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Editorial

Atypical Meningioma: State of Art and Future Perspectives

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While meningiomas are often seen as harmless growths, a notable portion of these tumors display a more aggressive nature. These tumors are categorized as atypical or anaplastic meningiomas, falling into grade II and grade III according to the World Health Organization (WHO) [1]. The reported occurrence of these tumors differs extensively, ranging from 1.5% to 35% of all meningiomas, mainly due to differences in grading [2]. However, with the adoption of the new WHO grading system [3], it is likely that the actual number is closer to the higher end of this range. Among high-grade meningiomas, atypical meningiomas outnumber anaplastic meningiomas by approximately six to one [4]. High-grade meningiomas can both develop as new growths or progress from lower-grade tumors. Unlike benign meningiomas that have a low recurrence risk of about 10% after complete removal, atypical and anaplastic meningiomas are more aggressive and have higher recurrence rates ranging from 29% to 52% and 50% to 94%, respectively [5]. In contrast to benign meningiomas, which are influenced by estrogen levels and are more common in women, high-grade meningiomas are more often found in men [5].

The way that high-grade meningiomas look and act is very similar to benign meningiomas, which can make it hard to state how aggressive they are without histopathological examination. To date, reliable radiologic indicators of malignancy in meningiomas have not been identified. However, some features seen on magnetic resonance imaging (MRI) scans, like more pronounced edema around the tumor, and hyperintensity on diffusion-weighted imaging, and characteristic fluid-attenuated inversion-recovery (FLAIR) appearance of the brain-tumor interface, have been shown to provide a predictive value of high-grade nature of the lesion [6]. Using magnetic resonance spectroscopy might help to find out if a meningioma is nonbenign by showing higher levels of lipid and lactate, but more studies are needed to confirm these observations [7].

From a pathological perspective, anaplasia plays a critical role in the mortality of aggressive meningiomas [8]. The survival rate is significantly reduced to just 1.5 years for tumors classified as frankly anaplastic [8]. Conversely, tumors displaying brain invasion but lacking anaplasia have a median survival of 14.9 years when presenting with benign morphology and 10.4 years with atypical morphology [8]. Additionally, a high MIB-1 labeling index has been associated with tumor recurrence, although its utility is most evident in cases where certainty is lacking [9].

Age plays a critical role in predicting both survival and recurrence in aggressive meningiomas. Studies have demonstrated that age significantly influences survival rates following diagnosis [10]. For instance, individuals between the ages of 24 and 44 diagnosed with malignant meningiomas have an 84.4% chance of surviving for 10 years, whereas patients over 75 years old have a survival rate of 33.5% [10]. Furthermore, larger tumor size upon presentation is associated with a poorer prognosis, primarily because of the tumor's capacity to invade neurovascular structures [11]. In general, the outcome for anaplastic meningiomas still remains poor, with reported 5-year survival rates falling between 30% and 60% [12].

Surgical intervention continues to be the primary method of treatment for meningiomas that exhibit growth or are symptomatic. The surgical objectives and techniques for atypical and anaplastic meningiomas are akin to those employed for benign meningiomas. The primary aim for surgeons is to achieve a Simpson grade I resection whenever possible, which entails the complete excision of the tumor along with a margin of healthy dura and affected bone. However, complete removal is more complex for atypical and anaplastic meningiomas due to their propensity to adhere to the underlying brain. Research indicates that achieving gross total resection (GTR) significantly enhances long-term outcomes [13].

Meningiomas are tumors with a significant blood supply. When preoperative imaging shows large tumors with signs of increased blood flow, embolization may be done to aid in removal. Just like with benign meningiomas, the surgical removal of atypical and anaplastic meningiomas has a relatively low risk of severe complications, like infections at the surgical site, postoperative blood clots, deep vein thrombosis, and leaks of cerebrospinal fluid [14].

If achieving a complete resection is not possible, a subtotal resection (STR) is conducted, followed by adjuvant radiotherapy [15]. The decision to utilize adjuvant radiation therapy (RT) is determined by the degree of resection and the histological nature of the tumor. Adjuvant RT is typically advised for atypical and anaplastic meningiomas. Nevertheless, the utilization of RT for atypical meningiomas remains a topic of debate due to the absence of definitive guidelines [15]. The decision is often swayed

by the extent of tumor removal. Various studies have indicated that adjuvant RT following STR or biopsy enhances progression-free survival rates [15]. External beam RT (EBRT) or stereotactic radiosurgery (SRS) are frequently employed to mitigate the elevated recurrence rate associated with surgery alone.

For easily reachable tumors, it is advisable to prioritize complete removal through GTR, with adjuvant RT being considered only for cases of incomplete resections or instances of recurrence. Nonetheless, there remains a contentious discussion regarding optimal management strategies for atypical meningiomas, given their heightened risk of relapse post-GTR. Evidence suggests that post-GTR RT can enhance local control and decrease recurrence rates [15]. Typically, external beam radiotherapy (EBRT) is administered at a fractionated dose of 54 to 60 Gy over a span of 6 weeks, whereas SRS may be a viable option contingent upon the tumor's dimensions and location [15].

For certain instances of recurrent atypical and anaplastic meningiomas that show resistance to conventional treatments, the use of radioactive seeds (brachytherapy) has been explored. A study documented a median survival period of 8 years through the application of brachytherapy, although a significant portion of patients encountered complications such as wound breakdown or radiation necrosis, leading to the necessity of further surgical procedures [16]. Brachytherapy could be contemplated as an alternative treatment in cases where radiosurgery is not a viable option.

Regrettably, if patients do not show improvement with the standard initial treatments, the available options for further treatment become very restricted. Developments in biotechnology have enhanced our knowledge of meningiomas on a molecular level, sparking increased interest in targeted therapies as potential alternative treatments for aggressive meningiomas that have not responded to conventional therapy. Although several studies have been disheartening, certain medications like everolimus and bevacizumab have displayed some potential. Numerous clinical trials are presently ongoing, offering the possibility of expanding the range of tools available to combat this persistent disease.

In instances of unresponsive aggressive atypical and anaplastic meningiomas to conventional treatments, pharmacological intervention may be required. Clinical trials have been carried out to assess the efficacy of immunotherapeutic and hormonal agents, yet outcomes have proven to be limited. Unsuccessful outcomes with prior chemotherapeutic treatments have prompted the pursuit of targeted therapies. Potential molecular targets like platelet-derived growth factor (PDGF) receptors, epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR) have been examined for therapy [5]. Nonetheless, the effectiveness of targeted therapies in aggressive meningiomas is still under investigation, calling for further research to ascertain their advantages and constraints.

In brief, the prognosis for aggressive meningiomas, particularly anaplastic meningiomas, remains unfavorable. Primary treatment involves surgical intervention, with the goal of achieving complete resection whenever feasible. Additional radiation therapy is commonly advised, particularly for atypical and anaplastic meningiomas, in order to enhance local disease control and decrease rates of recurrence. Novel targeted therapies and ongoing clinical trials are being investigated as potential treatment modalities for aggressive meningiomas that do not exhibit response to standard treatments; however, their efficacy is still under evaluation. It is imperative for individuals with aggressive meningiomas to collaborate closely with a diverse team of healthcare professionals to establish the most suitable treatment strategy based on their specific circumstances.

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FT, GG: Conceptualization, Writing, Original draft. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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