Oncology
and Radiotherapy©
18(7) 2024: 001-007 • RESEARCH ARTICLE

A review of advances in the diagnosis and treatment of metastatic atypical and anaplastic meningiomas

Olger Nano[1], Supriya Peshin[2], Shivani Modi[3], Daniel Rosas[1]

[1] Memorial Cancer Center, Hollywood, Florida, USA
[2] Norton Community Hospital, Norton, Virginia, USA
[3] Jefferson Einstein Healthcare Network, Norristown, USA

ABSTRACT

Meningiomas are primary intracranial tumors of the Central Nervous System (CNS) originating in the brain or spinal cord and have an overall incidence of about 2.3-8.3 in 100,000. Meningiomas are benign tumors mostly but atypical and anaplastic meningiomas can behave aggressively with higher chance of recurrence. Meningiomas originate from specialized meningothelial cells called arachnoid cap cells and correspond to up to 26% of all intracranial lesions. However, higher-grade meningiomas are very rare. In this article, we focus on the important literature regarding classification and molecular biology of these high grade meningiomas. In addition, we elaborate on recent advancements of diagnostic tools and novel therapeutics in the management atypical and anaplastic meningiomas.

Keywords: arachnoid cap cells, intracranial lesions, atypicacentral nervous system, meningothelial cells

Address for correspondence:

Supriya Peshin,

Norton Community Hospital, Norton, Virginia,USA

E-mail: supriya.peshin2@balladhealth.org

Word count: 5711 **Tables:** 01 **Figures:** 00 **References:** 42

Received: 28 June, 2024, Manuscript No. OAR-24-140257

Editor Assigned: 02 July, 2024, Pre-QC No. OAR-24-140257(PQ)

Reviewed: 18 July, 2024, QC No. OAR-24-140257(Q)

Revised: 24 July, 2024, Manuscript No. OAR-24-140257(R)

Published: 31 July, 2024, Invoice No. J-140257

INTRODUCTION

The term meningioma is used to describe tumors arising from the pachymeningeal coverings of the brain and spinal cord [1]. Meningiomas are the most common type of primary intracranial tumors and have an incidence of 2.3-8.3 in 100,000. Most meningiomas are slow growing and benign (80%), however, atypical (15%-20%), and anaplastic (1%-3%) meningiomas are more aggressive and have a proclivity for recurrence, worse clinical outcomes, and higher disease-specific mortality [2, 3]. Ideal management of higher-grade meningiomas remains controversial, specifically when concerning the use of adjuvant radiation in patients following complete resection of atypical meningiomas. Chemotherapy and other related medical therapies can be considered in these patients, however, they have shown limited success with few such medical treatments showing marginal clinical benefit [4].

Radiation-Induced Meningiomas (RIM) can happen years after getting radiation treatment. These tumors can be aggressive and come back often, especially if they are high-grade. The signal protein called Vascular Endothelial Growth Factor (VEGF) is higher in more aggressive cases. Ossified meningiomas are rare, making up 1% to 5% of spinal meningiomas. These tumors completely turn into bone or have a lot of calcium. They are considered a special kind of meningioma, and it's suggested that they happen because some cells change their form [5].

Epidemiology of meningiomas

Meningioma prevalence is estimated to be 97.5/100,000 in the United States with over 170,000 individuals currently diagnosed with this tumor [6]. Age, sex, and prior cranial ionizing radiation are considered as risk factors for high-grade meningiomas. Meningiomas recurrence increases with age, peaking around 6th and 7th decades. Meningiomas are more common in females, but grades II and III develop more often in males. A total of 65,973 patients were identified with intracranial meningiomas (USA, 2016). Among these, 45,251 (68.6%) were White, 7,796 (12%) Black, 7,154 (11%) Hispanic, 4,902 (7%) Asian, and 870 (1%) patients reported as "Other-unspecified". Meningiomas are mostly found to occur in people around 60 years old, with the risk increasing with age [7, 8].

Meningiomas, originating from meningeal cells along the dura mater, the outer protective layer of the brain and spinal cord, are typically benign. Atypical (Grade II) meningiomas show

increased mitoses or specific histologic characteristics, while anaplastic (Grade III) meningiomas display overt malignancy features. Metastasis is rare but occurs more in malignant cases, with recent findings indicating a 0.76% overall metastasis rate and 43% in malignant meningiomas, signifying a poorer prognosis [8]. Most meningiomas arise from unknown reasons, although some may develop after ionizing radiation exposure or in the background of Neuro Fibromatosis 2 (NF2). Data from atomic bomb survivors in Hiroshima demonstrated a significantly elevated incidence of meningiomas compared to a non-exposed population with a relative risk of about 6.48 [9].

