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Traditional and Recurrent Spheno-Orbital Meningioma (SOM) Comparison and Treatment Methods

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Abstract. Spheno-orbital meningiomas (SOM) are rare brain tumors that pose significant challenges to treatments due to their anatomical complexity and high recurrence rates. This literature review considers journals published between 2000 and 2024. Analysis will be drawn based on current surgical and nonsurgical interventions of primary and recurrent SOMs and emerging treatments. Besides that, the review will draw an in-depth description of genetic mutations, such as NF2 and PI3K/AKT/mTOR pathway activation; surgical techniques such as MTA, EEA, and ETOA; and factors contributing to increased recurrent risks. Although treatment options for SOM continue to advance, complete resection is still difficult to achieve, especially in patients with recurrent SOMs. Understanding the tumor biology, pathogenesis, and limitations in current treatments allows for more accurate and effective treatments.

Keywords: Spheno-orbital meningioma; SOM tumor biology; SOM treatments.

1. Introduction

Tumors are mutations that cause uncontrollable abnormal cell growth. It can be seen in various parts of the body. They are classified as benign or malignant depending on their behavior. Benign tumors typically do not disturb the normal functioning of surrounding tissues. Malignant tumors, on the other hand, aggressively spread to other areas in the body through the bloodstream and obtain nutrients from surrounding tissues [1]. The tumor is caused by mutations in the genetic material. Undetected errors during cell mitosis can lead to rapid, uncontrolled growth and division. The mutation may be inherited or later develop due to epigenetics or carcinogens such as smoking, obesity, radiation, and poor lifestyle choices [2]. When the tumor develops in the brain, it presents complex and unique challenges to physicians due to the brain's intricate structure and limited space. Although malignant brain tumors rarely spread to tissues beyond the central nervous system (CNS), they can still cause serious harm to individuals due to their rapid enlargement, putting pressure on nerves in the brain. Brain tumors are graded based on their behavior and size on a scale from 1 to 4, with 1 indicating the slowest growth and aggression and 4 representing a malignant, cancerous tumor. Nevertheless, benign tumors under grades 1 or 2 can pose a severe danger to the patient [3]. The continuous enlargement of the tumor may block the cerebrospinal fluid circulation in the brain, resulting in hydrocephalus– an enlargement of the brain's ventricles which impairs cerebrospinal fluid circulation and brain function [4].

Meningioma is one of the most common primary CNS tumors, originating in the brain, accounting for 37.6% of all such cases and 53.3% of benign CNS tumors [5]. The tumor is formed on the arachnoid layer in the meninges, which envelopes the spinal cord and the brain. Diagnoses are more frequent in women than men and more common in individuals over 70 years of age [5]. Although the root cause of meningiomas is not identified, people with early exposure to radiation or who have the genetic condition Neurofibromatosis type 2 [5], a rare genetic condition that causes tumor growth usually in the CNS [6], are at higher risk of developing meningioma [5]. Symptoms of meningiomas often differ depending on their location. Common symptoms include headaches, hearing loss, trouble speaking, and hypotonia. In severe cases, seizures or sudden vision changes may be experienced [7]. Physicians often use Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) to diagnose a meningioma [8]. Meningiomas are further classified into different groups, according to

the World Health Organization (WHO). Grade 1 meningiomas are the most common. They are slow-growing and mostly benign. Grade 2 atypical meningiomas are more aggressive and have a higher chance of recurrence after initial removal. Grade 3 anaplastic meningiomas are malignant, fast-growing tumors that can spread through the cerebrospinal fluid (CSF), requiring urgent treatment [9]. Traditional treatment methods include surgery and radiation therapy. Surgery may be inappropriate when the tumor is close to fragile structures such as the optic nerves or major blood vessels. Different types of radiation therapy are for similar considerations. Fractionated Stereotactic Radiotherapy (FSRT) and Intensity-Modulated Radiation Therapy (IMRT) are used to deliver radiation to sensitive areas over many sessions, while Stereotactic Radiosurgery (SRS) aims beams of radiation to a specific location [10].

SOM is a rare intracranial meningioma that arises at the sphenoid wing, extending to the orbit, as shown in Figure 1.

