JOURNAL OF HEALTHCARE SCIENCES

Volume 5 Issue 11 2025, Article ID: JOHS2025001114

http://dx.doi.org/10.52533/JOHS.2025.51104

e-ISSN: 1658-8967

Review

Spinal Cervical Meningiomas: An Integrative Review of Molecular Pathogenesis, Evolving Surgical Procedures, and Pathway to Personalized Management

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Received: 13 October 2025, Accepted: 31 October 2025, Published: 10 November 2025.

Abstract

Spinal meningiomas are a major portion of primary spinal tumours that often affect the thoracic and cervical areas. The goal of this review is to provide an integrative and comprehensive synthesis of spinal cervical meningiomas, examining their molecular biology, classification, diagnostic strategies, surgical progression, and novel systemic treatment options. The Cochrane Library, Web of Science, PubMed/MEDLINE, and EMBASE database searches were conducted between August 2025 and December 2024. Based on inclusion/exclusion criteria and following a screening, full-text review, and data extraction procedure for English-language publications between January 2015 and August 2025, a narrative synthesis approach was employed to combine findings from different study designs and identify knowledge gaps. According to the 5th edition of the World Health Organization (WHO) Central Nervous System (CNS) tumors classification update from 2021, which included molecular markers (Telomerase reverse transcriptase (TERT) promoter mutations, Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) deletions), spinal meningiomas differ from intracranial meningiomas in that they are more likely to have Neurofibromatosis Type 2 (NF2) mutations. Radiotherapy was more effective for subtotal resection, recurrence, or high-grade tumors; systemic therapies (targeted agents, immunotherapy, and Somatostatin receptor 2 (SSTR2)) are emerging; early surgery improves quality of life; advanced imaging (Magnetic Resonance imaging (MRI), Computed Tomography (CT), and Gallium-68 DOTATATE Positron Emission Tomography (68Ga DOTATATE PET)) improved diagnosis and follow-up; and surgery is the mainstay, with minimally invasive or endoscopic approaches reducing recurrence, complications, and Simpson Grade 1 or 2 resection associated with a lower rate of recurrence. This review showed that the understanding of the pathophysiology of spinal meningiomas, in addition to integrating molecular markers into the grading criteria, results in accurately predicting clinical behaviour. It suggested that molecular profiling, advanced imaging, minimally invasive surgery, and future tools like liquid biopsy and AI-based radiomics can all be combined for the early detection and diagnosis of spinal menangiomas, optimize treatment, and improve quality of life. Additionally, this review elucidates that a multimodal, personalized framework is the way of the future of managing cervical spinal meningiomas.

Keywords: *Meningioma, spinal, cervical, recurrence, minimally invasive, Simpson grade*

Introduction

Meningiomas are recognized primary tumors of the central nervous system (CNS) that frequently arise from arachnoid cap cells in the brain and spinal cord meninges (1, 2). Although most of them are benign, 20% can develop into high-grade tumors that need more aggressive treatment (3). Additionally, they are the most prevalent benign intradural tumors in adults within the spine; their prevalence is lower throughout the neuraxis (4, 5). About 25% of spinal cord tumors and 1.2-12.7% of all meningiomas are spinal meningiomas (SM) (6, 7). Spinal meningiomas are often solitary, slow-growing, and non-invasive tumors (8). They are usually observed at the thoracic level, with 9% of the cases being asymptomatic (8). However, in advanced cases, SM results in pain, sensory and motor disturbances, gait abnormality, and sphincter dysfunction (8). Clinical manifestations of SM depend on the exact location of the spinal compression and the size of the tumor (8). Pain is the most reported symptom of SM, ranging between 42% to 87%; however, the most alarming symptoms are the motor disturbances, which are present in 33% to 93% of the reported cases (8). Motor symptoms vary from slight weakness to complete motor deficit (8). Motor symptoms include balance and gait disturbances (8). Whereas sensory clinical manifestations of SM are reported in 16% to 84% of the cases, and they include aching, tingling, numbness, paresthesia, anesthesia, and hypoesthesia (8).

Spinal menangiomas account for 25-46% of primary spinal tumors and are more common in women. Their frequency also rises with age (9). With low rates of recurrence and good functional recovery after resection, the prognosis is generally favorable. Magnetic resonance imaging (MRI), intraoperative ultrasonography, neuromonitoring, the operative microscope, and ultrasonic cavitation aspirators have better results and diagnostic methods (10). Furthermore, currently used treatments are minimally invasive, endoscopic, and robot-assisted, being used in conjunction with traditional methods. While aiming to reduce morbidity and maintain oncological safety, open laminectomy and hemilaminectomy remain procedures requiring significant effort to lower patient risk (11).

According to the World Health Organization (WHO), grade 1 (benign), grade 2 (atypical), and grade 3 (anaplastic) are the classifications of meningiomas (12). The basic treatment for recurrent tumors is still surgical resection (6), but additional measures like radiation or repeat surgery are sometimes needed (12, 13). Even after total resection, some histological subtypes exhibit more aggressive behavior and a propensity for early recurrence (13).