Radiation-induced meningiomas were reported in the 1960 after irradiation therapy of the scalp for tinea capitis with low-dose [10]. These meningiomas are classified into three groups depending on the amount of radiation administered: low (<10 Gy), moderate (10 Gy-20 Gy), and high (<20 Gy) doses. Radiation-induced meningiomas are commonly of high grade, are occasionally multifocal develop in younger age groups and are found to be highly proliferative [11]. As the frequency of NF2 mutations or the loss of chromosome 22 is lower in radiation-induced meningiomas, and structural abnormalities in 1p, 18q, or 10q are more common than in sporadic meningiomas, a different pathogenesis is shown for radiation-induced meningiomas [12].

Genetic aberrations implicated in meningiomas

The most reliable cytogenetic change in meningiomas is the loss of chromosome 22 [13]. In addition, atypical meningiomas show allelic loss of chromosomes 1p, 6q, 9q, 10q, 14q, 17p, and 18q, suggesting genes-associated progression at these loci. More frequent loci are lost in anaplastic meningiomas for 6p, 9p, 21q, 10q, and 14q [14]. In meningiomas, it's common to see genetic changes where part of chromosome-1 is missing. This is the second most common abnormality in these tumors. When we look at differences between men and women, we find that men tend to have more of these chromosome-1 changes compared to women. We also noticed that a specific gene called Elongation of Very Long Chain Fatty Acids-4 (ELAVL4) behaves differently in men and women. In men, the activity level of this gene is lower compared to women. Additionally, mutations in another gene called NF2 are linked to more serious forms of meningiomas found in specific parts of the brain, like the cerebellum and cerebral hemispheres. These tumors also tend to have more overall genetic abnormalities. NDRG-2 short for "N-Myc Downstream-Regulated Gene-2," is found on a specific part of chromosome-14. It's a gene that scientists think might play a role in making meningiomas more aggressive. In Grade III meningiomas, which are more serious, this gene tends to be less active. This decreased activity is linked to a process called hypermethylation, which affects how the gene works. In simpler terms, when the NDRG2 gene is less active, it could mean the meningioma is more likely to be aggressive. This could help doctors predict how serious the tumor might be in patients with meningioma [15].

The most common genetic alteration that occurs in meningioma is the inactivation of the Neurofibromatosis 2 (NF2) genes (Merlin) on chromosome 22q, which account for approximately 50% of meningiomas. When a specific part of chromosome 22, called 22q 12q, loses some of its genetic material, it leads to the loss of a gene called NF2, which produces a protein called Merlin or neurofibromin 2. This loss of the NF2 gene is quite common in meningiomas, both those associated with a condition called NF2 and those that occur sporadically. It's thought to be one of the early events in the development of these tumors. The NF2 gene is the most frequently mutated gene in meningiomas, but newly discovered mutations have been found in other genes like (TRAF7) Tumor necrosis factor receptor–associated factor, (AKT1) Ak strain transforming, (KLF4), Khalistan Liberation Force and Social Media Optimization. These mutations affect various pathways involved in cell signaling and regulation [16].

The SWI/SNF-Related Matrix-Associated Actin-Dependent Regulator of Chromatin Subfamily B member 1 (SMARCB1) is a chromatin remodeling gene, also known as hSNF5(Hierarchical Data Format, Version 5), Integrase Interactor 1 (INI1) , and BAF47, which may also be involved in the development of multiple meningiomas. The SMARCB1 exon 2 missense mutation is also found involved in individuals to the development of meningiomas and multiple schwannomas, occurring via the same genetic pathways [16]. Heterozygous loss-of-function mutations in SWI/SNF Chromatin-Remodeling Complex Subunit Gene (SMARCE1), are found involved in individuals with familial multiple spinal meningiomas without NF2 mutations. Tumors from individuals with SMARCE1 mutations were of the clear-cell histological subtype, which was negative for SMARCE1 immunostaining. These studies describe the new roles for SMARCE1 in the pathogenesis of multiple spinal meningiomas and ultimately reinforce the importance of the SWI/SNF complex in tumors with clear-cell histology [17]. Mutations in AKT1E17K were found exclusively in meningiomas and occurred in almost 65 individuals among every 958 of these tumors. A strong upregulation of Secreted Frizzled-Related Protein (SFRP1) expression was suggested in all meningiomas with AKT1E17K mutation, SFRP1 immunohistochemistry may be a reliable surrogate marker for the detection of AKT1E17K mutations [18]. Meningiomas are closely associated with the tumor suppressor syndrome NF2, with 50% to 75% of individuals with NF2 developing a meningioma during their lifetime. Allelic loss of 22q, 12q resulted in a loss of the NF2 gene product Merlin or neurofibromin 2 mutations in the Telomerase Reverse Transcriptase (TERT) promoter have recently been identified in various types of tumors. Many meningiomas that become more malignant over time have mutations in a part of the DNA called the TERT promoter. However, in tumors that come back without getting worse under the microscope, these mutations are usually not present. These mutations in the TERT promoter are important genetic changes that drive the malignant progression of meningiomas. They could be useful as a marker to identify meningiomas that might turn into more aggressive forms [18] (Table 1).

