J, Tuleasca C, Hopewell JW, Castinetti F. Commentary: The Impact of Insulin-Like Growth Factor Index and Biologically Effective Dose on Outcomes After Stereotactic Radiosurgery for Acromegaly: Cohort Study. Neurosurgery. 2020 Sep;87(3):E301–2. http://dx.doi.org/10.1093/neuros/nyaa123. PubMed. 1524-4040

Professor John W Hopewell
Green Templeton College
43 Woodstock Road
Oxford OX2 6HG
United Kingdom
john.hopewell[at]gtc.ox.ac.uk