Minireview Article

Innovations in Spinal Hemangioblastoma Management

Abstract:

Introduction: Spinal hemangioblastomas are benign, rare neoplasms of spinal cord vasculature. They may occur as solitary lesions or with associated intracranial hemangioblastomas, this association is seen in Von Hippel Lindau syndrome (VHL).

Aims: This literature review serves to highlight various innovative therapeutic modalities used to treat this pathology. This review highlights twenty original research articles and analyzes the current treatment modalities.

Results: Surgical resection is carried out with either an: open or microsurgical approach with either an endoscopic or minimally invasive technique. The specific surgical intervention depends on the spread of the neoplasm. Pre-operative angiography is a critical predictor of surgical success. Arterial embolization may also be conducted preoperatively to minimize neoplasm vascularity. Stereotactic radiosurgery often conducted with gamma knife or LINAC, has remarkably improved treatment. Pharmacologic therapies such as Bevacizumab (an anti-angiogenic chemotherapeutic).

Key Words: Spine, Hemangioblastoma, Oncology, Orthopedics- Oncology, Von-Hippel Lindau

Introduction: Several histologically diverse tumors affect the spinal cord, the most common include meningiomas, schwannomas (nerve sheath tumors), astrocytomas and ependymomas. Collectively, these represent more than 75% of primary spinal cord tumors [(1)]. spinal hemangioblastoma constitutes 2-3% of spinal tumors. [(2)] Hemangioblastomas may arise from any central nervous system (CNS) structure. Though benign, they may be associated with a morbidity likely secondary to compression.

Spinal hemangioblastoma is strongly associated with Von-Hippel Lindau Syndrome (VHL). [(3)] VHL is a genetic disorder characterized by multiple tumors within the body, including renal cell carcinomas, pheochromocytomas, and CNS hemangioblastomas. Among the latter, spinal hemangioblastomas contribute up to 40% of the overall incidence, with an increasing incidence among the elderly (>60 years of age). Studies have demonstrated that spinal hemangioblastomas in cases of VHL rarely occur in isolation and are often associated with other hemangioblastomas i.e. within the cerebellum, medulla, pons etc. [(4)] Presenting symptoms of a spinal hemangioblastoma depend upon tumor location (thoracic, cervical region etc.); however patients usually experience some degree of back pain, limb weakness of paresthesia. [(5)] Rarely life-threatening subarachnoid hemorrhages may occur.

The diagnosis of spinal hemangioblastoma is usually suspected with a careful history, and confirmed with radio-imaging techniques i.e. CT or MRI (with gadolinium contrast) scans. Imaging may also illustrate the presence of a syrinx, alongside the tumor. Angiography may also be useful in determination of the extent

of the tumor's angiogenesis. Total surgical resection which may be carried out with either an **open** or an **endoscopic** approach is the mainstay of treatment.

(1) Open Spine Surgery: C. Fenger was the first to attempt open spinal surgery for tumor resection in the late 19th century. However, Eiselsberg then later C. Elsberg (in the 20th century) performed the first successful open surgery for tumor resection. Later, Fred Epstein et al also removed spinal tumors in pediatric patients (2003). [6] The open spinal approach is conventionally done through a large midline incision in the back, microsurgical instrumentation is utilized for complete tumor resection. Intraoperative MRI imaging, and neurophysiological analysis are often used to assist the intraoperative management. [6, 7]

(2) Endoscopic Surgery: Minimally Invasive Spinal Surgery involves a small incision in the back. Most literature indicates that both open and endoscopic methods yield similar results however, minimally invasive surgery is associated with a significantly lower risk of bleeding, thus minimizing scarring and promoting rapid recovery. [8]

Depending upon the size of the tumor, spinal surgery may be performed via laminectomy or hemilaminectomy. Hemilaminectomy is preferable intervention as it minimizes risk to the vertebral column and reduces operative blood loss. [9] Some surgeons emphasize pre-operative chemoembolization of vessels minimizing tumor growth. Chemicals such as polyvinyl alcohol (PVA), n-butyl cyanoacrylic acid (NBCA) etc. may be used for chemoembolization. [10]