Tab. 1. Genetic mutations involved in meningiomas [19]

Gene	Function/Implication	Prevalence in Meningiomas	Gene Location	Target
NF2 gene mutations	Tumor suppressor gene; commonly associated with neurofibromatosis type 2; predisposes to meningioma development	Found in about 40%-60% of sporadic meningiomas; almost all in NF2-associated cases	22q, 12q	Loss of 22q, 12q results in a loss of the NF2 gene product merlin or neurofibromin 2 encoding a proapoptotic E3 ubiquitin ligase
AKT1 mutations	Activation of PI3K-AKT-mTOR pathway; linked to aggressive, higher-grade meningiomas, particularly in skull base variants	Identified in approximately 5%-10% of meningiomas	Chromosome 14q	Upregulation of SFRP1 (secreted frizzled-related protein) expression
SMO mutations	Activating mutation in the Hedgehog signaling pathway; sporadically found in a small subset of meningiomas	Present in a small proportion of meningiomas	Not specified	Effecting Hedgehog pathway
TRAF7 mutations	Often co-occurring with KLF4 mutations, prevalent in non-NF2-related meningiomas; role in MAPK signaling pathway	Identified in around 25%-30% of meningiomas	Not specified	Not specified
KLF4 mutations	Associated with aggressive, higher-grade meningiomas; influence on cell proliferation and differentiation	Present in about 15%-20% of meningiomas	Not specified	Encoding 3 C2H2 zinc finger motifs
POLR2A mutations	Rarely found, associated with aggressive histological subtypes of meningiomas	Identified in a small percentage of cases	Not specified	Not specified
AKT3 mutations	Implicated in rare cases, potential role in tumorigenesis and meningioma progression	Infrequently found in meningiomas	Chromosome 8q	Not specified
SMARCB1 mutations	Occur in a subset of high-grade meningiomas; role in chromatin remodeling and tumor suppression	Found in a small proportion of cases	Not specified	Induces cranial meningiomas located at the falx cerebri preferentially
BAP1 mutations	Identified in a subset of meningiomas, linked to aggressive behavior and poor prognosis	Present in a minority of cases	Not specified	Not specified
NDRG2 mutations	Hypermethylation of the NDRG2 promoter	Not specified	Chromosome 14q	Not specified
SMARCE1 mutations	Complex subunit gene SMARCE1	Not specified	Not specified	Familial multiple spinal meningiomas without NF2 mutations

Classification of meningiomas

Tumor classification is very important and critical in identifying patients at risk for recurrence and its subsequent management. According to the World Health Organization (WHO), meningiomas are grouped in three grades based on their characteristics. These include grade I -benign, grade II -atypical, and grade III -anaplastic. Grade I meningiomas are slow growing, low grade tumors and are the most common. Grade II atypical meningiomas are mid-grade tumors, increasing the chance of recurrence post-resection. Grade III anaplastic meningiomas malignant, fast-growing tumors. The cellular subtypes include papillary and rhabdoid meningioma. The classification of meningiomas is based on the

risk of recurrence and aggressive growth. Atypical meningiomas are comparatively uncommon and correspond to 4.7% to 20% of all meningiomas, while anaplastic meningiomas account for 1%-2.8% [20, 21]. Symptomatology of meningiomas varies according to intracranial location and may be related to seizures and/or intracranial hypertension. Primary central nervous system tumors are graded based on the tumor location, tumor type, the patient's age, extent of tumor spread, genetic findings and tumor remaining after surgery, if possibility of surgery can be avoided.