Modern advances in molecular neuro-oncology are revolutionizing our knowledge and approach to categorizing meningiomas. More accurate tumor behavior prediction and treatment strategy guidance are now possible because of combined genomic, transcriptomic, and epigenetic analysis, which goes beyond histopathology (14). The future treatment of spinal meningiomas is being shaped by these molecular discoveries, as well as developing minimally invasive surgical techniques (14, 15). Despite this, these advances are not yet fully integrated into a unified understanding of spinal cervical meningiomas. The goal of this review is to present an integrative and comprehensive synthesis of spinal cervical meningiomas, exploring molecular biology, classification, diagnostic strategies, surgical progression, and novel systemic treatment options.

Methods

Literature Search

A comprehensive literature search was initially conducted in December 2024 and subsequently updated through August 2025 to ensure the inclusion of the most recent advances in research and clinical practice. The process was deliberately structured to be transparent and reproducible, thereby establishing a reliable foundation of evidence for this review. Searches were performed in major electronic databases, including PubMed/MEDLINE, EMBASE, Web of Science Core Collection, and the Cochrane Library. To maximize both sensitivity and specificity, the

http://dx.doi.org/10.52533/JOHS.2025.51104

strategy incorporated a combination of Medical Subject Headings (MeSH) and free-text keywords.

The scope of the search was broad and encompassed tumor-related terminology such as spinal meningioma, cervical meningioma, intradural extramedullary tumor, and spinal cord neoplasm. It further extended to molecular biology terms such as molecular profiling, genetics, DNA methylation, and gene expression, as well as WHO classification markers like NF2 and CDKN2A. Additionally, terms relating to surgical management, including laminectomy, laminoplasty, minimally invasive approaches, endoscopic spine surgery, and robotic techniques, were integrated. Keywords related to adjuvant and systemic therapies, such as radiotherapy, stereotactic radiosurgery, targeted therapy, immunotherapy, theranostics, bevacizumab, and 177Lu-DOTATATE (177Lu-DOTATATE), were also included. Finally, diagnostic and prognostic aspects were captured using terms such as "prognosis," "recurrence," "quality of life," "radiomics," "artificial intelligence," "liquid biopsy," and "circulating tumor DNA."

Study Eligibility

Inclusion criteria were carefully defined to ensure the quality and relevance of the evidence base. Studies were considered eligible if they specifically addressed spinal meningiomas, with cervical lesions explicitly identified where possible, or intradural extramedullary tumors in which meningiomas represent a significant subgroup. Only studies published in English between January 2015 and August 2025 were included. Furthermore, the review emphasized high-quality evidence such as systematic reviews, meta-analyses, randomized controlled trials, prospective studies, large retrospective cohort analyses, and seminal case reports. Within this body of literature, preference was given to the most recent systematic reviews and meta-analyses, as these provide the strongest evidence-based conclusions. Excluded from consideration were conference abstracts, editorials, and publications that lacked peer review.

Screening and Data Extraction

All articles retrieved from the searches were subjected to a rigorous screening process. Initial evaluation was based on the relevance of titles and abstracts, after which eligible studies underwent full-text review. Data from each article included was systematically extracted and organized thematically to reflect the structure of this report. This ensured a logical flow of information and facilitated the synthesis of findings across different domains of tumor biology, classification, clinical management, and prognostic evaluation.

Data Synthesis

The selected studies were synthesized using a narrative approach. This method allowed integration of evidence derived from a variety of study designs, ranging from clinical trials to large cohort analyses. Such an approach enabled the construction of a comprehensive and coherent overview of the research landscape. The synthesis not only traced the evolution of knowledge from fundamental insights into tumor biology through to contemporary clinical interventions but also revealed key gaps in literature. By identifying these limitations, the review highlights areas that warrant further investigation and underscores the aspects of research that have broad clinical relevance. Ultimately, this approach ensured that the review provides a reliable summary of existing evidence and valuable direction for future research.

Pathobiology and Classification of Meningiomas

The biological understanding of meningiomas has been shifting significantly, moving away from a purely histological system toward one that incorporates molecular data to better predict clinical behavior **(Table 1).** This transition is particularly important for spinal meningiomas, which often display distinct molecular features. For many years, the WHO grading system has been the dominant framework for classification and remains a central factor in determining prognosis and guiding the decision for adjuvant therapy in symptomatic cases. The WHO system divides meningiomas into three grades based on histological features (6, 9). Grade 1, which accounts for the majority of meningiomas,

http://dx.doi.org/10.52533/JOHS.2025.51104

represents benign, slow-growing tumors with low recurrence rates and includes most spinal meningiomas. Grade 2 encompasses atypical tumors, which are more cellular, demonstrate higher mitotic activity, and carry a substantially greater risk of recurrence. Grade 3 comprises malignant tumors that are rare but highly aggressive, characterized by very high mitotic rates, rapid local invasion, and frequent recurrence. While histopathological classification provides a useful framework, it is limited by subjectivity, interobserver variability, and the inability to capture the biological heterogeneity that may exist among tumors assigned to the same grade.

