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Update on Meningiomas

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate patients with grade II and III meningiomas for possible implementation of adjuvant radiation therapy.
2. Describe options of systemic treatment of refractory meningiomas with hydroxyurea, somatostatin analogues, or CAV multi-agent chemotherapy.

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ABSTRACT

Although meningiomas are the most common tumor in the central nervous system, their incidence, epidemiology, and clinical outcomes have historically been poorly defined. This has been attributed to their benign course, difficulty obtaining histologic diagnosis, and lack of uniform database registration. Their clinical behavior can range from a silent incidentaloma to a lethal tumor. Projections of an aging population should raise medical awareness of an expectant rise in the incidence of meningiomas. This disease increases with advancing age, has a female predilection, and exposure to ionizing radiation is associated with a higher risk for disease development. There have been minimal advances in treatment, except in radiation therapy. Although no U.S. Food and Drug Administration–approved systemic therapy exists, there are treatment options that include hydroxyurea and sandostatin. Currently, no molecularly targeted therapy has provided clinical benefit, although recurring molecular alterations are present and novel therapies are being investigated. ***The Oncologist*** 2011;16:1604–1613

INTRODUCTION

Meningiomas are the most common primary brain tumor as well as the most common intradural spinal tumor [1, 2]. Hospital-based series have found ~20% of all primary brain tumors to be meningiomas, whereas autopsy reports are closer to 30% [3, 4]. Despite a large majority being classified as benign

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Table 1. World Health Organization (WHO) grading system

WHO grade	Frequency	Pathologic features	Histologies	Recurrence rates
Grade I	80%–90%	Pleimorphic; occasional mitotic figures; lacks criteria of anaplastic or atypical meningiomas	Meningothelial, psammomatous, secretory, fibroblastic, angiomatous, lymphoplasmacyte rich, transitional, microcytic, metaplastic	7%–20%
Grade II	5%–15%	≥4 mitotic figures per 10 high-power fields; three of the following: (a) increased cellularity, (b) small cells with high N:C ratio, (c) prominent nucleoli, (d) sheet-like growth, (e) necrosis; or brain invasion	Clear cell, chordoid, atypical	30%–40%
Grade III	1%–3%	≥20 mitotic figures per 10 high-power fields or frank anaplastic features	Papillary, rhabdoid, anaplastic	50%–80%

lesions, there is great heterogeneity in histology, recurrence rates, aggressiveness, symptoms, and survival outcomes.

Meningiomas arise from arachnoidal cells of the leptomeninges and may occur anywhere arachnoidal cells are located. Tumor location is a critical factor determining prognosis and therapy options, especially surgical resectability. The majority of meningiomas are found in the supratentorial compartment, most commonly along the dural venous sinuses in the cerebral convexity, parasagittally, and in sphenoid wing regions [5]. Less common sites of supratentorial origin include the optic nerve sheath, cerebellopontine angle, and choroid plexus [5–8]. Spinal locations are the primary site in ~12% of patients with meningiomas and are the most common intradural spinal cord and cauda equina tumor [7, 8]. Multifocal lesions are found in ~9% of patients on imaging and 16% of patients in autopsy studies [5, 9, 10].

World Health Organization Grading System

Meningiomas are classified according to the World Health Organization (WHO) grading system (Table 1) [11]. Over 80%, and more likely closer to 90%, of meningiomas are classified as WHO grade I [12]. The most common histologies in this category are meningothelial, fibroblastic, and transitional meningiomas [13]. Grade I lesions have pleomorphic features and occasional mitotic figures. Although this category is classically defined as benign, there is a high degree of intraclass variability, with recurrence rates in the range of 7%–20% and varying rates of progression to higher grades.

Atypical meningiomas are classified as WHO grade II and include 5%–15% of meningiomas [12]. Either high mitotic activity (four or more mitoses/10 high-power fields of 0.16 mm^2) or having three of the five features of greater cellularity (small cells with a high nucleus-to-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and necroses) defines the meningioma as grade II. Chordoid and clear cell meningiomas have a more aggressive course, with a high rate of recurrence, and are also classified as grade II [14]. Recurrence rates are in the range of 30%–40% and the presence of high mitotic activity and micronecrosis with pseudopalisading are strong risk factors associated with a high recurrence risk [12]. Data also demonstrate a small but statistically significant higher risk for death in patients with grade II meningiomas than in age- and sex-matched U.S. cohorts [15].

