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METHODS

Recurrent meningioma: When to intervene

Mohammad-Reza Hosseini-Siyanaki[1], Zahra Hasanpour Segherlou[1], Sophie Liu[2], Mohammed A. Azab[3], Majid Khan[4] and Brandon Lucke-Wold[1]*

[1]Department of Neurosurgery, University of Florida, Gainesville, FL, United States
[2]Department of Neuroscience, University of Johns Hopkins, Baltimore, MD, United States
[3]Department of Neurosurgery, University of Cairo University, Cairo, Egypt
[4]College of Medicine, University of Reno, Reno, NV, United States

***Correspondence:**
Brandon Lucke-Wold,
Brandon.Lucke-Wold@neurosurgery.ufl.edu

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Meningioma occurs most frequently as a benign tumor central nervous system that is common in old females. Radiation exposure and deletion of the NF2 gene are known risk factors. However, there is no consensus about the role of sex hormones. Meningiomas are usually benign tumors, but 6% can be anaplastic or atypical. Most asymptomatic patients do not require treatment, but complete surgical resection is recommended for symptomatic patients. If a tumor returns after being resected previously, it is recommended to be resected, followed by radiotherapy in some cases. Meningiomas (benign, atypical, and malignant) recurring after standard treatment fails could be treated with hormone therapy, chemotherapy, target therapy, and calcium channel blockers.

Keywords: meningioma, recurrent meningioma, surgical treatment, chemotherapy, hormonal therapy, target therapy

1. Introduction

Meningiomas more than 30% of all brain tumors and are female-dominant tumors (1, 2). The recent estimation of the meningioma incidence rate in the population was 9.12 per 100,000 (2). The etiology of the tumor is not completely understood yet. Some data show the relationship between sex hormones and meningioma, but other data do not support this theory (2). Meningiomas are mostly benign tumors that grow slowly and have a good prognosis. But almost 20% of them will show recurrence after complete surgical resection (3). Meningiomas can become malignant and 0.1–1% of all these tumors metastasize to further destinations (4–8). The World Health Organization (WHO) classifies meningiomas according to their degree of anaplasia, necrosis, invasion of the brain, and amount of mitosis. Based on the WHO classification, there are three grades: benign (Grade I), atypical (Grade II), and malignant (Grade III) (3, 4). Meningiomas are often Grade I, benign, and cured after gross surgical resection. Grade II tumors represent almost 5–15%, and almost 1–3% are Grade III (1). Approximately 20% of meningiomas are Grade II (atypical) or Grade III (malignant), with a recurrence rate of up to 41% within 5 years (3). Higher-grade meningiomas show a low survival rate even following surgery and adjuvant treatment, and their 10-year survival rate is 50–80% (1). In a meta-analysis, Grade I meningiomas had a 29% of progression-free survival (PFS) rate during 6 months and this rate for Grade II/III tumors was 26% after systemic medical therapy (9). In some studies, meningiomas recur after surgical treatment at a rate of more than 20% (10). Rolandic meningioma has more relapse and disability than convex meningioma (11). Some patients will experience recurrence despite getting different treatment plans, including surgery, radiotherapy, and systemic therapy (12). Longer follow-up after treatment

Abbreviations: GTR, gross total resection; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; STR, subtotal resection; EBRT, external beam radiotherapy; SRS, stereotactic radiosurgery; GH, growth hormone; HU, hydroxyurea; IFN-a, interferon-alpha.

in patients has shown a 47% recurrence rate after 25 years, but we cannot determine which patient is going to experience recurrence based on WHO grading, which means we cannot determine which patient needs adjuvant therapies and which does not need it (13). Tumors with Simpson Grade IV should be watched for recurrence, and for recurrence control, we can use preoperative tumor embolization (14). Another risk factor in another study was the doubling time of the tumor. Tumors with a doubling time of fewer than 3 years had markedly higher MIB-1 SI, and those with a doubling time of less than 1 year had a higher risk of developing malignancy (4). In another study on spinal meningioma, younger patients had a recurrence rate significantly higher than older ones. Other risk factors include the size of the tumor (large tumor has more recurrence rate) and plaque lesions.