Table 1. Key updates to the 2021 WHO CNS5 Classification of Meningiomas about the WHO 2016 classification

Feature	WHO (2016) Classification (42)	WHO CNS5 (2021) Classification (43)	Clinical Significance of the Change
Primary Classification Basis	Primarily histopathology (mitotic count, cellular features)	Integrated histopathology and molecular genetics	Moves toward a more objective and biologically relevant classification.
Brain Invasion	A criterion for Grade 2 (Atypical)	Remains a criterion for Grade 2 (Atypical)	Confirms the prognostic importance of this feature.
Key Molecular Markers for Grading	Not used for grading	TERT promoter mutation and/or CDKN2A/B homozygous deletion are standalone criteria for Grade 3	Elevates tumors to the highest grade based on aggressive biology, even with benign histology, mandating more aggressive treatment and surveillance 9
Specific Histologic Subtypes	Choroid and clear cell subtypes are designated as Grade 2	Choroid and clear cell subtypes remain designated as at least Grade 2	Reinforces the inherently higher recurrence risk of these specific subtypes.14
Nomenclature	Roman numerals (e.g., Grade II)	Arabic numerals (e.g., Grade 2)	Standardizes nomenclature across CNS tumor classifications 14

Advances with WHO CNS5

A major development came with the publication of the 5th edition of the WHO classification of central nervous system tumors (CNS5) (10), which for the first time integrated molecular markers into the grading criteria. This step formally recognized that certain genetic alterations provide a more accurate reflection of tumor behavior than histology alone. In this updated system, two molecular events—the telomerase reverse transcriptase (TERT) promoter mutation and the homozygous deletion of Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B)—are now sufficient to classify a tumor as Grade 3. The TERT mutation allows tumor cells to avoid senescence and achieve replicative immortality, while CDKN2A/B deletions disrupt cell cycle regulation, leading to uncontrolled proliferation (16, 17). These refinements mean that a meningioma that might appear benign under the microscope can be reclassified as malignant if it carries such molecular alterations, a change that has direct therapeutic implications by necessitating adjuvant radiation and more intensive surveillance (18).

http://dx.doi.org/10.52533/JOHS.2025.51104

Molecular Distinctions in Spinal Meningiomas

A central advancement in the field is the recognition that spinal meningiomas are not merely intracranial tumors occurring at a different site; however, they constitute a biologically distinct group (2, 3). This finding challenges the traditional practice of extrapolating intracranial data to spinal tumors. Molecular profiling has shown that spinal meningiomas are strongly associated with mutations in the neurofibromatosis type 2 (NF2) gene or deletions on chromosome 22q, events that inactivate the tumor suppressor protein merlin and drive tumorigenesis (2, 6). In contrast, many intracranial meningiomas, particularly those located at the skull base, are NF2-wildtype and instead harbor mutually exclusive mutations in genes such as TRAF7, KLF4, AKT1, and SMO (6). These mutations are rarely present in spinal meningiomas. This divergence in molecular signatures carries direct clinical significance, as targeted therapies under investigation for intracranial meningiomas, such as AKT1 inhibitors, would not be effective in most patients with spinal tumors. Consequently, there is a pressing need to develop clinical trials and therapeutic approaches that specifically address the molecular context of spinal meningiomas rather than relying on generalized models across the neuraxis (2, 3, 7).

Emerging Prognostic Tools

Although the WHO CNS5 classification represents an important step forward, the rapid progress of molecular neuro-oncology is already producing prognostic tools that may surpass histology in predictive accuracy. One such advancement is DNA methylation profiling, which identifies stable epigenetic patterns that classify meningiomas into molecular subgroups with strong correlations to recurrence and survival outcomes (12). Recent evidence indicates that methylation-based classification predicts progression-free survival more reliably than the WHO 2021 grading system (13). Because this method relies on an objective and standardized pipeline rather than subjective interpretation, it can more accurately stratify risk. For example, a histologically benign Grade 1 tumor could be identified as high risk through methylation profiling and managed with closer follow-up or adjuvant therapy, whereas a conventionally high-grade tumor with a favorable molecular profile could be spared unnecessary treatment.

Another powerful approach is transcriptomic analysis, which examines gene expression patterns to capture the functional biology of tumors. RNA sequencing studies have identified three molecular subtypes of meningiomas (A, B, and C), with subtype C showing the poorest outcomes, marked by deregulation of the DREAM (DP, RB-like, E2F, and MuvB) complex and increased proliferative activity (4). Building on these findings, a clinically validated 34-gene expression signature has been established that stratifies patients into low-, medium-, and high-risk categories for recurrence. This tool has the potential to reduce overtreatment, as it has been estimated that nearly one-third of patients in a validation cohort could have avoided unnecessary radiation therapy without compromising disease control (13).