Anaplastic or malignant meningiomas are classified as WHO grade III and account for 1%–3% of cases [12]. These tumors show frank anaplastic features or a mitotic index of ≥20 mitoses/10 high-power fields of 0.16 mm^2. Because of the aggressive nature of rhabdoid and papillary variant meningiomas, they are designated as WHO grade III as well. Grade III tumors have higher frequencies of local invasion, recurrence, and metastasis. Prognosis is poor in this group of patients, with recurrence rates of 50%–80% and a median survival time as low as <2 years [16].

Current Epidemiology

In the U.S., the age-adjusted incidence rate of meningiomas was 3.76 per 100,000 person-years for men and 8.44 per 100,000 person-years for women in 2004–2006 based on the most recent Central Brain Tumor Registry of the United States report, released in 2010 [1]. Excluding sex-specific organ and germ cell cancers, meningiomas have one of the largest gender incidence differences. Almost 98% of meningiomas are classified as nonmalignant (WHO grade I or grade II), whereas ~2% of meningiomas are classified as malignant. Of nonmalignant meningiomas, 45% are diagnosed by radiological means alone, whereas just over half (53%) are histologically confirmed. The incidence of meningiomas increases with age, especially after age 65 years, affecting women more than men and African Americans more frequently than whites [1, 4, 17]. Previously reported incidence rates of meningiomas in the U.S. may be an underestimation because benign brain tumors were not required to be reported until January 2004 as per Public Law 107–260.

Larjavaara et al. [18] conducted a study incorporating data from four clinical sources: neurosurgery clinic, pathology, hospital, and autopsy databases from November 2000 to June 2001. They found age-standardized incidence rates of 2.2 per

100,000 person-years for men and 9.6 per 100,000 person-years for women. Interestingly, almost one third of the cases that were found had not been reported to the national cancer registry, raising concern for underreporting in national registries. From 1985 to 1999, improved and more frequent use of brain imaging resulted in an increase in the incidence and prevalence of meningiomas [19]. Participants in the Rotterdam Scan Study underwent screening magnetic resonance imaging (MRI), which showed the prevalence of undiagnosed meningiomas to be 0.5% in subjects aged 45–59 years and 1.6% in subjects aged >75 years [20]. Autopsy studies estimate that 2%–3% of the population have incidental meningiomas, of which 8%–16% are multiple [3, 21]. With an aging population, it is expected that the prevalence will increase.

Risk Factors

Exposure to ionizing radiation is the strongest modifiable risk factor seen in the literature. Data on other modifiable risk factors, such as cell phone use, occupational exposures, cigarette smoking, and head trauma, remain inconclusive [22]. Nonmodifiable risk factors include increasing age and female gender, with females having a higher incidence during reproductive years [17, 23]. There has been conflicting data on the influence of endogenous or exogenous hormones affecting the risk for meningiomas [22, 24–28]. Genetic and familial factors play a role in the risk for meningiomas and likely in the development of meningiomas (most established after exposure to ionizing radiation, see below).

Radiation

Ionizing radiation has been firmly linked to a higher risk for meningiomas based on cranial radiation in the tinea capitis cohort, atomic bomb survivors, patients exposed to dental radiographs, and patients exposed to radiotherapy for other medical illness. Approximately 20,000 immigrants to Israel in 1948–1960 received low-dose cranial radiation for treatment of tinea capitis [29]. A cohort of 10,842 irradiated individuals were followed and, when compared with matched, nonirradiated sibling controls, were demonstrated to have a relative risk of 9.5 (95% confidence interval [CI], 3.5–25.7) for developing meningioma [30–32]. Data from survivors in Hiroshima and Nagasaki showed a higher risk for all brain tumor types, with higher risks associated with closer proximity to the atomic bomb epicenter [33–35]. Dental radiographs were linked to meningiomas in Los Angeles County, with a fourfold higher risk when exposed to diagnostic, full-mouth dental x-rays either before 1945 or before the age of 20 years [36, 37]. This was confirmed in a case–control study in Washington wherein full-mouth series performed before 1985, when higher doses of radiation were used, were associated with a higher risk for meningiomas (odds ration [OR], 2.06; 95% CI, 1.03–4.17) [4]. A greater risk with high doses of ionizing radiation exposure was also observed in patients treated for head and neck cancers and those treated with cranial irradiation for acute lymphoblastic leukemia (ALL) [38–43]. In a cohort of 2,169 survivors of ALL, 14% of individuals developed meningiomas, with a latency period of 20.6 years [40]. Radiation-associated meningiomas can have a long latency period, with the incidence continuing to increase as a function of time and having shorter latency periods with higher doses of radiation and younger age at exposure [43, 44]. Radiation-associated meningiomas are also more likely to be atypical or malignant and multifocal [39, 45, 46].