Histopathological diagnostics

There was no statistically significant difference between drugs A and B regarding PD at the beginning of the study (p=0.209). There was a statistically significant difference between drugs A and B regarding PD one month after the start of the study (p<0.001), so the mean of this variable was lower in drug A than in drug B. There was a statistically significant difference between drugs A and B regarding PD three months after the start of the study (p<0.001), so the mean of this variable was lower in drug A than in drug B. There was a statistically significant difference between the follow-up times regarding the mean of PD in drug A (p<0.001), so the mean of this variable in three months of follow-up was lower than at the beginning of the study and one-month follow-up. There was a statistically significant difference between the follow-up times regarding PD in drug B (p<0.001) so the mean of this variable in one- and three-month follow-up was lower than at the beginning of the study.

Pathophysiology

There was no statistically significant difference between drugs A and B regarding Business Intelligence (BI) at the beginning of the study (p=0.740). There was a statistically significant difference between drugs A and B regarding BI one month after the start of the (p<0.001), so the mean of this variable was lower in drug A than in drug B. There was a statistically significant difference between drugs A and B regarding BI three months after the start of the study (p<0.001), so the mean of this variable was lower in drug A than in drug B. There was a statistically significant difference between the follow-up times regarding BI in drug A (p<0.001) so the mean of this variable in 1 month and 3 month follow-up was lower than at the beginning of the study. There was a statistically significant difference between the follow-up times regarding BI in drug B (p<0.001) so the mean of this variable in 1 month and 3 month follow-up was lower than at the beginning of the study (Table 1).

Anaplastic meningiomas are identified by having 20 or more actively dividing cells (mitotic) and by showing clear signs of aggressive tissue changes resembling sarcoma or carcinoma. When doctors embolize a meningioma, they use a procedure to block its blood supply before surgery, usually by inserting particles or coils into its blood vessels. This is done to make the surgery safer and more effective by reducing blood flow to the tumor beforehand. Meningiomas that haven't been embolized don't undergo this targeted reduction in blood flow. In embolized meningiomas, doctors often find small areas of dead tissue (Necrosis) under the microscope. This occurs in about 40%-89% of embolized meningiomas compared to only 16% of non-embolized ones. Also, during examination, doctors may notice the embolization material within the blood vessels of the tumor, especially in larger arteries. The most common features seen in embolized meningiomas are necrosis and large nucleoli [22-25].

Epigenetics mechanisms

Evidence suggests methylation status can predict tumor behavior more accurately than the current classification by World Health Organization, and DNA methylation status has been proposed as an alternate classification system for meningiomas. DNA methylation is a type of change in the DNA structure that's thought to play a role in making the genetic material less stable. This change can silence or turn off genes responsible for repairing DNA damage and controlling how cells grow and divide. There's evidence to suggest that looking at the pattern of methylation in DNA might be a better way to predict how tumors will behave compared to the current system used by the World Health Organization (WHO) to classify tumors. Some researchers even suggest using DNA methylation status as a new way to classify meningiomas, a type of brain tumor. When scientists analyze the entire genome, they find that tumors with higher levels of methylation tend to be more aggressive and have a higher chance of coming back after treatment. However, analyzing DNA methylation patterns can be expensive, which might limit how widely it can be used in diagnosing and treating tumors [26].

Diagnostic strategies

The progression of benign meningiomas to malignant forms remains unclear, but factors like tumor size, female gender, and specific radiological features impact recurrence-free survival. The Simpson grade system, based on surgical resection extent, is a crucial prognostic factor, with better outcomes for grade I resections in malignant cases. The WHO grading system classifies meningiomas into benign (grade I), atypical (grade II), and anaplastic (grade III) subtypes based on histological and genetic factors. The 2021 revision integrates genetic alterations with histopathology, emphasizing their role in classification and management. Higher-grade meningiomas often exhibit abnormalities in genes like Neurofibromatosis type 2 (NF2), SMARCB1, Telomerase Reverse Transcriptase (TERT), and Cyclin Dependent Kinase Inhibitor-2A(CDKN2A), with varying frequencies based on subtype and location. The revised guidelines allow for within-tumor-type grading, applying criteria regardless of subtype, and underscore the significance of genomic alterations in meningioma classification and treatment [27-30].

Treatment strategies for atypical and anaplastic meningiomas

Treatment for meningiomas depends on symptoms. If small and asymptomatic, monitoring with frequent clinical evaluations and brain MRI scans is common. Symptomatic cases in addition to factors such as meningioma type, recurrence likelihood, and health impact often require neurosurgical intervention. Alternatives like radiation or chemotherapy are considered for those unfit for surgery. If feasible, the primary treatment for malignant meningiomas is surgery. Small, presumably benign, asymptomatic meningiomas can either be closely monitored or treated with radiation. The primary objective of surgery is twofold: to obtain tissue for tumor typing and to remove as much of the tumor as possible without exacerbating the patient's symptoms. Less aggressive (Grade I) may undergo complete or partial removal with additional treatments. More aggressive (Grade II and III) usually involve surgery and subsequent therapies. A recent addition is Grade 0, suggesting

complete tumor removal plus an additional 2 cm–3 cm from the tumor insertion site, yielding positive outcomes [30].