Bridging Histology and Molecular Classifiers

Despite these advances, a gap remains between the official WHO CNS5 diagnostic framework and the demonstrated predictive power of molecular classifiers. Clinical decisions continue to be guided primarily by histological grade, particularly regarding the recommendation of adjuvant radiation, even though molecular methods provide superior predictions of recurrence (4). This discrepancy can lead to overtreatment in patients with histologically high-grade but molecularly low-risk tumors, or undertreatment in patients with histologically benign tumors harboring high-risk molecular signatures. Bridging this gap is essential to move toward precision medicine in meningioma care. Incorporating molecular profiling techniques such as DNA methylation and gene expression analysis into clinical guidelines would enable a more accurate assessment of prognosis, reduce unnecessary interventions, and better align treatment strategies with the biological realities of individual tumors (19).

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Clinical Presentation and Advanced Imaging

The diagnosis of cervical spinal meningioma relies on a careful combination of clinical history and advanced neuroimaging. Because symptoms often develop slowly, maintaining a high level of clinical suspicion is essential, as delays in diagnosis are common (20, 21).

Symptomatology and Neurologic Exam

Cervical spinal meningiomas usually present with gradually progressive symptoms due to compression of the spinal cord (myelopathy) and/or adjacent nerve roots (radiculopathy). The median time from symptom onset to diagnosis can exceed 11 months (14). As the tumor enlarges and exerts pressure on the spinal cord, patients may develop manifestations of myelopathy. These include gait disturbance and imbalance, which occur in approximately 47% to 93% of patients at presentation (22). Motor deficits in the upper or lower extremities may range from mild clumsiness to severe paresis, while sensory complaints such as numbness, tingling, or a defined sensory level on the trunk are also frequent (14). In advanced cases, sphincter dysfunction, including urinary or bowel incontinence, may arise (3). When cervical nerve roots are compressed, patients often report radicular symptoms such as pain, numbness, or weakness distributed in a dermatomal or myotomal pattern affecting the neck, shoulders, and arms. Pain is a particularly common presenting complaint, occurring in 5% to 46% of patients with spinal pathology (14).

A thorough neurological evaluation is indispensable for localizing the lesion and determining the extent of neurological deficit. Clinical findings may include hyperreflexia, abnormal reflexes such as a Babinski sign, spasticity, and quantifiable motor or sensory impairments consistent with spinal cord compression (3).

Imaging

Magnetic resonance imaging (MRI), both with and without contrast, remains the gold standard for diagnosing spinal meningiomas (23). MRI provides superior anatomical detail of the tumor, its relationship with the spinal cord, and adjacent neural elements. Typical MRI features include a well-circumscribed intradural, extramedullary mass displacing the spinal cord, usually separated from it by a cerebrospinal fluid cleft. On imaging, the lesion is generally isointense to the spinal cord on T1-weighted sequences and isointense to slightly hyperintense on T2-weighted sequences. Following administration of gadolinium, meningiomas typically exhibit intense, homogeneous enhancement. A characteristic “dural tail” sign—enhancement extending from the dural attachment—is often seen. Although calcifications strongly suggest meningioma, their absence does not exclude the diagnosis, and in some cases, the appearance may mimic other tumors, such as schwannomas (23).

Computed tomography (CT) serves as a complementary modality. It is particularly sensitive to detect calcifications such as psammoma bodies and provides crucial detail about osseous changes, including hyperostosis or osteolysis at the tumor’s dural attachment. These findings are important for surgical planning, especially when implants for stabilization may be required (23).

Functional imaging has significantly advanced the diagnostic and management approach to meningiomas. Most meningiomas demonstrate overexpression of somatostatin receptor type 2 (SSTR2) (13). The radiolabeled somatostatin analog [68Ga] DOTATATE binds specifically to these receptors, enabling precise tumor visualization using positron emission tomography (PET). In selected clinical contexts, [68Ga] DOTATATE PET has shown greater sensitivity and specificity compared to conventional MRI (13). This imaging modality is particularly valuable in three scenarios: differentiating tumor recurrence from post-treatment changes, defining tumor boundaries for surgery or radiotherapy (including intraosseous extension), and identifying candidates for SSTR2-targeted radionuclide therapies. Current guidelines acknowledge its role in surveillance and treatment planning when conventional imaging is insufficient (13).

http://dx.doi.org/10.52533/JOHS.2025.51104

Surgical Management

Surgical resection remains the dominant form of treatment for symptomatic cervical spinal meningiomas. The primary goals of surgery include accomplishing maximal safe tumor resection to avoid recurrence, decompressing the spinal cord and nerve roots to improve or preserve neurological function, and acquiring a specimen for definitive histopathologic and molecular diagnosis (24). The pathophysiology of meningiomas and surgical armamentarium have changed considerably over the last decade, moving toward less invasive techniques that assure tumor removal, neurological safety, and reduce the potential for iatrogenic injury (24). Our understanding of the teratogenic nature of meningiomas, including their proclivity for local invasion or recurrence, whether radioresistant or radiation-associated, has changed considerably, as has the recommended surgical approach when managing patients (24).