Stereotactic Radiosurgery: Neuro-oncological advancements have enabled the use of stereotactic radiosurgery for pre-operative reduction of hemangioblastomas. Developed by Horsley & Clarke in the early 1900s, it was not until the latter 20th century that radiosurgery became widely acknowledged as a major treatment modality for CNS tumors. Gamma Knife radiosurgery and Linear Accelerator (LINAC) are the primary modes of administering radiation and shrinking tumors by direct exposure to radiation beams. [11]

Material & Methods: The articles for this literature review were obtained through PubMed Central (PMC) or Google Scholar, with the keywords: Spinal Hemangioblastoma; Management of spinal hemangioblastoma; Minimally Invasive Surgery for spinal hemangioblastoma. Initially more than 30 articles were selected. Further selection criteria included clinical trials, retrospective studies or case series / case reports (from 2000-onwards). Systematic reviews and meta-analysis related articles were excluded from further analysis. After exclusion, findings from 20 original articles have been assessed in this final review.

Results: Selected articles are systematically summarized. The articles have been further categorized by treatment modality (Tables 1-4).

Table 1: Surgical Intervention of Spinal Hemangioblastoma.

Sr. No.	Article	Authors	Journal	Year of Publication	Main Findings
1.	Surgical Management of	Chanland Roonprapunt,	Neurosurgery	2001	**19** spinal **hemangioblastoma** cases were post-operatively reviewed. Each

	Isolated Hemangioblastomas of the Spinal Cord [12]	V. Michelle Silvera et al			patient had undergone **spinal MRI & angiography** followed by **posterior laminectomy**. This technique resulted in complete tumor removal. Nearly 70% of patients demonstrated improved functional status. The remaining 30% stabilized and did not deteriorate upon subsequent follow-up.
2.	Intramedullary hemangioblastomas: timing of surgery, microsurgical technique and follow-up in 23 patients [13]	A. Boström, F-J. Hans et al	European Spine Journal	2008	This study reviewed **23 intramedullary hemangioblastoma** cases. Most tumors were located within the cervico-thoracic region. Almost 1/3rd of patients had a VHL diagnosis. Patients underwent **microsurgical resection** via **hemilaminectomy, partial hemilaminectomy** or **laminectomy**. On follow-up, 18/23 patients stabilized with 5 patients demonstrating significant recovery. 1 operation resulted in the formation of a CSF fistula. Another patient developed tumor recurrence.
3.	Safety and Efficacy of Intradural Extramedullary Spinal Tumor Removal Using a Minimally Invasive Approach [14]	Richard J. Mannion, Adrian M. Nowitzke et al	Operative Neurosurgery	2011	In this study, **13 intradural spine tumors** were resected via hemilaminectomy with **neuronavigation assistance**. This minimally invasive surgery resulted in complete tumor resection in 12/13 patients. Patients tolerated the operation well. One case had to be converted to an open approach because of the tumor location.
4.	Early microsurgical treatment for spinal hemangioblastomas improves outcome in patients with von Hippel–Lindau disease [15]	Ali Harati, Jarno Satopää et al	Surgical Neurology International	2012	In this study, **17** patients with **hemangioblastomas** (cervical, thoracic & lumbar) underwent **micro-surgical operations**. 11 patients had underlying VHL. Every operation except 1 resulted in complete tumor resection. The majority of patients did not demonstrate any post-operate neurologic deficits.
5.	Surgical Outcome of Spinal Cord Hemangioblastomas [16]	Chang Hyun Park, Chang-Hyun Lee et al	Journal of Korean Neurosurgical Society	2012	16 patients with **spinal hemangioblastoma** were assessed in this study. 10 patients underwent gross total resection while the other 6 underwent partial resection. Every operation involved **microsurgical technique**. Only 19% of patients demonstrated statistically significant postoperative improvement. The condition of the remaining either stabilized or worsened.
6.	Intramedullary Hemangioblastomas: Surgical Results in 16 Patients [17]	Andrei F Joaquim, Enrico Ghizoni et al	Neurosurgical Focus	2015	In this study, **16** patients with **intramedullary hemangioblastoma** underwent microsurgical operations. Of the 16 patients, 7 had VHL. Most tumors were localized in the cervical & thoracic