These recurrent tumors mostly had been misdiagnosed as nerve sheath tumors or lymphoma (15).

2. Diagnosis

Diagnosis of meningiomas is challenging because of the slow tumor progression dynamics (i.e., the tumor arises from the membranous layers surrounding the brain and spinal cord, not from neurons) (16, 17). Furthermore, meningioma symptoms are usually subtle and easily mistaken for other health conditions (e.g., migraine disorder and nausea) (18). Preliminary diagnosis is done via computerized tomography (CT) or magnetic resonance imaging (MRI) or using contrast dye (19). However, a biopsy with pathology analysis is necessary for a definitive diagnosis. Their initial management is often advocated with the presence of adverse symptoms and when growth is noted on serial imaging (20). This can include neurosurgery, radiation therapy, or a combination of both. However, although gross total resection (GTR) is an admirable goal, achieving GTR is very challenging, and surgeons often employ safer margins to avoid surgery-related comorbidity and adverse outcomes (e.g., skull base meningiomas) (20–22). Meningiomas recur over time, especially when patients receive less than GTR resections (13, 23). Management of recurrent meningioma is similar to primary treatment, mainly involving repeat surgery, but can involve adjuvant therapeutics, though the alternatives are less promising than surgical intervention (23).

As mentioned previously, meningioma growth (and regrowth) is monitored through serial imaging studies. Both CT and MRI are valuable imaging modalities used in the diagnosis of meningioma status, including during post-surgical surveillance for recurrence. Meningiomas are typically intracranial extra-axial masses; thus, their appearance is broad-based with dural attachment (22, 24). However, they can also extend in a wide sheet-like manner (25). Therefore, because of the broad range of visual appearances in imaging studies, different imaging modalities are used for their respective advantages. Furthermore, researchers have employed machine learning and artificial intelligence technologies to aid in meningioma diagnoses (primary and recurrent), which hold promising value in tumor diagnosis and recurrence (26, 27). In the following, we describe MRI and CT imaging for meningioma diagnoses and their respective implications.

2.1. MRI

MRIs provide a clearer, more detailed picture, often allowing for the delineation of changes, such as swelling, to be visualized and noted (19). In MRI, meningiomas are typically hypo-iso-intensive on T1 and iso-hyper-intensive on T2 (24, 28). In most cases, dura tail is present on post-contrast imaging, helping to identify meningioma from other neural pathologies (i.e., schwannoma) (29). Apparent diffusion coefficient (ADC) values of meningiomas vary in diffusion-weighted imaging (DWI) (30). Further, perfusion imaging usually reveals higher relative cerebral blood flow and blood volume in meningiomas (31). Another feature to help distinguish meningioma is the presence of a CSF cleft between the mass and the brain parenchyma (i.e., crescent on T2 imaging), although these clefts usually disappear in higher-grade meningiomas because of the invasion of the tumor (19). Most meningiomas (including benign and malignant meningiomas) have edema in adjacent brain tissues (32). A small subset of meningiomas display other features, including hemorrhage, tumor necrosis, cyst formation, and fatty infiltration (33). As the meningioma growth increases, the underlying brain is displaced inward (24).

