

EPIDEMIOLOGY

Meningiomas comprise 36.6% of all primary CNS tumors, as reported by histology, and 53.2% of nonmalignant primary CNS tumors in the USA [2]. Meningioma has an overall incidence of 8.3 per 100,000 persons during the period 2010–2014, which has increased over the past decade from a rate of 4.52 during the period 1998–2002 [2,3]. Meningioma incidence is age dependent, increasing from 0.14 per 100,000 in children 0–19 years to 37.75 per 100,000 in the 75–84 year age group. It remains unclear if the increased overall incidence of these tumors is true or due to more frequent incidental detection of these tumors by neuro-imaging or improved accuracy of disease reporting. Data also reveal an increasing incidence with age and increased prevalence in African–Americans compared with Caucasians and 2.27:1 female predominance. It is thought that this female predilection correlates, at least in part, with endogenous sex hormone levels and is even higher (~3:1) during child-bearing years [4]. Of those meningiomas with documented WHO grades, 81.1% are grade I (typical), 16.9% are grade II (atypical) and 1.7% are grade III (anaplastic) [2]. Ionizing radiation to the skull is considered a risk factor for the development of meningioma, with a six to tenfold relative risk following a variable latency period, and without a clear dose-response relationship [5]. Furthermore, epidemiological associations, such as a history of head trauma, cigarette smoking, mobile phone usage, oxidative stress, and diet, have been consistently shown as associated with a significantly increased risk of meningioma, although such studies are often confounded by recall biases and frequently lack pathologic confirmation. There are several familial syndromes that predispose meningioma development, with the most common hereditary cause being neurofibromatosis type 2 (NF2), an autosomal dominant condition. In the general population, phenotypic NF2 is rare and seen in <1% of meningioma cases. Other notable meningioma-associated syndromes include Li-Fraumeni, Gorlin, von Hippel-Lindau, Cowden disease, and multiple endocrine neoplasia (MEN) type 1 [1].

TYPICAL CLINICAL PRESENTATION

The presentation of meningiomas, like other CNS tumors, depends upon their location. Meningiomas can be found arising from any intracranial or spinal dural surface. Identification of such intraventricular meningiomas is very difficult because of their no symptoms presentation. These Meningiomas are typically not fast-growing or infiltrative lesions, and they have an insidious symptom onset. Many are discovered incidentally on brain imaging. While there is no pathognomonic presentation of meningioma, clinical symptoms of headache due to increased intracranial pressure, focal neurological (including cranial nerve) deficits, or generalized and partial seizures caused by focal mass effect, are typical. Personality changes, confusion, and altered level of consciousness can be seen, especially in anterior (frontal) or parasagittal meningiomas, and they may be initially misdiagnosed as dementia or depression [6]. The differential diagnosis of a patient presenting with such symptoms is quite broad and should include other intracranial lesions (such as glioma or metastatic tumors).

NATURAL HISTORY & PROGNOSIS

An important concern for patients and clinicians is the natural course of tumors, especially when incidentally detected. While biopsy or resection is the only method to definitively confirm the diagnosis. Although histopathologic analysis, a typical radiologic appearance is often sufficient and remains the most common technique for diagnosing meningioma. Several observational studies have shown a linear growth rate of 2–4 mm/year for asymptomatic meningioma. Some tumors, however, display nonlinear, exponential growth patterns or no growth at all, underscoring the importance of surveillance imaging in untreated patients [7]. Moreover, it is thought that larger, symptomatic meningiomas have a different natural history

and more aggressive growth patterns, but since these tumors are rarely left untreated, their true natural history is not well understood. The estimated 10-year overall survival for meningioma is 57.1 and 77.7% for patients at a younger age at diagnosis (20–44 years) [2]. The natural history of grade II and grade III tumors is much more aggressive, with rates of recurrence at 5 years approximating 50% for grade II tumors and 90% for grade III tumors. These recurrences translate into meningioma-specific mortality in these patients, with 10-year overall survival rates of 53% for grade II patients and 0% for grade III patients, despite aggressive therapeutic efforts. The term progression in meningiomas is used to describe the growth of the residual tumor. It can also be used to describe the transformation from a lower to a higher grade tumor (e.g., from grade I to WHO grade II). Although there is often stability following nonsurgical treatment with radiation therapy, meningiomas rarely demonstrate a decrease in size. There has not been a consensus definition of treatment response or progression for meningioma, but a response assessment in neuro-oncology (RANO) working group currently seeks to establish one for the clinician and clinical trial use. Various strategies to assess tumor growth have been evaluated, such as linear 2D versus volumetric 3D growth versus growth rate, but none is a standard [7–9]. The use of change in cross-sectional area is routinely utilized in high-grade gliomas [10] and volumetric reduction has been successfully utilized in trials of systemic therapies for subependymal giant cell astrocytomas [11]. Most published studies of meningioma treatment have applied imaging-based endpoints as the primary outcome measures, the potential impact on survival is difficult to say because meningiomas often remain radiographically stable in response to nonsurgical treatments.