					spinal cord. Gross resection was achieved in nearly all patients. Post-operatively, most patients stabilized. 2 patients demonstrated significant neurologic improvement. One patient rapidly declined clinically. Thus, the authors concluded that the probability of post-operative improvement was related to a patient's pre-operative status.
7.	Comparison of Open and Minimally Invasive Surgery for Intradural-Extramedullary Spine Tumors [(18)]	Albert P Wong, Rishi R Lall et al	Neurosurgical Focus	2015	This was a retrospective analysis that included **45** patients with **intradural spinal tumors.** They were surgically resected either with an **open** (18) or a **minimally invasive** (27) **surgery**. The minimally invasive surgery resulted in decreased hospital duration, and intraoperative blood loss. Complete tumor excision was more likely achieved with the open technique.
8.	Diagnosis and microsurgical treatment of spinal hemangioblastoma [(19)]	Xuezhen Li, Jianzhen Wang et al	Neurological Sciences	2016	In this retrospective study, **microsurgical resection** was performed on **25** patients with spinal **hemangioblastoma**. Nearly 2/3rd of patients had an underlying VHL diagnosis. **MRI** & **intraoperative fluoroscopic angiography** aided in mapping the surgical course. Every operation resulted in complete tumor removal. 22 of the patients demonstrated significant clinical improvement at 1 week follow up.
9.	Functional Outcome After Resection of Von Hippel-Lindau Disease-Associated Cauda Equina Hemangioblastomas: An Observational Cohort Study [(20)]	Gautam U. Mehta, Blake K. Montgomery et al	Operative Neurosurgery	2017	In this cohort study, **15** patients with **spinal hemangioblastomas** underwent resection via a **laminectomy** approach. More than 90% of operations resulted in complete or resection. On follow-up, 83% of patients had stabilized, 11% showed significant improvement and the rest demonstrated clinical worsening.
10.	Spinal cord hemangioblastomas: significance of intraoperative neurophysiological monitoring for resection and long-term outcome [(21)]	Sebastian Siller, Andrea Szelényi	Journal of Neurosurgery	2017	The authors conducted a retrospective analysis with **24** patients with **spinal hemangioblastoma**, mostly located in the cervical region. All patients underwent microsurgical tumor resection. Most surgical interventions were accomplished with either **hemilaminectomy or laminectomy**. 95% of operations resulted in complete tumor resection. **Intraoperative neurophysiologic studies** monitored neurologic functionality. After long term follow-up, almost 90% of patients demonstrated improvement in tumor grades. Moreover, a relationship between negative

					intraoperative neurophysiology and poor patient prognosis was observed.
11.	Minimally Invasive Microsurgical Resection of Primary, Intradural Spinal Tumors is Feasible and Safe: A Consecutive Series of 83 Patients [(22)]	Maja Formo, Charlotte Marie Halvorsen, Daniel Dahlberg et al	Neurosurgery	2018	**83** patients with various spinal tumors were treated with **minimally invasive surgery**, **2 hemangioblastomas** were diagnosed. Complete tumor removal was achieved in nearly 90% of operations. 11% of patients had complications (CSF leakage, surgical infections etc.) On follow-up, more than 90% of patients retained the ability to perform daily functions.
12.	Minimally invasive resection of spinal hemangioblastoma: feasibility and clinical results in a series of 18 patients [(23)]	Marie T. Krüger, Christine Steiert et al	Journal of Neurosurgery	2019	In this study **18** patients with **19 hemangioblastomas** were assessed. Nearly 90% of patients had VHL. A **Minimally invasive surgery** was performed on all patients. Pre and post-operative patient status was assessed with the McCormick grading system. Complete surgical resection was achieved in all cases with no complications. Following surgery, tumor grade stabilized or improved in ~95% cases.

