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EDITORIAL (BY INVITATION)

From the perspective of pseudo-progression rather than treatment failure, how long should we wait before considering treatment failure if large cystic enlargement occurs after Gamma Knife radiosurgery for vestibular schwannoma? Insight into pseudo-progression based on two case reports

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The paper from Shin Jung et al. is raising a very important issue: pseudo-progression after radiosurgery.

In the early 1990s, we observed in patients operated for vestibular schwannomas (VS) by Gamma Knife radiosurgery (GKS) a phenomenon of transient increase in the years following the radiosurgical intervention [1]. The real existence of this phenomenon was for a while controversial but is nowadays well documented and confirmed both in VS [7] and metastasis radiosurgery. At this time, the definition of cure given by Christer Lindquist was prevailing: an acoustic at 3 years after GKS smaller than at the time of the radiosurgery was still controlled at 10 years and then considered cured [16]. Since these old ages, the demonstration has been done that VS can be much larger at 3 years than at the time of the radiosurgery and still turn out to be cured on the long term [15]. Thus, it is obvious that based on the ancient definition of failure, we have been resecting VS after GKS based on the wrong conviction they were failing to respond to GKS. A very important aspect is that pseudo-progression is statistically significantly much more marked in patients with more pronounced growth before GKS [1]. In 2016, Marston et al., in a small cohort of VS with a rather short follow-up, found that only patients with limited or no demonstrated growth before were demonstrating stability and those with clear growth before were bigger at last follow-up and then considered as potential failures [11]. Consequently, they concluded that pretreatment growth rate was a predictor of tumor control following GKS for VS [11]. In fact, in our understanding, this conclusion was biased by the too short follow-ups leading the authors to assimilate pseudo-progression to the absence of tumor control [15]. Recently, we reviewed our historical cohort of more than 5000 VS operated by GKS over the last 30 years. Anne Balossier in this work has studied the morphological evolution of VS on the long term after GKS and has been able to identify 5 very different patterns of volumetric evolution after GKS. Four of these 5 patterns are including a phase of pseudo-progression aggregating 86.8% of the patients. The only pattern with no pseudo-progression is representing only 13.2% of the cases! In 2 of these patterns, the maximum of the pseudo-progression is occurring, in average, after the 2-year timeline even sometime as late as 5 years after GKS. The two case reports appearing in this issue of Acta Neurochirurgica are then of utmost importance. They are confirming well the importance of taking into account the existence of late pseudo-progression at the time of decision-making when there is a doubt about a failure of GKS in VS. In other words, like the authors, we consider it is making sense in front of a significant enlargement in the, at least, 5 years following GKS, to postponed resection as long as this enlargement is well tolerated by the patient.

A significant proportion of the literature is likely to be biased by failure mis-definition.

In the absence of understanding of why patients are displaying so different pattern of volumetric evolution after GKS, we are in need of biomarkers enabling us to predict the efficacy or failure earlier. The key is certainly in a better understanding of the biological cascade of events occurring in the VS after GKS and biological determinants of growth rate before [5].

In a retrospective study of 44 patients with VS, Soni et al. have analyzed the tumor apparent diffusion coefficient (ADC)

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before and after GKS [17]. Patients with tumor control had higher pretreatment ADC values than patients with tumor progression, but ADC values did not differ between patients with pseudo-progression and those with true progression at early posttreatment follow-up [17]. Although the mechanism which is triggering and maintaining growth in VS remains unclear, there is evidence for a strong role of "inflammation." There is an inconsistent association between tissue proliferation indices and tumor growth. In resected VS, the quantity of macrophages infiltrating the tumors is demonstrated to be related to volumetric growth of VS [2]. This finding is suggesting that such biomarkers assessing intratumoral inflammation may predict growth [10], help to select patients for targeted therapies [18] and be relevant for monitoring of VS after GKS! PET imaging studies have confirmed that inflammation and vascular permeability may be biomarkers of growth [10]. More growing VS are displaying significantly higher [12] C-(R)-PK11195-specific binding (BP_{ND}) which means higher inflammation. In both sporadic and NFII VS, tumor vascularity and Iba1 + macrophage density have been shown to be associated [9]. The authors observed in immunofluorescence imaging cellular co-localization between Iba1 + and VEGF and concluded that VEGF expressing macrophages are a cellular link between angiogenesis and inflammation in VS [6]. They suggest that VEGF/VEGFR1 expressing macrophages may be a driver of VS growth which may be a possible mechanism of Avastin in targeting inflammation in NF2-related VS. Graffeo et al. are proposing that macrophage density is predicting facial nerve outcome in addition to tumor growth after subtotal resection of VS [4].

The role of macrophages as potential markers of outcome in VS managed with SRS is an interesting field of research. Although we know that there is no correlation between tumor size and hearing function at diagnosis, we have evidence that pro-inflammatory cytokines secreted from VS are ototoxic [19] with resected VS in patients with poor hearing found to secrete more TNF alpha which is inducing cell death in murine cochlear explants [3]. In our experience, the patient tends too loose less hearing after SRS. These observations are leading to question if radiosurgery can halt secretion of injurious factors like TNF alpha. Prabhu et al.'s group has reported that high T2 signal of the modulus of the cochlea was a sign of injured cochlea and a negative prognosis factor for functional hearing preservation [12]. More and more, we are discovering the "non-lesional" functional effects of radiosurgery [13, 14].

John Liu et al. are showing that radiosurgery is sufficient for "epigenetic reprogramming of neural crest to immune-enriched schwannoma by remodeling chromatin accessibility, gene expression, and metabolism to drive schwannoma cell state evolution and immune cell infiltration" [8].

Nowadays, safety efficacy of SRS is well demonstrated in vestibular schwannomas. However, the acknowledgement of pseudo-progression phenomenon is making mandatory a long follow-up of at least 5 years and sometime longer to confirm the cure of the tumor! A better understanding of the subtle changes occurring over time in VS after SRS may provide us with biomarkers of tumor control allowing to monitor over time the efficacy of SRS and demonstrate much earlier the efficacity of SRS even in absence or far before tumor shrinkage.

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