THE ROLE OF ADVANCED IMAGING

Magnetic resonance imaging (MRI) is the standard modality for the radiologic diagnosis and surveillance of meningioma. In patients who cannot undergo MRI, contrast-enhanced computed tomography (CT) may be used. MR typically reveals a dural-based, homogeneously enhancing, and well-circumscribed lesion. Benign meningioma will characteristically have a thickened, contrast-enhancing dural tail, and tumors are isointense to gray matter on non-contrast sequences. On CT, intralesional calcification is common, and bony changes, such as hyperostosis and a ‘beaten brass’ appearance of the remodeled skull, can also be seen in tumors located along the convexity. While patients generally present with a solitary tumor, multiple meningiomas may be seen (‘meningiomatosis’), particularly in syndromic patients, but the finding of multiple extra-axial lesions should raise suspicion for metastases. The dural tail is not pathognomonic for meningioma and may also be seen in metastases or hemangiopericytomas, but is frequently useful in distinguishing meningioma from other lesions (such as schwannoma) where it is absent [12]. Central necrosis is not specific for malignant meningiomas as this finding also is seen in benign tumors. Involvement of cerebral vessels is a common feature, particularly for skull base meningiomas, which may abut or encase the carotid and basilar arteries, or their branches. Cystic features are rarely seen [12]. Although these characteristics of meningioma are reliable aids in diagnosis, conventional MR cannot predictably determine the pathological grade for meningioma or its growth potential. The conventional MR can be unreliable for discerning early recurrence versus treatment-related radiographic changes such as mild dural thickening. Thus, there is a growing need for applying advanced MR imaging techniques and nuclear medicine studies in meningioma surveillance. The use of positron emission tomography (PET) is not yet common, but it’s very useful in tumors, where surgical biopsy is not feasible [13,14]. Similarly, the use of 18-Fluoro-ethyl-tyrosine (18-FET) PET may aid in the visualization of skull base meningioma compared with MRI [15]. The utilization of tryptophan metabolism via α -[(11)C]-methyl-L-tryptophan PET (AMT-PET) may provide insight into tumor grade among meningiomas [16]. Similarly, MR spectroscopy (MRS) studies of meningioma reveal features of increased choline and alanine peaks combined with decreased N-acetyl aspartate and creatinine peaks in comparison with normal brains [17]. The application of MRS to tumor grade is not well established, but an elevated lactate peak

characteristic of necrotic tumor tissue can be seen in atypical meningioma [18]. Lipid peak elevation on MRS is a marker of micronecrosis seen in atypical and malignant tumors but is also seen in low-grade microcystic variant tumors [12].