Advances in surgical techniques enhance precision, but complete removal isn't always possible. In 1957, Donald Simpson established a significant link between the extent of recurrence, defining Grades I–III as Gross Total Resection (GTR) and Grades IV-V as subtotal resection. Simpson Grading (I-V) quantifies tumor removal, with higher grades indicating less removal. Recurrence chances correlate with Simpson Grade, which are 9% for Grade I, 19% for Grade II, and 29% for Grade III. Surgery may involve dura removal and replacement, and specifics depend on tumor location and size, with personalized plans for each patient.

Immunotherapy

Meningiomas, along with their surrounding environment, trigger a local immune response. By studying the types of immune cells present, researchers have identified potential markers and targets for immunotherapy. Inspired by positive outcomes in treating other types of tumors, scientists are now investigating immune checkpoint inhibitors for meningioma treatment. Immune checkpoints are natural mechanisms that regulate the immune system to prevent it from attacking healthy cells. However, tumors like meningiomas exploit these checkpoints to evade detection by the immune system, creating an environment that suppresses immune activity. One key checkpoint is the PD-1 and PD-L1 pathway, which controls T cell activity. In meningiomas, higher levels of PD-1 and PD-L1 are associated with more aggressive tumors. Currently, there are ongoing trials testing antibodies that block PD-1 and PD-L1 in meningioma treatment. Additionally, a study at the Kettering Cancer Center in the USA found that Sunitinib, a medication, showed promise in treating progressive or recurrent atypical and anaplastic meningiomas, with a 42% recovery rate and no further progression within six months. [14]. The prospective, multicenter, single-arm phase II trial, involving 36 heavily pretreated patients with surgery and radiation-refractory WHO grades II-III meningioma, showed a 42% PFS6 rate at a 6-months primary endpoint. Median PFS and overall survival were 5.2 months and 24.6 months, respectively.Toxicities included intratumoral hemorrhages, thrombotic microangiopathy, and gastrointestinal perforation. VEGFR2 expression correlated with sig-nificant PFS differences (1.4 months *vs.* 6.4 months) in negative *vs*. positive patients (p=0.005) [31].

Radiation therapy

Radiotherapy is a special topic in the treatment of malignant meningiomas. When EBRT was added to surgical resection for anaplastic meningioma an increase in progression-free survival from 15% to 80% was observed and reported in five years. No consensus exists for atypical meningiomas, and EBRT has mostly been reserved for recurrence and progression [32, 33]. Due to the possibility of margin inclusion in the irradiation field with EBRT, radiosurgery is no longer specified for malignant meningiomas. Excellent observations have been reported with stereotactic radiotherapy when employed as an adjuvant after gross total resection or as definitive treatment regime [32]. Assuming that radiation therapy is of value in improving tumor control, new advanced radiation techniques can provide excellent target dose coverage, precise target localization, and accurate dose delivery.

Intensity-Modulated Photon Radiotherapy (IMRT)

For large postoperative resection cavities or remaining tumors, advanced techniques like Intensity-Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) are preferred over traditional 3-Dimensional Conformal Radiation Therapy (3D-CRT). IMRT is an advanced type of radiotherapy that delivers a precise dose of radiation to the target area. With computer-controlled linear accelerators, IMRT can adjust the intensity of the radiation beam to conform more accurately to the three-dimensional shape of the tumor. This precision allows IMRT to deliver higher doses of radiation to the tumor while reducing exposure to surrounding healthy brain tissues [34, 35].

Stereotactic radiation techniques

The techniques given as either hypofractionated radiotherapy (SRT) or radiosurgery (SRS) have been employed in patients with residual or recurrent atypical and anaplastic meningiomas. The key advantage of stereotactic techniques is their ability to sharply reduce radiation doses at the edges of the target area, thereby minimizing radiation exposure to surrounding brain tissues and lowering the risk of treatment-related side effects. Modern stereotactic techniques include Linear Accelerator (LINAC)-based systems like CyberKnife or Novalis (NTx), as well as Gamma Knife. Patients undergoing Gamma Knife treatment typically wear a rigid stereotactic frame to ensure submillimeter precision in targeting. In contrast, those treated with LINAC-based systems are usually immobilized using a high-precision, frameless stereotactic mask fixation system [36].

