Journal of Clinical Surgery and Surgical Research
2024 Volume 3, Issue 2
DOI: 10.59657/2992-9989.brs.24.027

BRS BioRes Scientia
Value your Research

Mini-Review Article

Open Access

Risk Factors for Recurrence of Schwannomas: A Mini-Review

Dzhamilya Murzaeva [1,2], **Darya Sitovskaya** [2,3*], **Yulia Zabrodskaya** [2,4]

[1]*Tyumen State Medical University, Ministry of Health of the Russian Federation, Odesskaya st, 54, Tyumen, Russia.*
[2]*Polenov Neurosurgical Institute – Branch of Almazov National Medical Research Centre, Mayakovskogo st, 12, Saint-Petersburg, Russia.*
[3]*Department of Pathology with a course of forensic medicine named after D.D. Lochov, St. Petersburg State Pediatric Medical University, Litovskaya st., 2, Saint-Petersburg, Russia.*
[4]*The North-Western State Medical University named after I.I. Mechnikov, Kirochnaia st, 41, Saint-Petersburg, Russia.*
**Corresponding author: Darya Sitovskaya.*

Abstract

Schwannoma (ICD-O code 9560/0) is a rare, slow-growing, benign tumor that affects the nerve sheaths. Currently, there are no definitive biomarkers that can accurately predict the likelihood of relapse. This leads to challenges in postoperative monitoring of patients, repeated surgeries, and a decline in quality of life. Therefore, there is a need to identify prognostic and predictive factors that can impact the progression of schwannomas. In this mini-review, we will discuss the role of the proliferative activity marker Ki67 and the tumor microenvironment in recurrent schwannomas.

Keywords: schwannoma; recurrent; ki67; tumor microenvironment

Introduction

Schwannoma (ICD-O code 9560/0) is a slow-growing benign tumor of the nerve sheaths that occurs with an incidence of 1 in 100,000 [1-2]. It exhibits a highly variable morphological picture. Histogenetically, tumors of the peripheral nerve sheaths originate from a limited number of cells: schwannocytes, fibroblasts, perineurial cells, and the variety of nosologies is determined by a combination of various neoplastic cells. Schwannocytes develop into schwannomas, neurofibromas, hybrid nerve tumors, malignant peripheral nerve sheath tumors (MPNST), and malignant melanotic peripheral nerve sheath tumors (MMPNST). Fibroblasts participate in the formation of neurofibromas, hybrid tumors of nerves and MPNST, and perineurial cells form perineuriomas and MPNST with perineurial differentiation [1-3]. Typically, schwannomas and neurofibromas develop sporadically, but in 10% of cases, they can be associated with neurofibromatosis types 1 and 2, and schwannomatosis [1,3]. Among benign tumors of the nerves, neurofibromas most often undergo malignant transformation. These tumors can recur and become malignant in MPNST, which is reflected in increased proliferative activity in an atypical neurofibroma of uncertain biological potential. The grade of this type of tumor has not been determined and was previously classified as grade 2. However, schwannomas of a similar subtype with a potentially unfavorable clinical course have not been identified. Since the time of Cushing, schwannomas have been considered a homogeneous group of slowly growing tumors [1-3]. To date, extremely rare cases of malignancy of schwannomas into malignant tumors of the peripheral nerve sheaths have been described, especially after radiation therapy [4-7]. Isolated reports indicate the possibility of developing angiosarcomas from schwannoma [8-10], as well as the appearance of rhabdomyoblastic differentiation [11-12].

After neurosurgical treatment, the clinical behavior of schwannomas can vary greatly. As a result, many specialists are interested in identifying factors that may influence the outcome. Currently, the most widely accepted measure of postoperative tumor control is the volume of surgical resection. Studies have shown that relapse rates after total resection range from 0.05% to 9.2%, while with subtotal resection, the rate can be as high as 44% [13]. This means that the risk of relapse is 10 times higher for patients who undergo subtotal resection compared to those who have total resection. Additionally, patients who undergo almost total resection (with removal of 95% of the tumor) have a 3 times higher risk of relapse compared to those who have total resection [14-15]. However, there have been cases of relapse even after total tumor resection [15]. Currently, there

are no clear biomarkers that can accurately predict the likelihood of relapse. This leads to challenges in postoperative patient monitoring, potential need for additional surgeries, and a decrease in quality of life. Therefore, it is crucial to continue researching prognostic and predictive factors that may impact the progression of schwannomas [16].