HISTOPATHOLOGY

The pathognomonic histologic feature of a meningioma is the formation of spherical meningotheial cells, called whorls, which eventually mineralize into psammoma bodies. Central chromatin clearing is also common in tumor nuclei, as are cytoplasmic invaginations into the nuclei, known as intranuclear cytoplasmic pseudo inclusions. However, these features are often unmarkable or absent in many meningiomas. A range of histologic patterns and findings can be seen that often mimic other soft tissue tumors, as indicated by the numerous variants just among benign grade I tumors: meningotheial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacytic and metaplastic[19]. Approximately 70–80% of meningiomas are positive for progesterone receptors and, to a much lesser degree, estrogen receptors [20,21], consistent with the epidemiologic preponderance of meningiomas in females, and strongly suggesting a hormonal component to tumor growth. Since the publication of revised WHO 2016 guidelines, meningiomas are classified as grade II ‘atypical’ tumors if they have either 4⁺ mitoses per ten consecutive high-power fields (using a 40× objective) or brain invasion, defined as meningioma pushing into the underlying cortex without an intervening layer of connective tissue [22]. In other words, a meningioma that is adherent to the underlying brain is not necessarily graded II, as there must be an unequivocal invasion of the tumor into the gray matter. If neither feature is present, at least three of the following five histologic criteria must be evident to arrive at a grade II diagnosis: intratumoral micronecrosis not caused by presurgical thrombolytic therapy; patternless sheets of tumor cells; prominent nucleoli (i.e., readily visible with a 10× objective); high cellularity; and tumor cells with scant cytoplasm relative to nuclear size (small cell changes) [23]. Brain invasion, which has been shown to be an independent adverse marker of tumor recurrence, is now used as a standalone criterion for a grade II diagnosis [24]. Although elevated mitoses and invasion are each regarded as sufficient for a grade II classification, multiple grade II features usually occur within the same atypical tumor, for example, invasion plus increased mitoses, sheet-like growth pattern and areas of high cellularity with small cell changes. Likewise, the other two subtypes of grade II meningiomas, clear cell, and choroid, almost always show additional findings like elevated mitotic activity, micronecrosis, and invasion. In fact, the most efficient microscopic evaluation of a meningioma, which usually involves multiple blocks of large tissue fragments, is to scan all the slides at lower power (2× or 4× objective) while looking for foci with micronecrosis, patternless sheets of cells, and high cellularity, as those areas are more likely to show elevated mitotic activity[25-27]. Brain invasion is also most readily identified at lower power by scanning the periphery of the tumor; in cases with equivocal brain tissue involvement, an immunostain for glial fibrillary acidic protein will usually highlight reactive astrocytosis if the tumor is invading the brain. Grade III anaplastic meningiomas often resemble high-grade sarcomas and will show most or all of the features of grade II atypical tumors, but the only required finding is 20⁺ mitoses per ten consecutive high-power fields. This means that meningiomas with 4–19 mitoses, a very broad range, all still fall within the grade II spectrum. Rhabdoid and papillary morphologic variants are automatically graded III[28]. Whereas adjuvant radiotherapy is generally withheld in grade I tumors and nearly always given in grade III tumors, a grade II designation offers the clinician much less guidance in the decision to administer or refrain from radiation – a continuing source of controversy, and frustration, among clinicians (discussed below).

MOLECULAR BIOLOGY

Despite these impressive studies, advanced molecular diagnostics have not yet revolutionized the workup and classification of meningiomas, as has been the case for gliomas. With the possible exceptions of *TERT* promoter mutations[29–31], most correlations are not sufficiently robust for identifying patients that need postsurgical radiation and closer follow-up. It is important to emphasize that none of these molecular markers can replace traditional WHO grading. Interestingly, and in contrast, methylation profiling of meningiomas has consistently shown a great deal of promise for identifying patients whose tumors are at the greatest risk of recurrence and progression[32–35]. While each WHO grade showed nonrandom subclass associations, histologic grade and methylation class did not always correspond with each other. In such cases, outcome data unequivocally showed that methylation class was a superior predictor of eventual recurrence than histological grade and in particular was able to more accurately assign recurrence risk among grade II meningiomas. Some grade I tumors had a methylation pattern associated with higher grade meningioma and these grades I tumors had higher rates of recurrence than grade I tumors lacking this methylation pattern[36–38]. The seminal studies suggest that epigenomic profiling may eventually supplant traditional light microscopy-based diagnosis and grading of dural-based tumors like meningioma. The identification of specific genes that are most differentially methylated and differentially expressed among the meningioma superclusters and subclasses will likely reveal key drivers of aggressive tumor behavior and potentially indicate innovative therapeutic targets.