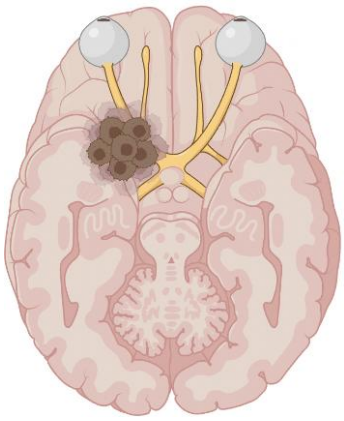

Figure 1. represents the location of the tumor in spheno-orbital meningioma. The image shows a superior view of the brain; the area marked with dark cells is the tumor in SOM. It is close to the optic nerves of the eye; pressure on the optic nerve may result in symptoms such as changes or loss of vision.

Surgery in this area is especially difficult due to its proximity to vital structures, the superior orbital fissure, and the cavernous sinus [11]. The superior orbital fissure allows the three motor nerves that control the extraocular muscles of the orbit to pass through [12]. The cavernous sinus allows the passage of the superior ophthalmic vein of the orbit and the superficial middle cerebral vein of the brain [13]. Meningioma resection surgery is one of the primary treatment methods for SOM; other approaches include microsurgical transcranial (MTAs), endoscopic endonasal (EEAs), and Endoscopic transorbital (ETOAs) [14]. Despite the plentiful treatment options, it is extremely difficult to remove all parts of the tumor. While high-dose radiation therapy can effectively control the tumor, it may result in the patient's gradual loss of vision [15]. As a result, recurrent spheno-orbital meningiomas became a major concern in SOM treatments.

This literature review aims to compare the surgical outcomes among patients with spheno-orbital meningioma. By examining the existing evidence, the review seeks to provide clinicians with valuable insights into the advantages and limitations of different SOM and recurrent SOM treatments and the possible future treatment advancements.

2. Methodology

This literature review adopted a narrative review approach. Peer-reviewed articles published between 2000 and 2024 were identified using PubMed, Google Scholar, and ScienceDirect. Keywords included “spheno-orbital meningioma”, “recurrent meningioma”, “NF2 mutation”, “PI3K/AKT/mTOR”, and “skull base surgery”. Articles were selected based on relevance to tumor biology, surgical outcomes, and therapeutic advances.

3. Pathogenesis of SOM

Orbital meningiomas are initiated on the arachnoid cap cells with secondary involvement of the orbit through bone invasion of the lateral roof of the orbit, leading to visual impairments [16]. Mutations such as the deletion of the NF2 gene on chromosome 22q that encodes the tumor suppressor Merlin cause uncontrollable cell proliferation [17]. Bone invasion in SOM is triggered by the stimulation of bone hyperostosis in nearby bones and tissues. The invasion is also driven by tumor cells that infiltrate into the bone marrow and spongy bone. The invasion can lead to structural changes in the affected bone, potentially pressing nerves and blood vessels [18]. Although this is often diagnosed using magnetic resonance imaging (MRI) and computed tomography (CT), due to the limited treatment options, this factor is not reflected in the WHO grading of the tumor [9]. Besides that, SOM secretes molecular mediators such as osteopontin (OPN) and matrix metalloproteinases (MMPs), which both affect the proliferation of bone-promoting tumor expansion [19]. Symptoms become more apparent as the tumor extends into the orbit. Patients may experience proptosis, problems with ocular motility, and visual disturbances. In some cases, tumors may compress cranial nerves, leading to symptoms such as diplopia and vision loss [12].

Even though procedures are performed to remove the entire tumor or parts of the tumor, recurrent SOM poses a significant challenge. The recurrent SOM often displays increased aggressiveness, resulting in higher histopathological grades and complex growth patterns. Invasive growth can also affect the cavernous sinus and intraconal space, worsening PFS [10]. Furthermore, the mitotic index, a qualitative measure of the proportion of cells undergoing mitosis within a given cell population, suggests that patients with recurrent SOM tend to have higher mitotic indices than initial SOMs. In some cases, it can exhibit up to 22 mitotic figures per 10 high-power fields [20]. Additionally, patients with higher mitotic index when diagnosed with SOM often have a higher likelihood of developing recurrent SOM, thus, physicians may alter their treatment plans to accommodate [20].