The immunohistochemical marker Ki-67 is widely used in pathology as a prognostic and predictive marker in tumors of various locations. However, there are discrepancies in the use of Ki-67 as a "cut-off" for distinguishing between different types of tumors. For example, the 5th edition of the World Health Organization (WHO) classification of tumors of soft tissues and bones sets a "cut-off" of <20% for cellular schwannoma and ≥20% for malignant peripheral nerve sheath tumor. However, the 2021 WHO CNS classification states that Ki-67 values ≥20% do not necessarily indicate a malignant tumor. Studies have shown that Ki-67 values in schwannomas can vary, with higher values often seen in recurrent tumors compared to non-recurrent tumors. For example, in the study by Graffeo et al., the Ki-67 index was 1.4% in recurrent tumors and 1.2% in non-recurrent tumors. Similarly, in the study by Iannella et al., the Ki-67 index was 3.2% in recurrent tumors and 1.4% in non-recurrent tumors. These findings suggest that Ki-67 can be a reliable indicator of tumor prognosis. In a retrospective cohort study by Lesser T.H. (1991), a direct correlation was found between the growth of schwannomas and an increase in the level of Ki-67. This was also observed in a study by Prueter J. (2019), which included patients with both total and subtotal resection. However, in a study by Graffeo C.S. (2018), Ki-67 values did not correlate with tumor recurrence, possibly due to the use of subtotal resection and a small sample size. In earlier WHO CNS classifications (2016), Ki-67 was used as a threshold of 20% for distinguishing neurofibromas from MPNST, but in 2021 it was replaced by counting the number of mitoses (≥1.5 mitoses/mm^2), which may be more reproducible.

In schwannomas, histological examination distinguishes between the Antoni A and Antoni B regions, which were first described in 1920 by the Swedish pathologist Nils Ragnar Eugene Antoni (1887-1968). These regions were named after Antoni, while a similar structure known as Verocay bodies was described earlier in 1910 by Uruguayan neuropathologist Jose Juan Verocay (1876-1927). Verocay bodies are acellular eosinophilic spaces surrounded by cellular processes and a palisade of schwannocyte nuclei, which Verocay believed could help differentiate between "neurinoma" tumors and neurofibromas [22-23]. The Antoni A region is characterized by elongated cells with spindle-shaped asymmetric nuclei and bundles of cells, including Verocay bodies. The less cellular Antoni B region contains cells with round-oval hyperchromatic nuclei, a myxoid or microcystic matrix, and macrophage infiltration. While mitoses are typically not observed in schwannomas, cellular variants may exhibit single mitoses and high levels of Ki-67, indicating a potential for proliferation due to the schwannocytes themselves [1-2,24].

It is well-established that the tumor microenvironment plays a crucial role in tumor progression [24]. In schwannomas, the main component of the microenvironment is macrophages [25]. Recent research has shown that macrophages are a heterogeneous population and can be divided into three subclusters [26]. In a study by Hannan C.J., a direct correlation was found between the infiltration of tumor-associated macrophages (TAMs) and schwannoma growth, regardless of tumor size. Additionally, there was a direct correlation with tumor vascularization, as evidenced by higher concentrations of monocyte-recruiting chemokines in patients with growing tumors [27-29]. Kontorinis G. et al (2016) also noted that increased levels of neutrophils and lymphocytes can serve as predictors of recurrence in sporadic schwannomas [30]. Several studies have demonstrated that adrenergic signaling from sympathetic nerves in the tumor microenvironment promotes tumorigenesis [24, 31]. In a study by Huo Z. (2024), higher levels of vascular endothelial growth factor (VEGF) were observed in schwannomas with an aggressive course, while the authors did not find a difference in the ratio of M1 and M2 macrophages between growing and stable tumors [32-33]. Currently, there is evidence supporting the effectiveness of the antiangiogenic drug Bevacizumab in treating vestibular schwannomas [34]. Additionally, the authors observed an increase in the density of CD68+ macrophages and proliferation of immune cells in recurrent tumors [17]. Wach J. et al found that Ki-67/MIB-1 values ≥ 5% were associated with more unfavorable outcomes in surgical treatment of vestibular schwannomas, such as the development of facial paralysis. However, these values were also directly correlated with the number of CD45+ and

CD68+ cells in the tumor [25]. According to the results of studies by Nisenbaum E., higher levels of CD163+ expression in vestibular schwannomas were linked to hearing loss in patients [35].