2.2. CT

Conversely, CT combines X-ray images into a three-dimensional reconstruction, allowing abnormalities to be visualized, albeit at a lower resolution (24). Still, CTs are commonly used to measure tumor size for serial imaging surveillance as they are quicker to capture than MRI images. A clearly outlined lobular mass attached to a broad dural base is commonly visualized via contrast CT imaging. In comparison, on non-contrast CT imaging, meningiomas manifest as hyperdense extra-axial homogenous masses, which, respectively, enhance following contrast infusion (24, 29). Because of the slow growth characteristics of meningiomas, intratumor calcification is present. Moreover, dystrophic and metaplastic calcification can also occur, visualized as a hyperdense speckled mass (34). Bony changes (e.g., osteolysis and hyperostosis) associated with meningioma progression (or malignant Grade III

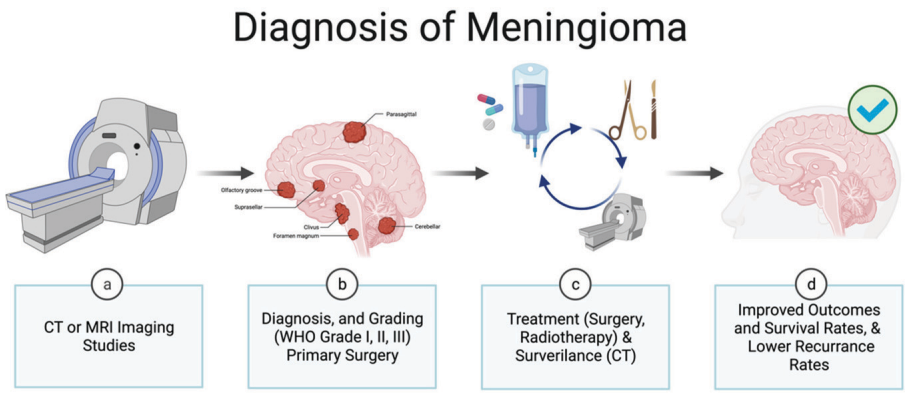

FIGURE 1 | Flowchart of Meningioma Diagnosis. **(a, b)** Primary surgical intervention is performed for histopathological confirmation following primary diagnosis via imaging studies, CT, and/or MRI. **(c, d)** After primary treatment (surgery and/or therapeutics), follow-up serial imaging studies are performed to evaluate for meningioma recurrence. Surgery, chemotherapy, and other methods will be used to treat a recurrence of meningioma.

meningiomas) are visualized well via CT and may also implicate osseous tumor invasion (**Figure 1**) (19).

3. Location and recurrence

Atypical meningioma most commonly occurs in cerebral convexity 57% of the time. There are interhemispheric falx (12%), posterior fossa (10%), frontobasal (6%), parasagittal (4%), tentorial (4%), sphenoid wing (4%), and cavernous sinus (2%) (35). The non-skull-base meningiomas are usually atypical, while the skull-base meningiomas usually have lower Ki67-MIB1 values coinciding with the low-grade meningiomas (**Figure 2**) (36). When other factors are controlled that may increase high-grade meningioma risk, it has been shown that atypical and malignant skull base meningiomas are less likely to develop (37). Several reports have published a higher rate of atypia and malignancy in parasagittal and convexity meningiomas (38–41). This may be related to the different embryological origins of the dura in skull-base and non-skull-base locations. Neoplasia tends to emerge from the dura originating from discrete embryological tissue as in non-skull-base locations (42, 43). Moreover, the location of the meningioma may determine its surgical resectability and prognosis.

4. Environmental factors determining recurrence

It is reported that head and neck irradiation is associated with an increased risk for meningioma incidence (44). Strojan reported a meningioma incidence risk of 0.53% at 5 years and 8.18% at 25 years after cranial irradiation (45). However, there is no evidence of the effect of radiotherapy on transformation to higher-grade tumors (46). A study by Phillips et al. found a correlation between traumatic brain injury and the incidence of meningioma (47). Hormonal factors may also be involved in the pathogenesis of meningioma explaining the high predominance of meningioma among females (48). During pregnancy, a meningioma may undergo aggressive behavior (49).