<u>Table 2</u>: Radiosurgery of Spinal Hemangioblastoma

Sr. No.	Article	Authors	Journal	Year of Publication	Main Findings
1.	Image-guided linear accelerator-based spinal radiosurgery for hemangioblastoma [(24)]	Michael T. Selch, Steve Tenn et al	Surgical Neurology International	2012	These authors used a linear accelerator (LINAC), to perform stereotactic radiosurgery to treat **spinal hemangioblastomas** in **9** patients. Tumors were mostly localized to the cervicothoracic region. 5 patients included had an underlying VHL diagnosis. Tumor radiation intensity was set around 12 Gy. On follow-up, tumor growth stabilized in ~90% of patients. No patients experienced any complications of radiotherapy.
2.	Image-guided stereotactic radiosurgery for treatment of spinal hemangioblastoma [(25)]	James Pan, Allen L. Ho et al	Journal of Neurosurgery	2017	These authors used **Cyber Knife** to treat **46 spinal hemangioblastomas** in **28 patients**. Almost 50% of patients had underlying VHL. A radiation dose between 15-35 Gy was used. Tumor stabilization or regression was achieved in >90% patients. Furthermore, no patients suffered from complications.

Table 3: Pharmacological Intervention of Spinal Hemangioblastoma.

Sr. No.	Article	Authors	Journal	Year of Publication	Main Findings
1.	Bevacizumab for the treatment of surgically unresectable cervical cord hemangioblastoma: a case report [(26)]	Ayman I Omar	Journal of Medical Case Reports	2012	This case-report involved treatment of a **cervical hemangioblastoma** with the VEGF inhibitor **Bevacizumab**. The lesion was deemed unfit for surgical excision. Post-treatment MRI scans demonstrated tumor regression. This was accompanied with improvements in the neurophysiological status of the patient.
2.	Antiangiogenic Treatment for Multiple CNS Hemangioblastomas [(27)]	Riklin C, Seystahl K et al	Onkologie	2012	This study included **2** patients with **hemangioblastomas** treated with **Bevacizumab**. The radiology of both patients improved post treatment.

Table 4: Chemoembolization and Intraoperative Angiography in Management of Spinal Hemangioblastoma.

Sr. No.	Article	Authors	Journal	Year of Publication	Main Findings
1.	Surgical Technique of Temporary Arterial Occlusion in the Operative Management of Spinal Hemangioblastomas [(28)]	Aaron J.Clark, Daniel C.Lu et al	World Neurosurgery	2010	The authors carried out a retrospective analysis of **20 spinal hemangioblastoma** cases at least 11 patients had VHL. Every tumor was completely excised with a **laminectomy** approach. Prior to surgery, 6 patients underwent **preoperative angiography. Five** patients subsequently underwent chemoembolization. Follow-up demonstrated stabilization in 13 patients, improvement in 5 patients, and worsening in 2 patients. In 5 patients' **temporary arterial occlusion** was effectively achieved with an **aneurysm clip,** to differentiate vessels supplying the tumor from those supplying the normal cord.
2.	Application of intraoperative indocyanine green videoangiography for resection of spinal cord hemangioblastoma: Advantages and	Shuyu Hao, Dezhi Li et al	Journal of Clinical Neuroscience	2013	Surgeons used **angiography with Indocyanine green dye** in **7** patients with spinal hemangioblastoma preoperatively. The vascularity of the tumor was well visualized in all except 2 patients. Total resection was