Simpson Grade

Determining the extent of surgical resection is one of the most effective predictors of long-term tumor control and recurrence-free survival (24). The Simpson grading system has been the standard way of classifying the extent of tumor and dural resection of cranial and spinal meningiomas and relating these to the risk of recurrence (7). The Simpson grades are one (macroscopical removal of the tumor, dural attachments, and abnormal bone), two (macroscopically complete removal of the lesion and coagulation of its dural attachment), through five (bona fide decompression or biopsy) (25). The long-standing primary goal of surgery has been Simpson Grade 1 or 2 resection, which has a lower rate of recurrence than other grades of resection (25). However, El-Hajj et al. (2022) (24) recently published a large-scale systematic review and meta-analysis that demonstrated no statistically significant difference in odds of recurrence between Simpson Grade 1 and Simpson Grade 2 resection (p=0.94) (24). This practice-changing study indicates that surgical morbidity is likely associated with a complete dural resection, and grafting (needed for Grade 1) cannot be justified if a total resection with complete coagulation of the dural attachment (Grade 2) is achievable (24). This implies a less aggressive dural procedure to reduce the likelihood of surgical complications such as cerebrospinal fluid (CSF) leaks, as long as the tumor has been completely resected.

Surgical Approaches

Traditionally, the surgical approach for spinal meningiomas has involved an open, posterior laminectomy. The surgical approach is performed with a midline incision, followed by dissection of the bilateral paraspinal musculature and excision of the spinous processes and lamina, allowing the dura to be visualized. The open approach is effective in providing wide exposure but has significant muscle injury, postoperative pain, and potential for delayed instability at the posterior spinal column (26, 27).

Minimally invasive surgery (MIS) techniques have developed as a viable alternative to open surgery. These techniques, such as unilateral hemilaminectomy using a tubular or expandable retractor, have equivalent intradural objectives while limiting the injury to the posterior midline osteoligamentous structures and paraspinal musculature (11). Sufficient evidence is now available to make comparisons between the conventional approach and MIS; however, MIS yielded more favorable results (11, 28).

The benefits of MIS developed from short-term effects, such as decreased postoperative pain and earlier recovery, to demonstrate significant long-term oncological and functional benefits, which can be achieved by properly selecting patients. Mirza et al. (2024) (11) conducted a systematic review analyzing over 4,600 subjects with intradural extramedullary tumors, reporting strong evidence demonstrating that MIS was better tolerated: the recurrence rate was much lower for minimally invasive surgery (1.4%) compared to open surgery (10.0%). The reason for this significant difference is unknown; however, it can be attributed to less tumor seeding in a more defined operative field. In addition to lower recurrence rates, MIS was found to cause fewer complications, including CSF leaks, and arguably greater postoperative functional improvement (15).

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Although using the endoscopy technique for treating intradural pathology is a newly developed approach, emerging evidence supports its safety and feasibility. Jung et al. (2024) (29) reported a case of resection of a cervical intradural meningioma via a biportal endoscopic technique, resulting in complete removal of the tumor and no evidence of recurrence at 18-month follow-up. The biportal endoscopic technique is distinctive, as it utilizes two small portals: one for visualization (the endoscope) and one for instrument manipulation (i.e., performing a hemilaminectomy and gross total resection of the tumor), yielding an excellent outcome for the neurological function of the patient (29). This report underscores the extraordinary possibilities offered by intradural tumors utilizing MIS, which allows for definitive oncologic surgery with a minimal iatrogenic footprint.

These data significantly change the risk-benefit ratio for surgery, disconnecting the surgical decision-making from a "big operation and a good resection" and a "small operation and faster recovery" to one where the less invasive approach may have better long-term results **(Table 2)**.

Table 2. Comparative outcome measures of open laminectomy, minimally invasive surgery (MIS), and endoscopic approaches for spinal meningiomas

Metric Outcome	Open Laminectomy	Minimally Invasive Surgery (MIS)	Endoscopic Surgery	Key Takeaway
Gross Total Resection (GTR) Rate	>90%	>90% (e.g., 96.4%)	Feasible in case reports	MIS and endoscopic techniques can achieve GTR rates comparable to open surgery.
Mean Blood Loss	~240 mL	~65 mL	Minimal	MIS and endoscopic approaches significantly reduce intraoperative blood loss.
Mean Length of Hospital Stay	~6.8 days	~4.4 days	Short (outpatient potential)	Less invasive approaches lead to shorter hospitalizations and faster recovery.
CSF Leak Rate	~14.3%	~11.1%	Low (technique dependent)	MIS is associated with a lower rate of CSF leak complications.
Recurrence Rate	~10.0%	~1.4%	Not established (short follow-up)	MIS demonstrates a significantly lower rate of tumor recurrence in long-term studies.
Postoperative Functional Improvement	Good (Mean McCormick change -0.64)	Better (Mean McCormick change -1.30)	Excellent in case reports	Patients undergoing MIS may experience greater neurological improvement.

