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Reply to comment by Hopewell JW, et al. on: Balossier A, et al. Gamma Knife surgery for recurrent or persistent Cushing disease

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We thank Doctor Hopewell and collaborators for their technical comment and interest in our publication related to biologically effective dose (BED) evaluation in context of Gamma Knife stereotactic radiosurgery for Cushing disease, which is reported for the first time in the literature [1]. We respectfully disagree that the BED values are incorrect and, particularly, with an error of more than 30%.

There is currently no golden standard approach for BED calculation for single fraction stereotactic radiosurgery. Moreover, there are various monexponential BED (slow and fast) approaches, including assuming no repair, infractional repair assuming a constant dose rate, infractional repair assuming non-constant dose rate or biexponential BED (and variations). Each of them has their caveats, which are not yet answered in the current literature. *Indeed, they result in variations – not errors – of BED calculations (which might not be necessarily neglectable)*. The publication by Jones et al. [8] in 2001 is referred to as "the pertinent advice (…) with explicit equations". Nevertheless, these equations *theoretically* discuss different radiotherapy fractionation schedules and not particularly single fraction stereotactic radiosurgery, and certainly no potential clinical impact for single fraction stereotactic radiosurgery. Such formulae are assumptions derived from pig epidermis or rat spinal cord [12], with the potential for studying sublethal damage repair, but cannot be directly extrapolated to the human body without further questioning [14].

Beam-on time and treatment time have been variably used in the current literature in the few studies showing a clinical impact of the BED approach in single fraction stereotactic radiosurgery [5, 14, 16]. We do consider that for the use of one isocenter (as in the case of the treatment of trigeminal neuralgia, for example), beam-on time (and not treatment time) should be used contrary to what is stated by some authors (indeed, couch in – couch out times are not part of sublethal repair as Cobalt-60 sources are closed).

For Leksell Gamma Knife models Perfexion and later, the same assumption can probably be made, as the time between shots has become negligible. For more ancient Gamma Knife models, treatment time has been indeed recommended, and should be ideally used when this information is available, which is seldom the case. This topic was already discussed when we published, for the first time, a BED impact for predicting arteriovenous malformations obliteration after stereotactic radiosurgery [16].

Hopewell et al. [7] suggested that the gap between isocenters may be ranging between 30 seconds to 15 minutes, which is not the case. In fact, a displacement between 2 isocenters with the 4 C model, i.e. the one used in the present study, is usually less than 1 minute and certainly not 6 minutes as suggested by Millar et al. [10] in the even older model B because the latter included manual collimator changes and manual coordinates setting of each shot with trunnions. Such would imply that potential BED errors calculated for such models (starting with the C) would be similar to potential physical dose (the current gold standard for SRS treatment prescription) errors. Of note, the Associated Editor of *The Journal of Neurosurgery* wrote that for retrospective studies, only beam-on time is available in radiosurgery records and not treatment time, as well as that BED calculation for multiisocentric plans is not simple and that beam-on time can be considered a surrogate for treatment time in particular instances [11].

The BED concept is not new, nor discovered by Hopewell and collaborators, who nevertheless had a theoretical contribution in suggesting such an approach for single fraction stereotactic radiosurgery. Initially, BED was discussed for radiotherapy (not stereotactic radiosurgery) to allow comparison of different dose / fractionation schemes in the setting of linear-quadratic model [9]. In 1982, Barendsen [2] proposed an analysis of responses of a variety of normal tissues in animals to fractionated irradiations and introduced the appealing concept of extrapolated tolerance dose. In 1989, Fowler [4] made a step forward to suggest BED as a unique concept, which celebrated 21 years of existence in 2010 (Fowler [3]). In 2013, Hopewell et al. [6] proposed that such a concept could be applied to stereotactic radiosurgery, in the frame of a purely theoretical publi-

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cation. The first study suggesting a clinical impact of BED was the one we published together with Dr Hopewell on stereotactic radiosurgery for trigeminal neuralgia [15] in 2019 (as mentioned above, one should ask whether using treatment time in that scenario was a correct choice as the patient was treated with one isocenter only), followed by other studies in which either beam-on or treatment time have been used [5, 13, 16].

Our group is certainly fascinated by the BED approach and particularly by its radiobiological implications of single fraction stereotactic radiosurgery. However, we do consider that equations derived from animal models (which are actually multiple), and their applications to human biological process, in the frame of single fraction stereotactic radiosurgery and not radiotherapy, should follow a certain number of steps and clinical trials, as we previously stated in an invited editorial to *Mayo Clinic Proceedings* [17].