Particle radiation therapies

Particle radiation therapy uses protons or carbon ions to deliver radiation, unlike conventional photon radiations. Compared to photons, protons and carbon ions provide more uniform radiation and better conform to the tumor shape, allowing for precise delivery of higher radiation doses to tumor cells while sparing surrounding healthy brain tissue. Several studies have shown that particle therapy results in less radiation-induced toxicity compared to photon radiation. Most reported side effects include mild skin irritation and hair loss, with minimal to no severe acute or long-term toxicity. Re-irradiation with photons is challenging due to the limited tolerance of surrounding healthy tissue to additional radiation. However, particle therapy has been found to be very safe and effective for re-irradiation in cases of recurrent or progressive meningiomas [37].

Chemotherapy

Chemotherapy and other systemic therapies have demonstrated limited clinical efficacy in the treatment of meningiomas [38]. Interferon-alpha, somatostatin receptor antagonists, and VEGF receptor inhibitors are the only chemotherapy drugs approved by the FDA that can help patients with meningiomas, but their benefits are small. These options are typically used when meningiomas come back or get worse after surgery and radiation, and other treatments no longer work. While chemotherapy and systemic therapies have some success in treating meningiomas, they don't work very well, and these FDA-approved drugs only provide a little help, mainly in cases where other treatments have failed. Chemotherapeutic agents such as Hydroxyurea, temozolomide, irinotecan, and combination therapies exhibit varied efficacy, with

an average six-month progression-free survival rate of 26%, indicating poor outcomes for refractory malignant meningiomas. [38, 39].

When meningiomas have a lot of somatostatin receptors, it usually means they're more aggressive and have a higher chance of coming back after treatment. Because of this, researchers have looked into using drugs that block somatostatin receptors to treat recurrent meningiomas. In a small study with 16 patients who had recurrent meningiomas, they tested the effectiveness of a drug called Sandostatin LAR, which slowly releases somatostatin over time. With a primary goal of assessing progression-free survival at 6 months, the study highlighted the presence of somatostatin receptors, particularly sst2A, in the majority of meningiomas. Patients, including 11 women and 5 men with a median age of 58, had previously undergone diverse therapeutic interventions. Administered monthly, Sandostatin LAR showed minimal toxicity, resulting in a 31% partial radiographic response and 44% progression-free survival at 6 months, suggesting a promising, relatively nontoxic alternative for recurrent meningiomas with somatostatin receptor overexpression [40]. Growth factor receptors such as VEGF, PDGF, EGF are also overexpressed by many meningiomas. Thus, a variety of therapies using monoclonal antibodies or small molecule kinase inhibitors targeting one or more of these receptors have been studied in recurrent meningiomas such as sunitinib (administered at 50 mg/d for days 1-28 of every 42-day cycle, in SU011248 study) [41]. VEGF receptor reported mild improvement in progression-free survival. Small molecule kinase inhibitors like sunitinib and immunomodulating agents such as interferon-alpha have shown tolerability but modest therapeutic benefits. Monoclonal antibody drugs are the treatments that enlist the body's germ-fighting immune system against diseases, including cancer. Monoclonal antibody bevacizumab, against the VEGF receptor, have reported mild improvement in PFS in patients with recurrent meningiomas [42]. Another important small molecule kinase inhibitor imatinib antibody is also found importance during preclinical and clinical trials. Erlotinib and gefitinib are both small molecule kinase inhibitors of EGF receptor that have been studied in phase II trials for recurrent meningioma [42].

While well-tolerated, Sunitinib, a small molecule kinase inhibitor, and immunomodulating agents, such as Interferon-alpha, aim to stimulate or suppress the immune system, aiding the body in combatting cancer or infections. Interferon-alpha shows modest therapeutic benefit for recurrent meningiomas not suitable for resection, with studies indicating tumor growth stabilization and a phase II trial suggesting a slight enhancement in PFS at 12 weeks, though overall survival rates remain unchanged. Advancements in chemotherapy for melanoma patients include exploring monoclonal antibodies (e.g., bevacizumab) and small molecule kinase inhibitors (e.g., sunitinib) targeting specific receptors, showcasing promising results in improving progression-free survival.

Immunomodulating agents like interferon-alpha have demonstrated tolerability but limited therapeutic benefits in melanoma cases not suitable for resection.