The use of robotic technology in surgery continues to evolve in spine surgery, with systems like Mazor X and ExcelsiusGPS more widely accepted (30). Current robotic systems are complex guidance systems for surgery; their current Food and Drug Administration (FDA)- cleared use is primarily for preplanning and accurately placing instrumentation (pedicle screws for spinal fusion). By modifying and adding intraoperative navigation systems, the robot navigates the surgeon's instruments along a defined

http://dx.doi.org/10.52533/JOHS.2025.51104

and preplanned path with accuracy through the sub-millimeter range, thereby reducing the potential risk of the misplaced screw or point of navigation and the radiation exposure to the surgical team (30). However, current robotics systems do not accomplish the dissection of soft tissue or tumor removal autonomously, which further limits their applicability in direct management of a cervical spinal meningioma to collateral use (30). An iatrogenic instability post wide laminectomy for a large, aggressive tumor requiring potential fusion with instrumentation can render robotic technology assistance relevant. However, the tumor resection itself remains a manual task performed exclusively by the surgeon. As this field evolves, autonomous robotics systems can possibly accomplish finer dissection for planned removal of soft tissue.

Adjuvant and Systemic Therapies

Although gross total resection is the aim for most spinal meningiomas, a small subset of patients requires treatment beyond surgical intervention due to the subtotal resection of the tumor, tumor recurrence, or early histological features suggesting an aggressive tumor. Some adjuvant and systemic therapies are emerging towards targeted, molecule-based therapies (5, 9).

Role of Radiation Therapy

Adjuvant radiation therapy (RT) is the standard of care in several clearly defined clinical situations (31). For individuals with a Simpson Grade 4 resection who undergo subtotal tumor resection, adjuvant RT is usually indicated for improving local control and delaying time to progression. In cases of tumor recurrence after initial surgery, RT is a primary treatment option, particularly if surgery is not a viable or ideal option. Furthermore, for higher-grade tumors, including WHO Grade 2 (atypical) and Grade 3 (anaplastic) meningiomas diagnosed de novo, adjuvant RT is indicated after a gross total resection due to their high innate risk of recurrence (31). The landmark Radiation Therapy Oncology Group (RTOG) 0539 trial provided a risk-stratified approach, which remains in general practice. It categorized patients into low-risk (i.e., gross total resection (GTR) of a Grade 1 tumor), intermediate-risk (e.g., GTR of a Grade 2 tumor), and high-risk (e.g., any Grade 3 tumor, or subtotally resected Grade 2 tumor) using observation for low-risk, and progressively increasing doses of RT for intermediate- and high-risk groups (31, 32). This approach elucidates the concept of completing individual postoperative management based on the patient's risk and tumor characterization.

Targeted Molecular Therapies

Historically, chemotherapy has demonstrated very little effectiveness in meningiomas (33). However, recently molecular drivers of meningioma have been targeted by drugs that utilize specific inhibitors for the inhibition of individual proteins or signaling pathways that are activated by a genetic mutation within the tumor (33). The Alliance A071401 trial is an example of targeted molecular therapies (34). A multi-arm "basket" trial was conducted on patients who have recurrent meningiomas, evaluating a specific targeted agent for patients based on their tumor genetic profile. Patients with NF2-mutant tumors, which are the most common form within the spine, were considered for a focal adhesion kinase (FAK) inhibitor, such as GSK2256098, given that the FAK pathway is activated downstream of NF2 loss. Whereas patients whose tumors had mutations in the SMO, AKT1, or CDK pathways were assigned the relevant inhibitors, vismodegib, capivasertib, and abemaciclib, respectively (34).

Immunotherapy and Theranostics

Two other innovative systemic approaches to treating meningiomas that are unresectable and radiotherapy refractory are being actively developed, including immune checkpoint inhibitors (ICIs) and somatostatin receptor 2 (SSTR2)-targeted theranostics **(Table 3).** ICI (e.g., pembrolizumab, nivolumab) are therapeutic agents that block the inhibitory immune system, allowing it to recognize and attack the cancer cells. This approach has changed the treatment scope in many cancers; however, it has shown limited success in meningiomas. This can be attributed to the low tumor mutational burden that is characteristic of most meningiomas (33).

http://dx.doi.org/10.52533/JOHS.2025.51104

Table 3. Emerging Systemic and Targeted Therapies of Spinal Meningiomas: 2022-2025