5. Surgical resectability and recurrence

For most cases of symptomatic meningioma, the primary treatment is surgical resection. Simpson grading is a well-known scale that guides the extent of meningioma resection, and there is a close relation between Simpson grading and the risk of recurrence (50). There is a high risk of early recurrence with high Simpson grades (III–V) (18, 51). With the more advanced neurosurgical imaging and navigation techniques, the authors believe that Simson grading has a limited value in predicting recurrence (52). Moreover, the extent of maximum resectability may be limited by the anatomical location of the tumor (53). Recurrence rates are correlated with Simpson grading in a variety of ways, ranging from a hazard ratio of 2.5 with each Simpson grade increase to a complete absence of any correlation (54, 55). Kira Marie et al. found that Simpson Grades III and IV correlate with recurrence only in convexity meningiomas, while they did not predict progression in falx/parasagittal meningiomas (52).

6. Radiotherapy and recurrence

6.1. Fractionated external beam radiotherapy

Radiotherapy is frequently used for symptomatic, primary, or recurrent Grade I meningiomas (20). For Grade II and

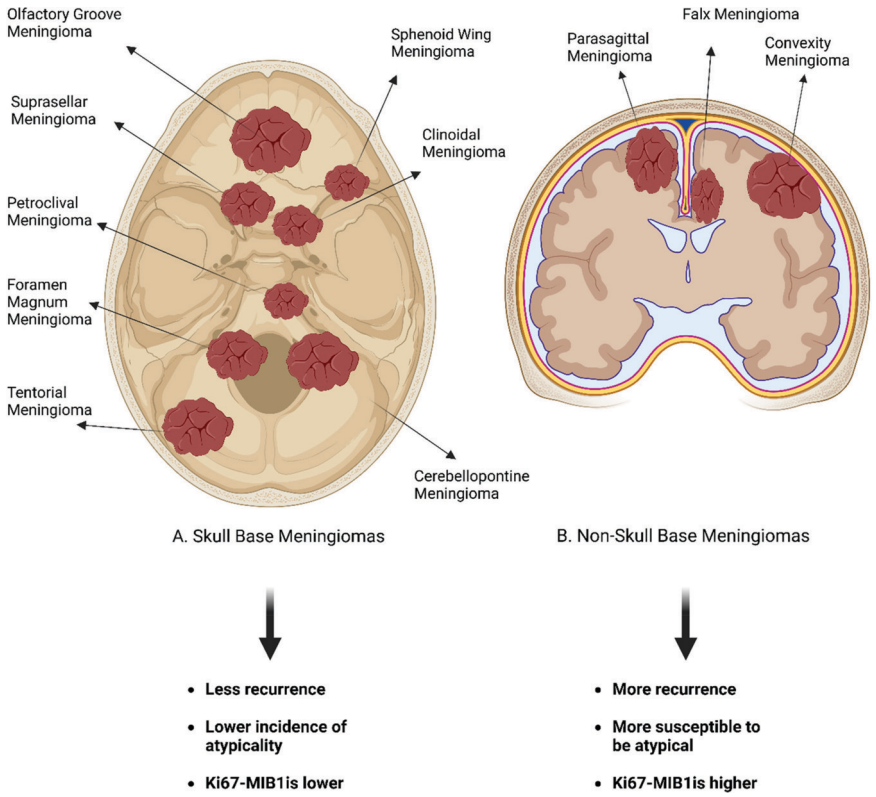

FIGURE 2 | (A) Skull-base meningiomas are rarely atypical and have lower Ki67-MIB1 values coinciding with the low-grade meningiomas, which decrease their recurrence risk. **(B)** Non-skull-base meningiomas are usually atypical and have higher Ki67-MIB1 values coinciding with the high-grade meningiomas, which increases their recurrence risk.

III meningioma GTR/subtotal resection (SR), postoperative radiotherapy is recommended (56). Similar to surgical management of meningiomas, radiotherapeutic modalities are dependent on a variety of factors, including tumor and patient characteristics. In Matani et al.'s study, predictors of external beam radiotherapy (EBRT) are correlated with WHO Grade III disease severity among patients with meningioma treated with radiation (57). Nonetheless, for WHO Grade I tumors, both stereotactic radiosurgery (SRS) and EBRT are acceptable treatment options, based on NCCN guidelines (57). However, because of the infiltrative nature of meningiomas, treatment strategies for WHO Grade III tumors are usually more limited (EBRT alone or surgery with EBRT) (57).

