Commentary: Fractionated Proton Beam Radiation Therapy and Hearing Preservation for Vestibular Schwannoma: Preliminary Analysis of a Prospective Phase 2 Clinical Trial

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This article outlines and reports on the preliminary results of fractionated proton beam radiation therapy (FPRT) to 50.4 to 54 Gy cobalt-gray equivalent (CGE) in 1.8 CGE fractions for acoustic neuroma/vestibular schwannoma in a prospective Phase 2 trial where the primary end point is serviceable hearing preservation.[1] This is a timely trial given the increasing popularity of proton therapy over the past decade, resulting in a substantial increase in proton centers in the United States over that time period[2,3] and the potential increased use of protons for benign tumors such as vestibular schwannoma.

Most noteworthy from this trial is the fact that the audiometrically assessed serviceable hearing preservation at 1 year after FPRT is 53%, which has thus far failed to achieve the predetermined goal of improving the 65% hearing preservation rate established by conventional photon radiation therapy[4-7] to 80% at 5 years. This rate of hearing preservation is also inferior to previous Gamma Knife radiosurgical reports involving audiometric evaluation.[8,9] These findings are particularly striking given that no patients in this study had neurofibromatosis type 2, which has been well-documented to adversely affect hearing preservation after conventional radiation therapy.[6,10]

Although the final 5-year results from this study remain pending, the current findings are consistent with previous literature indicating that despite the steep falloff superiority between target and normal tissue provided by protons (with reduced integral dose), normal intracranial tissue adjacent to the target (which in this case include the displaced VII and cochlear nerves and uninvolved vestibular branch) may receive a higher biologically equivalent dose in proton therapy because of an end-range increase in radiobiological effectiveness (RBE) above the value of 1.1 recommended by the International Commission on Radiation Units and Measurements for clinical use.[11] This factor may have contributed to the poor hearing preservation (33.3% with a median follow-up of 38.7 months) in a study of proton-

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based single-fraction stereotactic radiosurgery for vestibular schwannoma involving delivery of a median dose of 12 CGE[12] and in a more recent FPRT study combining FPRT with proton stereotactic radiosurgery (29% in patients with serviceable hearing before receiving protons) from the same institution.[13] For comparison, the reported hearing preservation after Gamma Knife radiosurgery is better despite longer follow-up (10-year actuarial rate of 44.5%).[8] Other factors such as plan conformality or patient selection in small series may also have influenced the hearing results.

Clinical data from different disease sites point to the importance of advancing the understanding of proton RBE. An analysis of patients with breast cancer treated with proton vs photon radiotherapy (RT) demonstrated lung fibrosis within the radiation field of proton-treated patients consistent with the RBE at the end of range exceeding the estimated 1.1 for proton RT. This was not found in photon-treated patients.[14] The potential for proton RBE to exceed 1.1 has marked implications for treating intracranial disease given the functional importance of tissue adjacent to treatment targets. To minimize this risk, in the current trial, at least 3 beams from different directions were used, but this strategy was not successful in the improvement of hearing preservation. Although the more rudimentary passive scattering beams were used in this trial, more conformal pencil beam scanning (PBS), that is now available, may not improve the toxicities outcomes. A study comparing passive scattering and PBS for prostate cancer revealed worse genitourinary toxicities with PBS.[15] Finally, it is also important to consider the increased financial toxicity of proton therapy in comparison with conventional photon radiation therapy.[16,17]

As we await further randomized controlled trials comparing protons and photons for central nervous system tumors,[18] the results of this current study should be interpreted with the disappointing understanding that protons for vestibular schwannoma have in fact resulted in worse, not better outcomes. Given the increased cost and limited accessibility of protons, advanced photon techniques should remain the standard of care for vestibular schwannoma based on the evidence presently available, allowing that there are no randomized comparisons to draw upon as is common in many clinical situations. One note of caution is that one should not extrapolate the results of this study to other central nervous system and skull base tumors because the recommendation for proton therapy for those tumors requires individual considerations based on the histology (hence the radiation dose required), the location, and the proximity to critical neural structures. The authors are to be commended for studying this patient population in a careful, prospective manner with strict adherence to audiometric assessment of hearing preservation, evaluation of cochlear dose impact on outcomes, and honesty in reporting their results. We look forward to further reports from this seminal trial as data mature.