Therapeutic Strategy	Molecular Target / Mechanism	Agent(s)	Summary of Recent Clinical Trial Findings (2022-2025)
Targeted Therapy	NF2 pathway (via FAK)	GSK2256098	Modest activity in recurrent NF2-mutant tumors; PFS-6 of 33% in Grade 2/3 meningiomas (34).
	SMO/Hedgehog pathway	Vismodegib	Responses reported in patients with specific SMO or PTCH1 mutations (44).
	PI3K/AKT pathway	Capivasertib	Investigational for AKT, PI3K, or PTEN mutations; early responses observed (45).
	CDK pathway	Abemaciclib	Investigational for tumors with CDK or NF2 alterations (45).
Immunotherapy	PD-1/PD-L1 axis	Pembrolizumab, Nivolumab	Mixed results: PFS-6 of 48% in one study of recurrent Grade 2/3 tumors, but primary endpoints often not met; durable responses in a small subset (46).
Radionuclide Therapy (Theranostics)	Somatostatin Receptor 2 (SSTR2)	[177Lu] DOTATATE (Lutathera®)	Highly promising; PFS-6 rates of 94% (Grade 1), 48% (Grade 2), and 0% (Grade 3) in early studies. Randomized LUMEN-1 trial (NCT06326190) is ongoing (47).

SSTR2-Targeted Theranostics is one of the most promising and broadly applicable systemic treatments in development for meningiomas. Nearly all meningiomas are characterized by high expression of SSTR2. Theranostics combines the fields of diagnostics and therapeutics with the use of SSTR2 for imaging and the therapeutic version of this structural design. After high SSTR2 expression is identified on a diagnostic organ and a [68Ga]DOTATATE PET scan, [177Lu]DOTATATE is then given (33). The DOTA portion of this therapeutic agent is a beta-emitting radionuclide that binds to the SSTR2 on the tumor cells and provides a very targeted dose of cell-killing radiation (33). Preliminary studies have shown good rates of progression-free survival outcomes; moreover, a Phase II randomized trial (LUMEN-1) is in process (35). This approach is appealing since nearly all meningiomas express SSTR2, which increases its therapeutic applicability, compared with other targeted molecular therapies that require driver mutations.

Prognosis, Recurrence, and Long-Term Survivorship

Overall, the long-term prognosis for patients diagnosed with spinal meningiomas is favorable, with most patients having benign tumors that are completely resected. However, a small percentage of patients will have tumor recurrence, and there is a large portion of survivors who have long-term quality of life issues that will only be managed entirely through diligence.

An Integrative Model to Predict Recurrence

Predicting the risk of tumor recurrence is a crucial component of postoperative surveillance, as it determines whether the patient requires adjuvant therapy. Recurrence risk is determined by using an integrative model of clinical, surgical, and

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pathological variables. A systematic review and meta-analysis of the published literature assessed all published literature to identify prominent independent predictors of recurrence (24). The review found that the single most powerful predictor is tumor grade. However, the estimated recurrence rate for surgically treated spinal meningiomas is 6%. The median follow-up of all the studies was approximately five years, which was heavily skewed, given that most meningiomas with resection are benign (24). The rate of recurrence rises rapidly with grade. The recurrence rates for WHO Grade 2 tumors can be as high as 50% and for WHO Grade 3 tumors, there are extremely high rates of recurrence, nearly 90-94% (36). The addition of molecular markers such as TERT and CDKN2A/B status allows for even more specific evaluation of these risk factors (36).

It also reported that subtotal (Simpson Grade 3 and 4) resection increases the odds of regrowth or recurrence of tumor compared with gross total resection (Simpson Grade 1 and 2) (24). Tumors located ventrally to the spinal cord had an increased odd of recurrence ($p = 0.02$). This can be attributed to the technical difficulty of achieving gross total resection of ventral tumors, in addition to the risk of neurologic injury, leading to surgeons performing a less aggressive resection (24). In addition, male sex was found to be an independent predictor of recurrence ($p=0.014$). The biologic basis for this is not known, but a hormonal effect of tumor growth could partially account for this (24).

Health-Related Quality of Life

For patients with benign spinal meningiomas, the prognosis is outstanding, with excellent survival rates expected, including a 5-year survival rate of nearly 87% for benign meningiomas, even in patients over 40 (7, 24). However, survival does not necessarily mean a complete restoration of pre-disease functioning. Survivorship can present a significant disease burden, which affects the health-related quality of life (HRQOL) across domains of physical, mental, and social well-being (37). Fortunately, for the majority of patients with spinal meningiomas, surgery is highly effective in improving neurological function and HRQOL. Early surgical treatment is associated with significant and sustained functional neurologic improvement in motor deficits, sensory loss, gait disturbance, and pain. This typically leads to a favorable return to work rate (24).

The two most relevant predictors of unfavorable neurologic outcome are the preoperative neurological baseline and the delay of diagnosis and surgical intervention (24). Therefore, after the diagnosis of a symptomatic cervical spinal meningioma, prompt surgical treatment is essential to maximize the potential for neurologic recovery and long-term quality of life. Delays in intervention can cause irreversible spinal cord injury and poor functional outcome.