	limitations [29]				achieved in 6 patients while 1 patient underwent partial removal. Post-operative complications were not observed in any patient.
3.	Role of Preoperative Embolization of Intramedullary Hemangioblastoma [30]	G Saliou, L Giammattei	Neurochirurgie	2017	This study involved Seven patients with **hemangioblastoma** of which 6 had underlying VHL. **Pre-surgical embolization** was achieved with **histoacryl glue agent**. 1 patient developed vertebrobasilar infarction/cerebellar dysfunction. Following embolization, complete resection was achieved in 6/7 cases. Due to complications, the authors emphasized that chemoembolization should not be used ubiquitously but should be restricted to certain select cases only.
4.	Surgical Treatment of Vascular Intramedullary Spinal Cord Lesions [31]	George M Ghobrial, Jason Liounakos et al	Cureus	2018	Thirty-six patients with **intramedullary spinal tumors** were isolated, of which **20** were diagnosed with spinal **hemangioblastomas**. Prior to surgical resection, **angiography and chemoembolization** was performed in several cases. **Microsurgical laminectomy** was performed on all patients. On follow-up none of the patients developed further neurologic deficits. Thus, the authors concluded that preoperative angiography & embolization were safe in the management of spinal vascular lesions.

Discussion: This review analyzes several novel surgical and non-surgical options for managing spinal hemangioblastomas. Surgical measures include open microsurgical procedure, and the newly developed minimally invasive endoscopic operation. Preoperative embolization techniques and intraoperative angiography may help achieve surgical excision. Apart from surgery, radiosurgery and pharmacological agents such as anti-angiogenic Bevacizumab may be clinically useful.

Studies show pre-operative MRI helps in the diagnosis of spinal hemangioblastoma. Baker, K. B et al concluded that spinal MRI with contrast accurately illustrates tumors. [32] Contrast-enhanced MRIs may distinguish intramedullary and extramedullary spinal hemangioblastomas. [33] In addition to neuroimaging, preoperative angiography may play an important role in assessing tumor vascularity. Deng, X., Wang, K et al [34] analyzed 92 patients with hemangioblastoma that underwent 102 spinal surgeries. 13 patients were selected for Digital Subtraction Angiography (DSA) while 15 patients underwent three-dimensional CT Angiography (CTA), preoperatively. Both groups of patients had remarkable feeding vessels to the tumor. However, this technique was directly responsible for at least 1 complication of bilateral lower limb paresis, questioning the procedure's safety.

Surgical dissection success is directly related to surgical accessibility. Deng, X et al achieved total tumor resection in 94% of tumors. Nearly 40% cases demonstrated postoperative neurologic improvement. Moreover, long-term follow-up revealed incomplete tumor resection was associated with an unfavorable patient prognosis ($p < 0.05$). Wind, J. J., Lonser, R. R et al [(35)] assessed demonstrated improved clinical outcomes in patients with VHL that underwent complete surgical excision. Van Velthoven, et al demonstrated improvement or stabilization in all patients in neurological deficits following resection. [(36)]

Stereotactic radiosurgery has demonstrated efficacy in treating hemangioblastoma. Chang, S. D et al showed the effectiveness of LINAC radiotherapy on tumor regression to be slightly more than 70%. [(37)] Some studies depict a cure rate as high as 90% on initial evaluation. [(35)]

Several authors stress the need for advanced follow-up in patients with a single spinal hemangioblastoma. Genetic analysis of VHL disease should be carried out in cases of hemangioblastoma. Moreover, patients with VHL should undergo annual MRI or ultrasonography to detect insidious intracranial (cerebellar or supratentorial tumors), retinal (hemangioblastomas) spinal or abdominal (renal cell carcinoma, pheochromocytomas etc.) masses. [(38)]

Conclusion: Spinal hemangioblastomas may occur sporadically or in association with Von Hippel Lindau syndrome. Management has improved tremendously in the past 20 years. Minimally invasive surgical therapy accompanied by preoperative angiography and/or chemoembolization, generally results in uncomplicated total or subtotal resection of these vascular tumors. Moreover, radiosurgical methods such as gamma knife radiosurgery & LINAC have demonstrated positive results. Chemotherapy with anti-VEGF agents may become a more common treatment modality. Collectively, the literature demonstrates promising data that results in not only decreased mortality rates, but also improved quality of life for patients with spinal hemangioblastomas.

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