SURGICAL TREATMENT

For many patients who present with meningioma, in particular asymptomatic tumors, observation with routine surveillance imaging alone is an acceptable strategy. For tumors that are growing or causing symptomatology, maximal safe surgical resection remains the standard of care for therapeutic management of meningioma. However, the ability to achieve complete resection may be limited by a number of factors, including tumor location; involvement of nearby dural venous sinuses, arteries, cranial nerves, and brain invasion into eloquent tissue; and other patient factors affecting the safety of surgery and anesthesia in general. All of these ultimately influence the decision as to whether to offer surgery, as well as the surgical approach and extent of resection planned. Neuroanatomic location dictates the surgical approach to meningiomas. Convexity meningiomas are relatively simple to approach and respect, but these account for only about one-sixth of meningiomas. Parasagittal tumors, while still superficial, are more complex to respect because they often involve or invade the sagittal sinus. Often, in instances where the tumor invades but does not completely occlude the sinus, the portion of the tumor within the sinus is not resected due to a high risk of air embolism, high-volume blood loss, or acute postoperative sinus thrombosis. Tumors at the base of the skull (sphenoid wing, olfactory groove, tuberculum sellae, cerebellopontine angle, or petroclival region) require more advanced surgical techniques and approaches to safely access the tumor without extensive brain retraction and injury. Recently, with advances in endoscopic technology and techniques, a number of midline anterior skull base tumors are being resected through an endoscopic endonasal approach [39]. Alternatively, radiotherapy should be considered as an upfront treatment approach if subtotal resection or operative morbidity is the likely outcome. Several principles of surgery on meningiomas are universally applicable. First, if possible, the blood supply to the tumor is addressed by coagulation, as meningiomas can otherwise have relatively high vascularity. Next, firm and often calcified tumors are debulked centrally in order to allow the tumor to be more safely and easily manipulated at its peripheral interface with the brain. Tumor capsules are carefully dissected from the overlying brain, cranial nerve(s), and neuro vasculature. Most often an arachnoid plane can be identified over the tumor surface, which may be dissected off the

tumor to protect the pia and neuro vasculature from injury. Unlike dural venous sinuses, the cranial nerves and arteries may often be enveloped or even encased by a meningioma, but they are rarely invaded by tumor, and identification of the arachnoid plane can allow for safe dissection of tumors from normal structures. The process of debulking centrally and dissecting peripherally is repeated until the full resection is achieved. After reconstruction of the dura with a dural patch substitute, any grossly involved bone is removed when possible, as recurrences may arise from invasion into the bone. Numerous factors, including venous sinus involvement, arterial or cranial nerve envelopment, and extensive involvement of the base of the skull, can preclude gross total resection. This accounts for, at least in part, the improved survival of patients with convexity meningiomas over those with parasagittal and skull base meningiomas [40]. Rates of recurrence for surgically treated meningiomas are impacted heavily by the extent of resection[41]. While recurrence rates after gross total resection in grade I meningiomas are quite low, they rise substantially with an increase in pathologic grade. Five-year recurrence rates after gross total resection in grade I meningiomas are reported as 7–23%, in grade II they are 50–55% and in grade III 72–78% [2,6]. With subtotal resection, the likelihood of progressive disease substantially increases [42]. Specifically, there is increased recurrence-free survival at 5 years in grade I tumors following Simpson grade 4 resection compared with Simpson grade 1–3 resection [43]. The benefit of gross total resection (Simpson grade 1–3) was more pronounced for tumors of the convexity than for parasagittal, paraspinal or skull base tumors and more clear for those tumors with high levels of proliferation (MIB-1 labeling index >3%) [43]. Thus, for completely resected WHO grade I meningiomas, it is reasonable to follow with routine surveillance imaging. For WHO grade I tumors that are incompletely resected, and for tumors of higher pathological grade (grade II or III), adjuvant treatment is necessary to avert, or at least delay, recurrence.

RADIATION THERAPY

For decades, radiation therapy (RT) has been the primary treatment for nonsurgically resectable growing tumors. It is also used as adjuvant therapy (postresection) and in the setting of recurrence for previously resected meningiomas. Both fractionated external beam RT (EBRT) and single-fraction stereotactic radiation (SRS) are employed. Unfortunately, there is a scarcity of strong data from randomized controlled clinical trials for radiotherapy of meningiomas, although several trials are currently ongoing. Much of the data for the role of both RT and surgical resection stems from retrospective or single-institution series. It is also important to emphasize that few high-quality studies have not directly compared surgery with RT for resectable tumors, nor have studies directly compared different radiotherapy delivery techniques or doses with each other. Proton therapy in particular has not been extensively studied for meningioma and its role is uncertain. Finally, evaluating treatment modalities based on solely recurrence rates may miss the complex nature of tumor- and treatment-related disability, symptoms, and toxicity. Generally, WHO grade I tumors are irradiated to a dose of approximately 50 Gy, while WHO grade II–III tumors are treated to approximately 60 Gy with daily fractions over 5–6 weeks using EBRT. While these doses are those employed by most clinical trials of RT in meningioma, optimum dosing, especially for grade II tumors has not been rigorously established. Single-fraction SRS is typically limited to tumors <30 mm diameter and for tumors not directly adjacent to (or compressing) radiation-sensitive structures such as the optic chiasm. Multifunction SRS can be utilized for larger-sized tumors. Brachytherapy using radioactive 125-Iodine seeds had been used infrequently for meningioma [44–47]. Long term toxicities of cranial radiotherapy are likewise dependent on the field size and location and may include endocrinopathies, cognitive effects, increased cerebrovascular events and/or secondary malignancy risks. When considering RT as the primary treatment modality, it must be noted that RT is not as successful as surgery at the relief of tumor-related neurological symptoms. However, for patients who are poor surgical