Other differences between SOM and recurrent SOM include genetic mutations such as AKT1, KLF4, and PIK3CA. Specifically, the AKT1 and PIK3CA mutations activate the PI3K/AKT/mTOR pathway, enhancing cell survival, proliferation, and tumor recurrence [21]. Elevated levels of Cyclin D1, a molecular marker that regulates cell cycles in recurrent SOM, also increase cell proliferation. This is caused by the disruption of mitosis during the G1 to S phase transition. The overexpression of Cyclin D1 limits apoptosis, which contributes to the uncontrollable growth of the tumor [22]. Common symptoms in recurrent meningiomas include sudden worsening of symptoms, more pronounced loss of vision, and new neurological deficits [12].

While SOMs are challenging to treat, understanding the tumor biology and the mutations can give significant insights into improving outcomes. Factors that promote bone invasion and genetic alterations in recurrent SOMs underline the complexity of complete recovery. Despite advances in imaging and surgical procedures, mitotic activities and molecular markers highlight the need for more targeted treatments.

4. Traditional treatments of SOM

Traditional treatments for SOM include microsurgical transcranial approaches (MTAs), endoscopic endonasal approaches (EEAs), and endoscopic transorbital approaches (ETOAs). Specifically, MTAs allow broader access to the tumor site, increasing the likelihood of total resection. However, this approach is often associated with higher risks of cranial nerve deficits [14]. Besides that, incomplete tumor removal can lead to recurrences; thus, resection of the affected bone is often crucial to minimize recurrence [14]. Nevertheless, SOM's proximity to critical structures, such as the cavernous sinus and optic canal, and the meticulous bone removal techniques required, make total resection extremely difficult to achieve. Surgeons often recommend alternative methods, such as radiotherapy, when extensive growth of SOM into the cavernous sinus is observed. Furthermore, when proptosis, the protrusion of the eye, is the primary symptom of SOM instead of major optical canal involvement, invasive craniotomy is often not the most optimal treatment [14]. EEAs, on the other hand, often

provide a precise image of the optic canal. Unlike MTAs, the tumor is accessed through the nasal cavity [14]. Due to its minimally invasive nature, recovery time is usually shortened with minimal complications after surgery. However, the endoscopic visualizations focus on midline lesions; accessing lateral extensions of SOMs is often challenging. Additionally, extensive bone invasion is difficult to access endonasally [14]. Therefore, EEAs are often performed through combination approaches such as transorbital methods to enhance tumor access and minimize invasiveness. Meanwhile, ETOAs insert an endoscope through the orbit. This provides direct access to the sphenoid wing. Although this method reduces recurrence rates and is less invasive, the orbit's intricate structure poses a significant challenge to the surgery. Restricted access to the tumor, especially when SOMs extend posteriorly, limits total removal. However, extensive tumor involvement in the cavernous sinus or other deep skull base regions may not be suitable for ETOAs. Besides that, tumors exhibiting a diffuse en plaque growth pattern, a "carpet-like" growth along the dura mater, are less manageable with ETOAs. Furthermore, prior surgeries that resulted in scarring in the orbital area may present challenges for ETOAs [14] as they reduce surgical space and may alter the tumor anatomy [14]. In conclusion, the treatments of SOMs require careful evaluation, planning, and execution. The tumor size, location, and features all play a vital role in the decision over the treatment implemented. MTAs offer the potential for extensive tumor resection but carry higher risks of cranial nerve deficits. While EEAs and ETOAs are less invasive, both have limitations in accessing regions of the brain. With that being said, combinations of these treatments can be performed to treat SOM, but the risks associated with these surgeries remain unavoidable.