In summary, fractionated radiosurgery or conventional fractionated EBRT is applicable when it is not possible to treat the tumor with a single fraction (20). This recommendation is supported by data only for recurrent, "high-risk" meningiomas in WHO Grade I tumors (20). When neurological symptoms are not present in patients with WHO Grade I meningiomas following incomplete resection, radiotherapy may not be necessary immediately after surgery (58). In fact, radiotherapy is prompted for patients with WHO Grade II meningiomas that have undergone a Simpson IV–V resection (59). For WHO Grade III, radical surgery is recommended, followed by fractionated EBRT (20).

6.2. Stereotactic radiosurgery

SRS is highly regarded as a minimally invasive method of treating recurrent meningiomas following surgery (60). Numerous publications have shown the safety and success of stereotactic radiosurgery for tumors in complex locations where surgical treatment is not feasible (61). In comparison with EBRT, SRS delivers lower radiation levels precisely without adversely affecting nearby tissues. There is still controversy as to whether SRS can improve tumor control as adjuvant therapy. Because SRS has been demonstrated to be effective in controlling small-to-moderate meningiomas, microsurgery combined with SRS results in high tumor control rates. The gold standard of meningioma surgical resection continues to be to minimize tumor effect, release vital neurovascular structures, and procure tissue samples for prognosis (60).

7. Adjuvant therapy and recurrence

Inoperable recurrent meningiomas are treated with hormones, chemotherapy, or targeted therapies.(62, 63).

7.1. Hormonal therapy

7.1.1. Estrogen and progesterone receptor antagonists

There is evidence that meningioma growth may be hormone-dependent both epidemiologically (predominance of females) and biochemically (70–80% express progesterone receptors, and 10–30% express estrogen receptors). Additionally, about 60% of meningiomas are stained for prolactin receptors (2, 64).

Meningiomas of advanced grade often lose their hormone receptor positivity. Because of this, recurrent benign meningiomas have been treated with hormonal therapies. There was no significant response to megestrol acetate, an oral progesterone agonist, in a small trial of nine patients (65).

Tamoxifen, an estrogen receptor antagonist, failed to show an advantage in inhibiting meningioma development in a Stage II review involving 19 patients with non-resectable meningiomas (66). This is likely due to the low frequency of meningioma-specific estrogen receptor expression in humans. On the other hand, progesterone receptor antagonists were alternatively viewed as potential treatment options in several studies because of the higher probability of progesterone receptor expression in meningiomas (66). However, a prospective, multi-center, randomized Phase III clinical trial with 180 participants failed to demonstrate any significant advantage of mifepristone (66). Furthermore, a recent study that looked at mifepristone in a pre-selected population with multiple meningiomas and a high progesterone receptor expression level found a sustained clinical and stabilization response. These studies support the use of mifepristone in future prospective clinical trials of populations and suggest that potential subgroups of meningioma patients can likely benefit from it (67).

7.1.2. Growth hormone and insulin-like growth factors I/II

Growth hormone (GH) has been studied in relation to meningiomas since initial observations that acromegaly increases the risk of meningiomas. IGF-1, which is synthesized by the liver in response to GH secretion, facilitates normal growth in combination with GH secretion. Meningiomas contain numerous GH receptors, which have been shown to decrease tumor growth *in vitro* when inhibited. Pegvisomant inhibits meningioma xenografts in mice by acting as a competitive antagonist of the GHR (68).

7.1.3. Somatostatin agents

Somatostatins are neuropeptides that are synthesized in the hypothalamus, regulating various physiological functions, such as neuromodulation, secretory inhibition, and cell proliferation (69).