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Dr Lo is a Member of Gamma Knife ICON Expert Group. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Saraf A, Pike LRG, Franck KH, et al. Fractionated proton radiation therapy and hearing preservation for vestibular schwannoma: preliminary analysis of a prospective phase 2 clinical trial. Neurosurgery. 2022;90(5):506-514.

2. Kerstiens J, Johnstone PA. Proton therapy expansion under current United States reimbursement models. Int J Radiat Oncol Biol Phys. 2014;89(2):235-240.

3. Waddle MR, Sio TT, Van Houten HK, et al. Photon and proton radiation therapy utilization in a population of more than 100 million commercially insured patients. Int J Radiat Oncol Biol Phys. 2017;99(5):1078-1082.

4. Andrews DW, Suarez O, Goldman HW, et al. Stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of acoustic schwannomas: comparative observations of 125 patients treated at one institution. Int J Radiat Oncol Biol Phys. 2001;50(5):1265-1278.

5. Chan AW, Black P, Ojemann RG, et al. Stereotactic radiotherapy for vestibular schwannomas: favorable outcome with minimal toxicity. Neurosurgery. 2005;57(1):60-70.

6. Combs SE, Volk S, Schulz-Ertner D, Huber PE, Thilmann C, Debus J. Management of acoustic neuromas with fractionated stereotactic radiotherapy (FSRT): long-term results in 106 patients treated in a single institution. Int J Radiat Oncol Biol Phys. 2005;63(1):75-81.

7. Maire JP, Huchet A, Milbeo Y, et al. Twenty years' experience in the treatment of acoustic neuromas with fractionated radiotherapy: a review of 45 cases. Int J Radiat Oncol Biol Phys. 2006;66(1):170-178.

8. Chopra R, Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC. Long-term follow-up of acoustic schwannoma radiosurgery with marginal tumor doses of 12 to 13 Gy. Int J Radiat Oncol Biol Phys. 2007;68(3):845-851.

9. Smith DR, Saadatmand HJ, Wu CC, et al. Treatment outcomes and dose rate effects following Gamma Knife stereotactic radiosurgery for vestibular schwannomas. Neurosurgery. 2019;85(6):E1084-E1094.

10. Fuss M, Debus J, Lohr F, et al. Conventionally fractionated stereotactic radiotherapy (FSRT) for acoustic neuromas. Int J Radiat Oncol Biol Phys. 2000;48(5):1381-1387.

11. McClelland S 3rd, Jaboin JJ, Watson GA, Zellars RC. Is the side effect profile of protons really safer than photons for intracranial disease? Clin Neurol Neurosurg. 2019;176:8-9.

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12. Weber DC, Chan AW, Bussiere MR, et al. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. Neurosurgery. 2003;53(3):577-578.

13. Koetsier KS, Hensen EF, Niemierko A, et al. Outcome and toxicity of proton therapy for vestibular schwannoma: a cohort study. Otol Neurotol. 2021;42(10):1560-1571.

14. Underwood TSA, Grassberger C, Bass R, et al. Asymptomatic late-phase radiographic changes among chest-wall patients are associated with a proton RBE exceeding 1.1. Int J Radiat Oncol Biol Phys. 2018;101(4):809-819.

15. Mishra MV, Khairnar R, Bentzen SM, et al. Proton beam therapy delivered using pencil beam scanning vs. passive scattering/uniform scanning for localized prostate cancer: comparative toxicity analysis of PCG 001-09. Clin Transl Radiat Oncol. 2019;19:80-86.

16. Bortfeld TR, Loeffler JS. Three ways to make proton therapy affordable. Nature. 2017;549(7673):451-453.

17. Fernandes RRA, Vianna CMM, Guerra RL, et al. Cost-effectiveness of proton versus photon therapy in pediatric medulloblastoma treatment: a patient volume-based analysis. Value Health Reg Issues. 2019;20:122-128.

18. Combs SE. Does proton therapy have a future in CNS tumors? Curr Treat Options Neurol. 2017;19(3):12.