candidates, including those whose tumors are surgically inaccessible, RT is often successfully employed for the control of local tumor growth. It is important to note that many meningiomas treated as such with RT do not undergo biopsy, which prevents histological confirmation of grade or molecular features. Thus, extrapolation about outcomes based on this limited information creates a bias in favor of surgical outcomes of pathologic WHO grade I meningiomas as compared with outcomes for 'radiographic' presumed WHO grade I meningiomas, which likely include some higher-grade lesions[48-49]. In one retrospective single-institution study of hypofractionated SRS for mostly grade I and II meningiomas, local control at 1 year was reportedly 95 and 71%, respectively, with no acute toxicities [50-51]. Another retrospective single-institution study found 100% progression-free survival and local control for tumors smaller than 9.1 mm³ volume [52]. It remains to be proved whether hypofractionated SRS has a more than niche role in the treatment of meningioma or how it compares with traditional EBRT techniques for lesions of similar size and pathological grade. Progression-free survival at 5 years for patients with grade III tumors who do not receive RT is worse: 28% following gross total resection and 0% for subtotal resection [55]. In the observational series, results from the addition of RT are promising: compared with surgery alone, EBRT (to 59.4 Gy) demonstrated only a 20% recurrence rate at 6 years versus 65% without RT [54], but there are conflicting findings from other teams [6]. Importantly, there is no consensus on the dose and timing of adjuvant RT for these more aggressive meningiomas. After surgery, these low-risk patients were followed with observation alone; preliminary data reported a recurrence-free survival of 86% in the low-risk group[56-60]. There is some concern in particular for inherently brain invasive tumors that the tightly conformal treatment plans used in SRS may decrease tumor control compared with EBRT techniques, resulting in undue recurrence, although for skull base meningiomas the radiation-related toxicity to normal structures may favor SRS. This implication is yet to be proven in a prospectively designed fashion and practice patterns differ. Current National Comprehensive Cancer Network (NCCN) guidelines for CNS tumors [61] recommend RT in several scenarios of meningioma care with Level 2A evidence. RT should be considered for small (<30 mm) asymptomatic meningioma at presentation, if grade II and subtotally resected or grade III regardless of resection volume, and in grade I tumors when sub-totally resected if there is a 'potential' symptom; pursue RT for large (>30 mm) asymptomatic tumors if grade III; and consider RT if WHO grade II or incompletely resected grade I. For symptomatic meningiomas at initial presentation, RT is recommended following surgery for any grade III and should be considered for any grade II tumors or large (>30 mm) incompletely resected grade I tumors. For surgically inaccessible tumors or surgically contraindicated patients, RT alone is also recommended. Upon recurrence, surgery (if accessible) followed by RT or re-RT, or RT alone (if inaccessible) is recommended. NCCN guidelines do not take into consideration patient age, tumor location or any molecular pathologic markers. No recommendation is made for EBRT versus SRS or proton versus photon sources. Recently published European guidelines (from EANO, the European Association of Neuro-Oncology [62]) also recommend RT for subtotally resected grade I tumors, either EBRT or SRS. For subtotally resected grade II meningiomas, EBRT is recommended with level C evidence, and either EBRT or observation in the setting of a gross total resection. Grade III anaplastic meningiomas are recommended to have EBRT regardless of the extent of resection with level B evidence. As with the National Cancer Institute (NCI)-sponsored guidelines, tumor location and molecular markers do not affect the recommended treatment strategy.