Conclusion

Researchers need to conduct future studies to examine the relationships between histologic variants of schwannomas, levels of proliferative activity, and macrophage phenotypes and secreted cytokines, as they may be linked to tumor recurrence and progression. By studying these relationships, it is possible to discover new methods for treating and preventing schwannoma recurrence, such as targeted therapies.

Declarations

Conflict of interest

The authors declare no conflict of interest.

Funding

The study was performed without external funding.

Author contributions

DM, DS, and YuZ contributed to the manuscript, revision, and investigation. All the authors read, approved, and equally shared the submitted version.

References

1. WHO. (2021). Classification of Tumours Editorial Board. Central nervous system tumours. Lyon (France). International Agency for Research on Cancer. *WHO classification of tumours series*. 5th ed, 6.
2. WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. Lyon (France). International Agency for Research on Cancer. 2020. WHO classification of tumours series. 5th ed, 3.
3. Shelehova K.V. (2023). Neoplasia and tumor-like lesions of peripheral nerves. Tutorial.
4. Behling F, Bersali I, Santacroce A et al. (2023). Transition of a vestibular schwannoma to a malignant peripheral nerve sheath tumor with loss of H3K27 trimethylation after radiosurgery-a case report and review of the literature. *Neurosurg Rev*, 915-922.
5. Boucher AB, Mendoza P, Neill SG et al. (2020). High-Grade Sarcoma Arising within a Previously Irradiated Vestibular Schwannoma: A Case Report and Literature Review. *World Neurosurg*, 44:99-105.
6. De Jesus O, Sánchez Jiménez JG, Santiago Quiñones G, Vélez R. (2021). Malignant peripheral nerve sheath tumour transformation of histological benign vestibular schwannoma after stereotactic radiosurgery in patients without neurofibromatosis. *BMJ Case Rep*, 11:14.
7. Hosmann A, Kamdar V, Misra BK. (2024). Malignant transformation of vestibular schwannoma following radiosurgery-a case report and review of the literature. *Acta Neurochir (Wien)*, 30:52.
8. Lakomkin N, Torres-Mora J, Dozois EJ, Spinner RJ. (2022). Angiosarcoma arising in a schwannoma of the peripheral nervous system: illustrative case. *Neurosurg Case Lessons*, 19:527.
9. Xiang Y, Yan L, Lin X, Zhang X et al. (2021). Posterior Mediastinal Epithelioid Angiosarcoma Arising in Schwannoma: A Case Report and Review of the Literature. *Front Surg*.
10. He B, Li YJ. (2019). Epithelioid angiosarcoma arising in Schwannoma: report of a case. Chinese, 8:156-157.
11. Tish S, Ross L, Habboub G et al. (2019). Malignant triton tumor diagnosed twelve years after radiosurgically treated vestibular schwannoma. *Clin Neurol Neurosurg*, 183.
12. Kudziev AV, Nazarov AS, Belyakov YuV et al. (2023). Surgical treatment of malignant triton tumor of the spinal root (a rare clinical observation). *Russian neurosurgical journal named after prof. A.L. Polenov*. (In Russ.), 15(2):140-144.
13. Hong B, Krauss JK, Bremer M et al. (2014). Vestibular schwannoma microsurgery for recurrent tumors after radiation therapy or previous surgical resection. *Otol Neurotol*, 35(1):171-181.
14. Jacob JT, Carlson ML, Driscoll CL, Link MJ. (2016). Volumetric analysis of tumor control following subtotal and near-total resection of vestibular schwannoma. *Laryngoscope*, 126(8):77-82.
15. Scheer M, Simmermacher S, Prell J et al. (2023). Recurrences and progression following microsurgery of vestibular schwannoma. *Front Surg*, 21;10:60-93.
16. Zhang Y, Long J, Ren J et al. (2021). Potential Molecular Biomarkers of Vestibular Schwannoma Growth: Progress and Prospects. *Front Oncol*, 27(11):14-41.