Pasireotide, a long-acting intramuscular somatostatin analog, targets more somatostatin receptors than existing medications (67). Somatostatin receptor expression in meningiomas is known to be high (90%), particularly in the SST2A subtype, but the function of these receptors is still unknown (66).

The efficacy of somatostatin and somatostatin analogs on meningioma growth has been the subject of contradictory research in both human and experimental studies. Roughly one-third of the patients had a partial response. Another one-third of the patients had stable disease, and the remaining one-third had clinical progression (66, 69).

7.2. Chemotherapy

Molecular mechanisms, such as cellular differentiation, cell proliferation, angiogenesis, and apoptosis, are targeted by chemotherapeutic agents (70). Unfortunately, chemotherapy treatment for recurrent meningiomas is constrained by a lack of tumor models and pre-clinical research, as well as a lack of knowledge regarding the molecular pathogenesis of meningiomas (71). For the treatment of meningiomas, numerous conventional cytotoxic agents, such as temozolomide, hydroxyurea, imatinib, trabectedin, and irinotecan, have been investigated over time (71). However, clinical trial outcomes have typically been disappointing. The use of cytotoxic, chemotherapeutic agents in treating recurrent meningiomas is not recommended because of low efficacy rates (56). In general, conventional chemotherapy approaches are reserved as last-line, salvage therapies for patients if surgery and radiation become refractory (72). Retrospective and prospective studies investigated the use of compounds such as hydroxyurea, temozolomide, irinotecan, and trabectedin. Trabectedin is a chemotherapeutic drug that has accrued data from *in vitro* meningioma studies, but its mechanism of action is still not widely understood (69). Trabectedin is currently the only chemotherapeutic drug examined in a multicenter, randomized study for recurrent meningiomas of WHO Grades II/III (56). Multidrug chemotherapy trials are still limited, regardless of the aggressiveness, malignancy, or resistance of recurrent meningiomas to surgery and radiation. A chemotherapy regimen consisting of cyclophosphamide, vincristine, and adriamycin is generally administered as an adjuvant treatment for malignant meningiomas (63). There are no data available on response rates, duration of responses, or toxicities related to other investigational regimens. Hydroxyurea (HU) inhibits ribonucleotide reductase, a growth factor involved in meningioma growth, and induces apoptosis in these cells. Several studies have shown that HU has limited activity. The response rates are low, although some patients appear to have stabilized their

disease (73, 74). Also, HU was shown to have modest toxicity, mostly manifested in the form of fatigue and anemia in patients with recurrent meningioma (75). A prospective multi-institution SWOG study (SWOG-S9811) was conducted to assess the effectiveness of HU in helping to treat meningiomas. However, the study ended early because of poor enrollment, and the initial results suggest moderate hematological toxicity and cytostatic activity (74).

7.3. Target therapy

Meningiomas and their molecular pathogenesis and molecular changes promoting meningioma growth are not well understood despite advances in molecular understanding. Several growth factors and pathways of signaling (i.e., PDGF, EGF, and VEGF) have been implicated (76, 77). PDGF drives cell proliferation both during normal development and in diseases, including cancer. Meningioma growth is believed to be influenced by PDGF (78, 79).

Over 60% of meningiomas express the EGF receptor (EGFR). Meningioma growth has been demonstrated to be stimulated by EGF and TGF-a *in vitro*, supporting the idea that autocrine/paracrine stimulation of EGFR might lead to the proliferation of meningiomas in humans. There has been an association between aggressive growth and TGF-a immunoreactivity in meningiomas (80).

