Letter: Stereotactic Radiosurgery for Vestibular Schwannoma in Neurofibromatosis Type 2: An International Multicenter Case Series of Response and Malignant Transformation Risk

To the Editor:

We read with interest the recent publication by Bin-Alamer et al[1] which reported the results of a multi-institutional retrospective cohort study assessing the outcomes of stereotactic radiosurgery (SRS) NF2-schwannomatosis (NF2-SWN)–associated vestibular schwannomas (VS). The authors described the results of SRS treatment of 328 VS in 267 patients, with a median follow-up duration of 59 months. The authors should be commended for gathering data on such a large number of patients afflicted by this rare tumor predisposition syndrome. However, their conclusion that "none of the patients with NF2-related VS developed a new radiation-related neoplasm or malignant transformation after SRS" is not supported by the data provided.

Although the median follow-up duration was 59 months, the number of patients followed up to 10 years was extremely low, with only 64 tumors assessable for freedom from alternative treatment at 120 months in the Kaplan-Meier curves in Figure 1B from their publication. This is of concern as it is well established that malignant progression/secondary malignancy (MP/SM) after radiation treatment can occur after a prolonged latency period of up to 30 years.[2] The overall rate of loss to follow-up in this study was high at 113/328 (35%). Furthermore, the cause of death for the 37 patients who died during the study period was not provided in the manuscript, meaning that death due to MP/SM may not have been accounted for. It is also notable that the authors report the overall study cohort of 267 patients as the denominator for the mortality calculation, when presumably the status of the patients harboring the 113 tumors that were lost to follow-up is not known. The authors have confirmed the observation from several previous studies that SRS to NF2-SWN–associated tumors is less effective than those for sporadic VS.[3-5] In this series, only 17/60 (28%) of the tumors demonstrating radiological progression underwent surgical resection. Therefore, in most of these cases, it was not possible to determine whether tumor progression occurred as a consequence of MP/SM. Moreover, there was no detailed breakdown of the volumetric growth rates after SRS in those patients who did not achieve tumor control. Therefore, the possibility must exist that tumors displaying rapidly progressive growth after SRS may have undergone MP.

The reported results are also at variance with those of a recently published population-based study from our group. This case-control study, encompassing all patients in the United Kingdom with NF2-SWN treated with radiation therapy for a VS, meningioma, or ependymoma, reported a 5% excess absolute risk of MP/SM when compared with nonirradiated control patients with NF2-SWN after 20 years.[6] The increased risk was particularly apparent in younger patients, with a cumulative risk of 6% noted in patients treated before age 25 years, compared with 2% in those treated thereafter. All patients with NF2-SWN in the United Kingdom are cared for in 1 of 4 nationally commissioned centers, and as such, there was no loss to follow-up in this study.[7] Moreover, the findings are in concordance with those of 2 previous publications, also from our group, demonstrating that high-grade glioma and malignant peripheral nerve sheath tumors do not arise at increased frequency in unirradiated patients with NF2-SWN and are only associated with irradiation of the central nervous system in NF2-SWN.[8,9]

In summary, although international collaborative efforts to gather data on treatment outcomes for patients with NF2-SWN are to be welcomed, we are concerned that the conclusions drawn by Bin-Alamer et al regarding the risk of malignant progression and secondary malignancy may be overly reassuring. This is particularly so when considering this retrospective case multicenter case series in the context of more statistically robust population-level analyses. In our view, although SRS remains a reasonable option in the management of NF2-SWN–associated tumors, there is a significant attendant risk of MP/SM which, in contrast to the message from this paper, should be factored into the decision-making process in these very challenging cases, particularly in younger patients.

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