SYSTEMIC TREATMENTS

Effective medical treatments for meningiomas are lacking. Presently, there is not an established role for chemotherapy or other systemic therapies following resection or biopsy for newly diagnosed meningioma. Current NCCN guidelines for meningioma recommend chemotherapy only in the setting of recurrent (progressive) disease when RT or further

surgical resection is not feasible [61]. Given the established efficacy and safety of EBRT even in eloquent and radio-sensitive areas of the brain (such as near the optic structures), this determination should be made in consultation with a radiation oncologist, with systemic therapy largely reserved for postradiotherapy progression. Generally, they have been observational or retrospective rather than prospective in design and often small, single-institution cohorts. A recent meta-analysis highlights the limitations of these prior medical trials in meningioma, including small study sizes, lack of randomization, and heterogeneous inclusion criteria [64]. Many studies are further encumbered by the use of radiographic diagnosis only and a lack of histopathological concordance of WHO grade. Hormone receptors have been identified as being broadly expressed on meningiomas, including the receptors for somatostatin (in particular, the SST2A subtype [70], growth hormone, and sex hormones: estrogen, progesterone and androgen [71]). Investigations of inhibitors and analogs for hormone receptors used with therapeutic intent have failed to demonstrate clinical activity in meningioma. In the largest trial involving this class of therapeutic, a Phase III prospective randomized trial of mifepristone (SWOG-S9005) in either primary or recurrent meningioma deemed to be unresectable, there was no difference in failure-free survival or overall survival. A Phase II trial of the somatostatin receptor pasireotide long-acting release (LAR) in recurrent meningioma that failed prior surgical or RT revealed a PFS-6 of 17% in the high grade (grade II/III) cohort and 50% in the low grade, grade I cohort and was well tolerated. There were no radiographic responses; however, in another small Phase II study of nine patients clinical with recurrent high-grade meningioma (WHO grade II/III, intramuscular octreotide failed to demonstrate clinical response or durable stability, but a PFS-6 of 44% was reported. Work on the molecular characterization of meningioma has also resulted in the identification of specific mutations that are potential therapeutic targets or help to stratify patients' risk of meningioma recurrence. There is also an ongoing clinical trial for meningiomas harboring mutations in the SMO (smoothed) gene and the NF2 gene using the targeted agents vismodegib and GSK2256098, an inhibitor of FAK, respectively. Nonchemotherapeutic modalities for meningioma treatment are also under investigation. For example, a pilot study using NovoTTF-100A (electromagnetic tumor treatment fields, currently FDA-approved for the treatment of newly diagnosed and recurrent glioblastoma) in recurrent atypical and anaplastic meningioma reported stable disease in four of six patients without any reported severe adverse events. A clinical trial using the tumor treating fields device for progressive WHO grade II and III meningioma is active, although this device is limited to supratentorial tumors.

CONCLUSION & FUTURE PROJECTIONS

These studies for the medical treatment of meningioma aim to expand the few available treatments for recurrent or nonsurgical cases of meningioma. Overall, the approach for newer studies is to be prospective in design, to use clearly defined inclusion criteria, select patients with histological confirmation or molecularly defined tumors, and to apply validated outcome measurements and comparable response assessment metrics, such as the RANO meningioma guidelines currently being created. In addition, the use of patient-centered outcomes for treatments and clinical trials may be applicable to meningioma both for more aggressive, higher grade tumors and for benign tumors for which symptomatic relief and quality of life rather than growth (or shrinkage) over a 6-month timeframe is valuable. Furthermore, the application of new classes of chemotherapeutics as well as pathway- and molecularly targeted drugs, as well as nonstandard approaches such as tumor-treatment fields for meningioma, signifies an invigorated interest in these common brain tumors that are often refractory to current treatments.

Recent advances in the mutations and methylation profiles associated with meningiomas may prove to influence our management of these tumors in the next number of years. It is possible

that a subset of patients may respond to targeted therapies. It is likely that a substantial shift in the standard of care to incorporate systemic therapies would be feasible in the 5–10 year time frame. This type of change could be quite impactful for both the patient and the clinician as meningiomas comprise the largest percentage of primary intracranial tumors. As the population in many countries ages, the incidence of these tumors will presumably increase, making well-tolerated efficacious therapies of even greater importance.

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Informed Consent

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Trial Registration

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