For a subgroup of meningiomas, preoperative endovascular embolization treatment has become common because meningiomas are frequently highly vascular tumors (72). The main mediator of abnormal angiogenesis in these malignancies has been identified as the vascular endothelial growth factor (VEGF) (66). Differing levels of VEGF expression have been linked to both the WHO grade of meningiomas and the level of peritumoral cerebral edema (66). Researchers have studied humanized monoclonal antibodies directly inhibiting VEGF (e.g., bevacizumab, Avastin) as therapeutic agents aimed at stopping or reversing tumor-related angiogenesis (67). Phase II trials are necessary because there are a number of small-scale retrospective studies with conflicting results. Inhibition of VEGF receptors has been shown to have considerable anti-tumor effects, indicating that VEGF plays an important role in tumor angiogenesis (63, 69). Bevacizumab, an anti-VEGF antibody, has shown dramatic improvements in cancer survival (63). Meningiomas express VEGF and VEGFRs, which increase with the grade of the tumor (69). When compared to benign meningiomas, VEGF expression is two times higher in atypical meningiomas and ten times higher in malignant meningiomas (63). Further, VEGF increases the morbidity of these conditions by causing peritumoral edema (63, 66, 69). There has been little research on VEGF and VEGFR inhibitors in meningiomas. However, they have the potential to reduce edema and inhibit angiogenesis (66). In an antiangiogenic trial involving sunitinib, an inhibitor of tyrosine kinases with anti-VEGFR and anti-PDGF activity, 1 out of 28 patients demonstrated a halfway radiographic reaction. The remaining 17 patients displayed stable illness (69).

8. Other treatments

8.1. Interferon-alpha

Meningioma cell lines cultured *in vitro* are inhibited by recombinant Interferon-alpha (IFN-a). A retrospective case series study was performed on 35 cases of recurrent unresectable meningiomas that had previously undergone irradiation and were unresectable. Evidence suggests that IFN-a has antiproliferative, immunomodulatory, and antiangiogenic properties. In this trial, the most common toxicity was fatigue, which led to reduced dosage (seven patients), stimulant treatment (ten patients), and discontinuation of therapy early (three patients).

Neuroradiographic findings indicate that IFN-a is cytostatic as there were no radiographic responses but, instead, a stable disease state. The study's primary objective of 40% PFS at 6 months was exceeded by 54%, indicating meaningful palliation. The median PFS was 7 months, despite the lack of radiographic responses (54 and 31%, respectively) (68).

8.2. Calcium channel blocker

Meningioma growth can be blocked by calcium channel antagonists such as verapamil, nifedipine, and diltiazem at clinically relevant doses, according to Ragel (81). Inhibition of calcium-dependent secondary messenger systems is believed to be the major mechanism by which calcium channel antagonists exert their antitumor effects (82).

Verapamil or diltiazem added to HU enhances *in vitro* and *in vivo* growth inhibition of meningiomas. However, seven patients are included in a clinical trial. Over the course of 14.5 months of follow-up, the patients failed to demonstrate significant radiographic response despite receiving 8.1 treatment cycles (74).

9. Conclusion

Meningiomas are commonly benign, growing slowly, and have a good prognosis. But there will be a poor prognosis once the tumor recurs. Meningiomas often recur after being removed. Histological factors such as MIB-1 and multiple mitoses may denote aggressive tumors. There

is a high incidence of atypical meningioma in cerebral convexity. The importance of MRI follow-up in the early detection of recurrent meningiomas cannot be overstated as, in addition to neurological deficits, meningiomas may develop into atypical or malignant tumors with a greater risk of recurrence because of more mitotic activity and brain invasion. Women were more likely than men to suffer from recurrent meningiomas. There is a possibility that a meningioma will become aggressive during pregnancy. Recurrent meningiomas could only be treated with surgery and radiation therapy. There have been modest successes with chemotherapy. Since the introduction of targeted therapies and immunotherapies, our understanding of complex tumor genomics has grown considerably. Combining surgery with target therapy can increase patients' survival.

Author contributions

BL-W and M-RH-S were the major contributors to the design of the study. M-RH-S, ZH, and SL were responsible for writing the first manuscript. M-RH-S and MK were responsible for revising the manuscript and validating the included studies. M-RH-S, MA, and MK contributed to editing graphs. BL-W and M-RH-S conceived the study and were in charge of the overall direction and planning. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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