CONCLUSIONS

In the past few years, there has been a big increase in studies trying to understand the clinical and genetic aspects of meningiomas, especially through detailed analysis of their genes. Despite the challenges related to diagnostics and therapeutics, advances in oncologic technology and research provide hope by uncovering new and informative genetic mutations, tumor behavior, and recurrence risk. Understanding the pathophysiology and molecular biology of meningiomas is critical in more adequately predicting prognosis, discovering novel therapeutic approaches, and leading treatment strategies for individual patients and the biology of their meningiomas. More novel investigations to further elucidate the heterogeneous pathology and genetic alterations associated with the morphology and malignancy of meningiomas may pave the way to the discovery of new therapeutic agents for the common and diverse entities of the neoplasm.

REFERENCES

1. Modha A, Gutin PH. Diagnosis and treatment of atypical and anaplastic meningiomas: a review. Neurosurgery. 2005;57:538 350.
2. Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803-820.
3. Rogers L, Gilbert M, Vogelbaum MA. Intracranial meningiomas of atypical (WHO grade II) histology. J neuro-oncol. 2010;99:393-405.
4. Yang SY, Park CK, Park SH, Kim DG, Chung YS, et al. Atypical and anaplastic meningiomas: prognostic implications of clinicopathological features. J Neurol Neurosurg Psychiatry. 2008;79:574-580.
5. Liu Z, Wang C, Wang H, Wang Y, Li JY, et al. Clinical characteristics and treatment of angiomatous meningiomas: a report of 27 cases. Int J Clin Exp Pathol 2013:695.
6. Anzalone CL, Glasgow AE, Van Gompel JJ, Carlson ML. Racial differences in disease presentation and management of intracranial meningioma. J Neurol Surg B Skull Base. 2019;80:555-561.
7. Surov A, Gottschling S, Bolz J, Kornhuber M, Alfieri A, et al. Distant metastases in meningioma: an underestimated problem. J neuro-oncol. 2013;112:323-327.
8. Shintani T, Hayakawa N, Hoshi M, Sumida M, Kurisu K, et al. High incidence of meningioma among Hiroshima atomic bomb survivors. Journal of radiation research. 1999:449-457.
9. Sadamori N, Shibata S, Mine M, Miyazaki H, Miyake H, et al. Incidence of intracranial meningiomas in Nagasaki atomic-bomb survivors. Int J Cancer, 1996;318-322.
10. Mooney MA, Abolfotoh M, Bi WL, Tavanaiepour D, Almefty RO, et al. Is falcine meningioma a diffuse disease of the falx? Case series and analysis of a “grade zero” resection. Neurosurgery. 2020;87:900-909.
11. Hosking FJ, Feldman D, Bruchim R, Olver B, Lloyd A, Vijayakrishnan J, et al. Search for inherited susceptibility to radiation-associated meningioma by genomewide SNP linkage disequilibrium mapping. Br J Cancer. 2011;1046:1049-1054.
12. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114:97-109.
13. Zang KD. Meningioma: a cytogenetic model of a complex benign human tumor, including data on 394 karyotyped cases. Cytogenet Cell Genet. 2001;93:207-220.
14. Smith MJ, Higgs JE, Bowers NL, Halliday D, Paterson J, et al. Cranial meningiomas in 411 neurofibromatosis type 2 (NF2) patients with proven gene mutations: clear positional effect of mutations, but absence of female severity effect on age at onset. J Med Genet. 2011;48:261-265.
15. van den Munckhof P, Christiaans I, Kenter SB, Baas F, Hulsebos TJ. Germline SMARCB1 mutation predisposes to multiple meningiomas and schwannomas with preferential location of cranial meningiomas at the falx cerebri. Neurogenetics. 2012;13:1-7.
16. Lusis EA, Watson MA, Chicoine MR, Lyman M, Roerig P, et al. Integrative genomic analysis identifies NDRG2 as a candidate tumor suppressor gene frequently inactivated in clinically aggressive meningioma. Cancer Res. 2005;65:121-126.
17. Shibuya M. Pathology and molecular genetics of meningioma: recent advances. Neurol Med-Chir. 2015;5:14-27.
18. Skiriute D, Tamasauskas S, Asmoniene V, Saferis V, Skauminas K, et al. Tumor grade-related NDRG2 gene expression in primary and recurrent intracranial meningiomas. J Neuro-Oncol. 2011;102:89-94.