5. Recurrent SOM

As bone invasions are more frequent in patients with recurrent SOMs, they pose a significant challenge to complete surgical resection [9]. In addition, bone invasions can infiltrate into adjacent anatomical structures such as the infra-temporal fossa, medial orbital wall, and the cavernous sinus. This extension into deeper, more urgent, and critical regions challenges the possibility of complete surgical removal of the tumor [15]. Furthermore, irregular bone edges caused by bone invasion are less apparent in imaging scans, and it is extremely challenging to distinguish a tumor-infiltrated bone from healthy bones with the naked eye [23], increasing the difficulty of surgeries. Aside from bone invasions, recurrent SOM often changes the molecular and genetic biology of the tumor. It is found that recurrent SOM patients have an increased frequency of chromosomal deletions. The deletions in chromosomes 1p, 6q, and 19p are often associated with tumor progression and recurrence [21]. The TERT promoter, a region of DNA that regulates the expression of the TERT gene that produces telomerase reverse transcriptase, also experiences mutations [20]. TERT promoter mutations, a frequent non-coding mutation in cancer [20], also cause an increase in telomerase activity, leading to cellular immortality [20]. Furthermore, high mitosis indices are often associated with higher WHO tumor grade. Specifically, WHO grade II, anaplastic, meningiomas express significantly higher mitotic activities compared to lower grades [3]. The mitotic indexes are correlated to predictive values for Progression-Free survival (PFS). Studies have shown that patients who experienced shorter intervals between recurrences also have high mitotic indexes [24]. Additionally, it also indicates a higher likelihood of brain invasion by the tumor, which often results in poorer outcomes after surgeries [24].

Due to the complex nature of recurrent SOM, preoperative preparations are often carefully planned as well. For example, advanced neuroimaging is used to identify soft tissue involvement and new bone invasion [9]; molecular profiling is done to determine TERT promoter mutations [25]; and histopathological profiling is done to examine the mitotic index of the patient [20]. Adjuvant Radiotherapy is also commonly used to treat recurrent SOMs, especially when complete surgical resection is not feasible. This non-invasive method targets residual tumor cells after partial resections to eliminate further growth. Studies have also shown that this method enhances PFS [9].

6. Advances in SOM treatment

Given the limitations and restrictions of current treatment options, scientists are working their way towards new approaches. Some of these treatments include Merlin, also known as neurofibromin 2 (NF2). Known for its functions as a tumor suppressor protein encoded by the NF2 gene located on chromosome 22 [16], Merlin Restoration Therapy in clinical trials aims to restore NF2 gene function to prevent tumor growth and recurrence. Although this study is under clinical trials, promising results demonstrate the significance of Merlin in meningiomas and offer ideal models for Merlin signaling research in the future [16]. Another therapy under development is Targeted Molecular Therapy. This therapy focuses on directly attacking cancer-specific molecules or pathways, such as the PI3K/AKT/mTOR pathway in recurrent SOMs [26]. This pathway is associated with cell proliferation and survival; overreaction of this pathway often aids tumor growth. Various inhibitors are developed to disrupt the signaling, and combination therapies have also been incorporated to enhance the effects. Understanding the molecular alterations in this pathway gives the possibility of personalized treatments that may be more beneficial to the patients [26]. Stereotactic Radiosurgery (SRS) became more precise with the development of better imaging techniques. It aims to minimize damage to surrounding healthy tissues and improve tumor control in recurrent SOMs. Moreover, the high-dose radiation delivered by SRS also shortens the treatment time required compared to standard radiotherapies. Results confirm that SRS is particularly effective for small, well-defined tumors, which is an ideal choice for recurrent SOM treatment [10].

7. Outlook and Conclusion

SOMs present risks due to their proximity to critical structures, often causing visual impairments and neurological deficits. Despite the benign classification according to WHO grading, they can become malignant tumors that exhibit aggressive behaviors.

SOM may be caused by genetic mutations (NF2, AKT1, and PIK3CA) and the abnormality in signaling pathways (PI3K/AKT/mTOR). The malfunctioning of these factors can cause bone invasion, tumor growth, and recurrence. With these understandings of the tumor biology of SOM, current treatments such as MTAs, EEAs, and ETOAs have significantly improved treatment outcomes. However, total resection of the tumor is still challenging to achieve. Although noninvasive treatments also present valuable advantages to SOM removal, they are often secondary considerations due to the possible side effects, such as vision loss.

Despite the current drawbacks, emerging therapies such as Merlin Restoration Therapy and Targeted Molecular Therapy hold promise to overcome these challenges. These therapies target specific genetic and molecular abnormalities, enhancing drug effects and providing more personalized treatments. Advances in SRS further highlight the potential of more accurate treatments, minimizing the risk of harm to vital structures.

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