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys. 1982 Nov;8(11):1981–97. http://dx.doi.org/10.1016/0360-3016(82)90459-X. PubMed. 0360-3016
3. Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010 Jul;83(991):554–68. http://dx.doi.org/10.1259/bjr/31372149. PubMed. 1748-880X
4. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989 Aug;62(740):679–94. http://dx.doi.org/10.1259/0007-1285-62-740-679. PubMed. 0007-1285
5. Graffeo CS, Donegan D, Erickson D, Brown PD, Perry A, Link MJ, et al. 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):538–46. http://dx.doi.org/10.1093/neuros/nyaa054. PubMed. 1524-4040
6. Hopewell JW, Millar WT, Lindquist C, Nordström H, Lidberg P, Gårding J. Application of the concept of biologically effective dose (BED) to patients with Vestibular Schwannomas treated by radiosurgery. J Radiosurg SBRT. 2013;2(4):257–71. PubMed. 2156-4639
7. Hopewell JW, Paddick I, Jones B, Klinge T. Letter to the Editor. Biologically effective dose and the treatment of AVMs. J Neurosurg. 2021 Jan;134(6):2007–8. http://dx.doi.org/10.3171/2020.9.JNS203545. PubMed. 1933-0693
8. 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
9. McMahon SJ. The linear quadratic model: usage, interpretation and challenges. Phys Med Biol. 2018 Dec;64(1):01TR01. http://dx.doi.org/10.1088/1361-6560/aaf26a. PubMed. 1361-6560
10. Millar WT, Hopewell JW, Paddick I, Lindquist C, Nordström H, Lidberg P, et al. The role of the concept of biologically effective dose (BED) in treatment planning in radiosurgery. Phys Med. 2015 Sep;31(6):627–33. http://dx.doi.org/10.1016/j.ejmp.2015.04.008. PubMed. 1724-191X
11. Osterman S, Sulman E, Kondziolka D. Editor's note. J Neurosurg. 2021.0022-3085
12. Pop LA, Millar WT, van der Plas M, van der Kogel AJ. Radiation tolerance of rat spinal cord to pulsed dose rate (PDR-) brachytherapy: the impact of differences in temporal dose distribution. Radiother Oncol. 2000 Jun;55(3):301–15. http://dx.doi.org/10.1016/S0167-8140(00)00205-X. PubMed. 0167-8140
13. Tuleasca C, Faouzi M, Maeder P, Maire R, Knisely J, Levivier M. Biologically effective dose correlates with linear tumor volume changes after upfront single-fraction stereotactic radiosurgery for vestibular schwannomas. Neurosurg Rev. 2021 Dec;44(6):3527–37. http://dx.doi.org/10.1007/s10143-021-01538-w. PubMed. 1437-2320
14. Tuleasca C, Knisely J, Levivier M. Reply to the letter to the editor regarding "Biologically effective dose for vestibular schwannomas: the truth and nothing but the truth". Neurosurg Rev. 2022 Jun;45(3):2497–8. http://dx.doi.org/10.1007/s10143-022-01804-5. PubMed. 1437-2320
15. Tuleasca C, Paddick I, Hopewell JW, Jones B, Millar WT, Hamdi H, et al. Establishment of a Therapeutic Ratio for Gamma Knife Radiosurgery of Trigeminal Neuralgia: The Critical Importance of Biologically Effective Dose Versus Physical Dose. World Neurosurg. 2019. PubMed. 1878-8750
16. Tuleasca C, Peciu-Florianu I, Leroy HA, Vermandel M, Faouzi M, Reyns N. Biologically effective dose and prediction of obliteration of unruptured arteriovenous malformations treated by upfront Gamma Knife radiosurgery: a series of 149 consecutive cases. J Neurosurg. 2020 Jul;134(6):1901–11. http://dx.doi.org/10.3171/2020.4.JNS201250. PubMed. 1933-0693
17. Tuleasca C, Vermandel M, Reyns N. Stereotactic Radiosurgery: From a Prescribed Physical Radiation Dose Toward Biologically Effective Dose. Mayo Clin Proc. 2021 May;96(5):1114–6. http://dx.doi.org/10.1016/j.mayocp.2021.03.027. PubMed. 1942-5546