Surveillance Protocols and the Effect of New Technology

After complete initial treatment, the patient enters a long-term surveillance stage to monitor recurrent tumors. This is primarily done with serial MRI scans done approximately 3-6 months post-operative to achieve a new baseline. After the first scan, the patient often has an MRI once per year for five years. These intervals can then be lengthened to every 1-to-2 years, for life, depending on the tumor's initial grade and risk characteristics (7). This conventional imaging approach will receive a companion approach with the rise of multiple new molecular technologies.

The Future of Management

The management of cervical spinal meningiomas is emerging towards a highly integrated and personalized future. It will not rely solely on broad treatment classifications based on tumor histology. However, it will utilize a convergence of advanced imaging, molecular information, and minimally invasive technologies to effectively treat the individual patient and tumor biology.

AI-Radiomics: Non-Invasive Tissue Characterization

Radiomics is an emerging field that utilizes artificial intelligence (AI) and machine learning (ML) algorithms to facilitate high-throughput extraction of a wide range of quantitative characteristics from

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a standard medical image, such as pre-operative MRI (38). The quantitative characteristics identified in medical images correlate with the biology and behavior of the tumor and often describe patterns and textures that are not visible to the human eye. The use of radiomics for meningiomas is exhibiting great promise for non-invasive virtual biopsy (38). ML-based models are being trained and validated to accurately predict critical data directly from a patient's pre-operative MRI. Examples of these applications include molecular subtypes, WHO grade, and recurrence risk (38, 39). This technology has the potential to revolutionize the pre-operative work-up process. It can enable the surgeon to retrieve a radiomics report from a routine MRI and pre-operatively stratify a patient's risk, which directly influences the degree of resection and whether adjuvant therapies will be needed before operating on the patient.

Liquid Biopsy

Liquid biopsy is a minimally invasive approach that analyzes expression profiles of biomarkers, particularly circulating tumor DNA (ctDNA), in bodily fluids (typically blood) (40). Liquid biopsy is particularly difficult with CNS tumors due to the blood-brain barrier and the limited amount of ctDNA that enters the peripheral circulation. However, recent studies confirmed that meningioma-specific mutations can be detected in the blood plasma of patients (40). Although the technology is still an emerging application for meningiomas and is not ready for translation into routine practice, it has enormous potential. The goal is to be a highly sensitive blood test to be used for postoperative surveillance. The test would detect molecular recurrence, which is ctDNA reappearing in the circulation from non-detectable tumor residual growth, before the tumor reaches a size that can be visible on MRI. This would provide the opportunity for much earlier intervention, such as systemic therapy, at minimal disease burden to improve long-term outcomes for patients at high risk of recurrence. Additionally, the discovery of liquid biopsy methods and the ability to detect molecular evidence of recurrence, before radiographic evidence and earlier treatments of intervention, while the tumor burden is lower and more manageable, serves as a potential advance in a new era of surveillance (40, 41).

According to WHO's 2021 CNS5 update, which introduced molecular markers such as TERT promoter mutations and CDKN2A/B deletions, spinal meningiomas show important biological differences from intracranial meningiomas, particularly in their higher frequency of NF2 mutations. This distinction refines diagnosis and classification, emphasizing the unique biology of spinal tumors. In terms of management, radiotherapy is most beneficial after subtotal resection, for recurrent disease, or in high-grade cases, while systemic therapies, such as targeted agents, immunotherapy, and SSTR2-based approaches, are emerging as potential treatment options. Early surgical intervention remains the cornerstone of therapy, as it significantly improves quality of life. Advances in imaging, including MRI, CT, and [68Ga] DOTATATE PET, have further enhanced diagnostic accuracy and follow-up. Overall, surgery remains the mainstay of treatment, with minimally invasive and endoscopic approaches offering advantages in reducing recurrence and complications and achieving a Simpson Grade I or II resection is strongly associated with a lower risk of recurrence.

Conclusion

The future management of a patient with cervical spinal meningioma will likely occur through a complex, multimodal, deeply personalized treatment algorithm. Advances in radiomics can facilitate pre-operative patients' risk stratification, in addition to a minimally invasive or endoscopic approach, which results in minimal post-operative complications and maximal outcome. Integration of the WHO CNS5 histopathological classification for systematic histological and molecular profiling will provide a systemic basis for risk assessment on which personalized adjuvant treatment decisions can be based. Periodic MRI in conjunction with a liquid biopsy to assess for molecular recurrence can allow earlier detection and intervention. This data-driven and biology-informed framework highlights

http://dx.doi.org/10.52533/JOHS.2025.51104

the future of neuro-oncology to provide more effective, less toxic, and personalized care for patients with cervical spinal meningiomas

Disclosure

Conflict of interest

There is no conflict of interest.

Funding

No funding.

Ethical consideration

Non applicable.

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

The author contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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