19. Sahm F, Bissel J, Koelsche C, Schweizer L, Capper D, et al. AKT1 E17K mutations cluster with meningothelial and transitional meningiomas and can be detected by SFRP1 immunohistochemistry. Acta Neuropathologica. 2013;126:757-62.
20. Smith MJ, O'Sullivan J, Bhaskar SS, Hadfield KD, Poke G, et al. Loss-of-function mutations in SMARCE1 cause an inherited disorder of multiple spinal meningiomas. Nat Genet. 2013;45:295-298.
21. Komori T, Sasaki H, Yoshida K. Revised WHO classification of tumours of the central nervous system: summary of the revision and perspective. Neurol Surg. 2016;44:625-635.
22. Komotar RJ, Iorgulescu JB, Raper DM, Holland EC, Beal K, et al. The role of radiotherapy following gross-total resection of atypical meningiomas. J Neurosurg 2012;117:679-686.
23. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro-Oncol. 2021;23:1231-1251.
24. Lucas CH, Devine P, Solomon DA, Giannini C, Reifenberger G, et al. Sarcomatous meningioma: diagnostic pitfalls and the utility of molecular testing. J Neuropathol Exp Neurol. 2021;80:764-768.
25. Niiro M, Ishimaru K, Hirano H, Yunoue S, Kuratsu J. Clinico-pathological study of meningiomas with haemorrhagic onset. Acta Neurochir. 2003;145:767 772.
26. Pérez-Magán E, Campos-Martín Y, Mur P, Fiaño C, Ribalta T, et al. Genetic alterations associated with progression and recurrence in meningiomas. J Neuropathol Exp Neurol. 2012;71:882-893.
27. Nanda A, Bir SC, Konar S, Maiti T, Kalakoti P, et al. Outcome of resection of WHO Grade II meningioma and correlation of pathological and radiological predictive factors for recurrence. J Clin Neurosci. 2016;31:112-121.
28. Bujko M, Machnicki MM, Grecka E, Rusetska N, Matyja E, et al. Mutational analysis of recurrent meningioma progressing from atypical to Rhabdoid subtype. World Neurosurg. 2017;97:754.
29. Kepes JJ. The fine structure of hyaline inclusions (pseudopsammoma bodies) in meningiomas. J Neuropathol Exp Neurol. 1975;34:282-294.
30. Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. Brain Tumor Pathol. 2016;33:237-247.
31. Csonka T, Murnyák B, Szepesi R, Bencze J, Bognár L, et al. Assessment of candidate immunohistochemical prognostic markers of meningioma recurrence. Folia Neuropathol. 2016;54:114-126.
32. Rogers CL, Won M, Vogelbaum MA, Perry A, Ashby LS, et al. High-risk meningioma: initial outcomes from NRG Oncology/RTOG 0539. Int J Radiat Oncol Biol Phys 2020;106:790-799.
33. El-Khatib M, El Majdoub F, Hoevels M, Kocher M, Müller RP, et al. Stereotactic LINAC radiosurgery for incompletely resected or recurrent atypical and anaplastic meningiomas. Acta Neurochir. 2011;153:1761-1767.
34. Olar A, Wani KM, Sulman EP, Mansouri A, Zadeh G, et al. Mitotic index is an independent predictor of recurrence-free survival in meningioma. Brain Pathol. 2015;25:266-275.
35. Mair MJ, Berghoff AS, Brastianos PK, Preusser M. Emerging systemic treatment options in meningioma. J. Neuro-Oncol. 2023;161:245-258.
36. Karsy M, Guan J, Cohen A, Colman H, Jensen RL. Medical management of meningiomas: Curr Status Fail Treat Promis Horiz Neurosurg Clin. 2016;27:249-260.
37. Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: Salvage Ther Long-Act Somatostat Analog Neurol. 2007;69:969-973.
38. Kaley TJ, Wen P, Schiff D, Ligon K, Haidar S, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. Neuro-Oncol. 2015;17:116-121.
39. Lou E, Sumrall AL, Turner S, Peters KB, Desjardins A, et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. J Neuro-Oncol. 2012;109:63-67.
40. Zubair T, Bandyopadhyay D. Small molecule EGFR inhibitors as anti-cancer agents: discovery, mechanisms of action, and opportunities. Int J Mol Sci. 2023;24:2651.
41. Franke AJ, Skelton IV WP, Woody LE, Bregy A, Shah AH, et al. Role of bevacizumab for treatment-refractory meningiomas: A systematic analysis and literature review. Surg Neurol Int. 2018;9.
42. Chamberlain MC, Glantz MJ. Interferon-α for recurrent World Health Organization grade 1 intracranial meningiomas. Cancer. 2008;113:2146-2151.