Published in final edited form as:

Otolaryngol Head Neck Surg. 2013 June ; 148(6): . doi:10.1177/0194599813478574.

Short-term Histopathology Effects of Gamma Knife Radiosurgery on a Vestibular Schwannoma

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Radiosurgery is a popular management strategy for vestibular schwannoma (VS), with approximately one-third of patients being treated with this modality today. The goal in radiosurgery is to halt tumor growth. Tumor growth control rates range from 70% to 97%.¹

The direct effect of radiation on tumor cells is DNA damage, triggering apoptosis. Immediate or delayed cell death may occur, depending on whether the cell is actively dividing. Because of the benign and slow-growing nature of VS, this effect may not account for the cumulative effect of radiation. Radiation also induces vascular damage, leading to ischemia and cell death. In a series of 5 patients who had microsurgical resection after stereotactic radiation, immunohistochemistry using antibodies directed against the vascular endothelial markers, factor VIII and CD34, demonstrated decreased staining with increasing isodoses and no staining at the tumor center.¹ Damage to the vascular endothelial cells occurs 2 to 4 months after radiation.

Here, we show results of a histological/immunohistochemical investigation of a VS tumor 5 months following treatment with radiosurgery. While prior studies have shown long-term radiation effects, this case represents a unique view into the short-term biological effects of schwannoma gamma knife irradiation, which may provide clues to radiation failure, tumor regrowth, and potential strategies for tumor control.

Case Report

A 77-year-old man with a right-sided vestibular schwannoma experienced imbalance and progressive hearing loss. Magnetic resonance imaging at the time of radiation revealed a 3.3-cm tumor and hydrocephalus. While tumors of this size associated with hydrocephalus are not routinely irradiated given the risk of posttreatment obstructive hydrocephalus, this patient's comorbidities and preference dictated the treatment course. He received 12 Gy at the 50% isodose line. The patient expired 5 months later due to unrelated causes.

Histopathology

Institutional Review Board approval was obtained from St Vincent Medical Center. Microscopic examination of hematoxylin and eosin (H&E)-stained sections revealed areas of apparent necrosis intermixed with areas demonstrating palisading schwannoma cells. There were blood vessels present with red blood cells evident in the lumen (Figure 1A). Neurofilament immunostaining revealed the location of the vestibular nerve at the periphery of the tumor (Figure 1C). There were clusters of proliferating cell nuclear antigen (PCNA)-positive cells, where the tumor appeared to have retained viability (Figure 2). Vascular endothelial growth factor (VEGF) immunostaining also demonstrated positivity in clusters,

which seemed to correlate with viable cells (Figure 2), as seen with PCNA staining and H&E.

In addition, the staining for ErbB growth factor receptor family members was sporadic but was positive in viable areas near blood vessels (Figure 2). While epidermal growth factor receptor (EGFR) and ErbB2 staining was sparse, ErbB3 immunostaining was more intense in viable areas (compare Figure 2D and E with Figure 2F).

Discussion

Post-irradiation effects fall under two distinct conditions: short-term and long-term. Previous histopathology reports have shown the long-term effects after tumor removal, due to radiation failure. While it is not possible to predict whether this VS tumor would have continued to grow, we can speculate about factors within the tumor that may predict escape from radiation-induced growth control. Lower overall PCNA staining has been demonstrated in VS that failed gamma knife compared with recurrent tumors after previous microsurgical resection.² A high index of PCNA staining, indicating the ability of a cell population to proliferate, has been associated with a greater recurrence and faster growth rate in VS.³

VEGF staining was investigated since VEGF is overexpressed in VS compared with normal Schwann cells.⁴ VEGF stimulates angiogenesis, suggesting that VEGF expression might correlate with the ability of a tumor to escape the effects of irradiation. In this tumor, areas of viable tumor seemed to be clustered around blood vessels and exhibited VEGF staining, suggesting either that radiation did not effectively treat these areas or that VEGF-induced angiogenesis promoted tumor survival. This evidence supports the potential for anti-VEGF targeted therapy, such as bevacizumab (Avastin), to control tumor growth in VS.⁴

The presence of ErbB family growth factor receptors suggests potential for response to growth factors. EGFR expression has been correlated with increased VS tumor size, indicating that it is a marker of progression.⁵ EGFR and ErbB2 have also been demonstrated in human VS, and ErbB3 has gained attention as a possible molecular target for tumor growth control. Our results suggest that ErbB3 expression in viable areas may play a role in schwannoma cell survival.

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Figure 1. Irradiated vestibular schwannoma histology. (A) Hematoxylin and eosin stain shows patent blood vessels (asterisks). (B) High power view demonstrates schwannoma architecture. (C) Neurofilament activity to peripheral nerve (arrow).

Figure 2. Proliferation marker immunostaining. Proliferating cell nuclear antigen in vestibular Schwannoma (A) and control (B). Vascular endothelial growth factor expression (C) surrounding blood vessels (bv); epidermal growth factor receptor (D), ErbB2 (E) WErB3 (F).