17. Graffeo CS, Perry A, Raghunathan A. (2018). Macrophage density predicts facial nerve outcome and tumor growth after subtotal resection of vestibular schwannoma. *Neurol Surg B Skull Base*, 79:482-488.
18. Panigrahi M, Kumar D, Vooturi S, Madigubba S. (2018). MIB index as predictor of recurrence in sporadic vestibular schwannomas, *World Neurosurg*, 20:1203-1207.
19. Iannella G, de Vincentiis M, Di Gioia C et al. (2017). Subtotal resection of vestibular schwannoma: Evaluation with Ki-67 measurement, magnetic resonance imaging, and long-term observation. *Int Med Res*, 45:1061-1073.
20. Lesser TH, Janzer RC, Kleihues P, Fisch U. (1991). Clinical growth rate of acoustic schwannomas: correlation with the growth fraction as defined by the monoclonal antibody ki-67. Skull Base Surg, 1(1):11-15.
21. Prueter J, Norvell D, Backous D. (2019). Ki-67 index as a predictor of vestibular schwannoma regrowth or recurrence. *J Laryngol Otol*, 133(3):205-207.
22. Joshi R. (2012). Learning from eponyms: Jose Verocay and Verocay bodies, Antoni A and B areas, Nils Antoni and Schwannomas. Indian Dermatol Online J, 3(3):215-219.
23. Urs AB, Kumar P, Augustine J et al. (2021). Pathological Diversity in Schwannomas of the Orofacial Region. *Asian J Neurosurg*, 16(2):402-405.
24. Hanahan D. (2022). Hallmarks of Cancer: New Dimensions. *Cancer Discov*, 12(1):31-46.
25. Wach J, Brandecker S, Güresir A et al. (2020). The impact of the MIB-1 index on facial nerve outcomes in vestibular schwannoma surgery. *Acta Neurochir (Wien)*, 1205-1213.
26. Baruah P, Mahony C, Marshall JL et al. (2024). Single-cell RNA sequencing analysis of vestibular schwannoma reveals functionally distinct macrophage subsets. *Br J Cancer*.
27. Hannan CJ, Lewis D, O'Leary C et al. (2023). Increased Circulating Chemokines and Macrophage Recruitment in Growing Vestibular Schwannomas. *Neurosurgery*, 92(3):581-589.
28. Ji ZZ, Chan MK, Chan AS et al. (2023). Tumour-associated macrophages: versatile players in the tumour microenvironment. *Front Cell Dev Biol*, 11:126-174.
29. Leisz S, Klause CH, Vital Dos Santos T et al. (2022). Vestibular Schwannoma Volume and Tumor Growth Correlates with Macrophage Marker Expression. *Cancers (Basel)*, 14(18):44-29.
30. Kontorinis G, Crowther JA, Iliodromiti S et al. (2016). Neutrophil to Lymphocyte Ratio as a Predictive Marker of Vestibular Schwannoma Growth. *Otol Neurotol*, 37(5):580-600.
31. Magnon C, Hall SJ, Lin J et al. (2013). Autonomic nerve development contributes to prostate cancer progression. *Science*, 341(6142):1236361.
32. Huo Z, Wang Z, Luo H et al. (2024). Single-cell transcriptomes reveal the heterogeneity and microenvironment of vestibular schwannoma. *Neuro Oncol*, 4:444-457.
33. Xu M, Wang S, Jiang Y et al. (2022). Single-Cell RNA-Seq Reveals Heterogeneity of Cell Communications between Schwann Cells and Fibroblasts within Vestibular Schwannoma Microenvironment. *Am J Pathol*, 192(9):1230-1249.
34. Hannan CJ, Lewis D, O'Leary C et al. (2020). Beyond Antoni: A Surgeon's Guide to the Vestibular Schwannoma Microenvironment. *Journal Neurol Surg B Skull Base*, 83(1):1-10.
35. Nisenbaum E, Misztal C, Szczupak M et al. (2021). Tumor-Associated Macrophages in Vestibular Schwannoma and Relationship to Hearing. *OTO Open*, 5(4):2473974X211059111.

Cite this article: Murzaeva D, Sitovskaya D, Zabrodskaya Y. (2024). Risk Factors for Recurrence of Schwannomas: A Mini-Review. *Journal of Clinical Surgery and Surgical Research*, BioRes Scientia Publishers. 3(2):1-4. DOI: 10.59657/2992-9989.brs.24.027

Article History: **Received:** May 01, 2024 | **Accepted:** June 03, 2024 | **Published:** June 07, 2024