Female Gender

Investigators have tried to link endogenous or exogenous hormone exposure to meningiomas because of observations of higher incidences in women of reproductive age, tumor expression of hormone receptors, an association with breast cancer, and changes in the size of meningiomas during pregnancy, the menstrual cycle, and menopause. Research involving endogenous hormone exposure has been conflicting regarding the risk for meningioma with age at menarche, menopausal status, parity, and ever having been pregnant [24, 25, 28, 47, 48]. Oral contraceptives and hormone replacement therapy have better evidence linking hormone replacement therapy with a higher risk [22, 24–27]. The OR for developing meningiomas in postmenopausal women who received hormone replacement therapy in Sweden was 1.7 (95% CI, 1.0–2.8), whereas the Nurses Health Study in the U.S. found a relative risk of 2.48 (95% CI, 1.29–4.77) [25, 27]. Links between breast cancer and meningioma have been observed in multiple studies and are theorized to be related to common risk factors, including age and gene–environment interactions [23, 49, 50].

Genetic Association

Type 2 neurofibromatosis (NF2), caused by a germline mutation on chromosome 22q12 and inherited in an autosomal dominant pattern, is the most common genetic condition associated with an elevated risk for developing meningiomas and schwannomas [51]. Most NF2 patients develop meningiomas that characteristically present earlier in life, with a higher frequency of multiple lesions than in sporadic cases [52]. Current data are conflicting regarding whether or not NF2-associated meningiomas are more aggressive than sporadic cases [53, 54].

Other inherited genetic links may exist, as evidenced by a population-based Swedish study. In 1961–2000, 1,845 cases of meningioma in Sweden were evaluated for familial clustering. Higher standardized incidence rates for developing meningioma were found if a parent was affected (3.06; 95% CI, 1.84–4.79) and if a sibling was affected (4.41; 95% CI, 2.10–8.14) [55].

Inherited susceptibilities to the effects of ionizing radiation may also exist. In the Israeli tinea capitis cohort, 525 families were divided into four groups based on irradiation exposure and disease status. In the group that received radiation and subsequently developed a meningioma, 11% of index cases had first-degree relatives who also developed meningiomas after exposure to radiation. In comparison, only 1% of controls that did not develop meningioma after radiation exposure had a first-degree relative develop meningioma after exposure to radiation (OR, 17.0; 95% CI, 2.6–720.3) [56].

Neither the Swedish nor the Israeli cohort included documented NF2 cases, suggesting the role of other inherited genes.

A study of 440 cases and controls, including 150 patients from the Israeli cohort, compared single nucleotide polymorphisms (SNPs) in 12 candidate genes from peripheral blood samples to evaluate the risk for developing meningioma between gene SNPs and radiation exposure. SNPs in the *Ki-RAS* (OR, 1.76; 95% CI, 1.07–2.92) and *ERCC2* (OR, 2.68; 95% CI, 1.00–2.84) genes were associated with a higher risk for developing meningiomas [57].

Other candidate genes that may affect meningioma risk include those encoding enzymes that mitigate damage from reactive oxygen species, metabolism and detoxification enzymes, cell-cycle control proteins, and genes involved in other DNA repair mechanisms. Superoxide dismutase (SOD) is an enzyme that scavenges reactive oxygen species to prevent DNA damage, and a higher risk for meningioma was seen with the C variant of SOD3, rs699473 (OR, 1.7; 95% CI, 1.1–2.7) [58]. The *GST* gene encodes enzymes that play a role in detoxification via glutathione-dependent reactions, and an association was seen between the *GSTT1* null genotype and meningioma (OR, 1.5; 95% CI, 1.0–2.3) [59]. Certain polymorphisms of the caspase-8 gene, a regulator of the cell cycle and apoptosis, have varying effects on the risk for meningioma. Subjects with the CASP8 Ex14–271A>T variant had a lower risk (OR, 0.5; 95% CI, 0.3–0.9) whereas those with the CASP8 Ex13+51G>C variant had a higher risk (OR, 3.6; 95% CI, 1.0–13.1) [60]. Meningioma risk associated with polymorphisms in DNA repair enzymes include a higher risk for meningioma with the T variant of the *GLTSCR1* (rs1035938) gene (OR, 3.5; 95% CI, 1.8–6.9) and with other candidate genes including the *ERCC4* (rs1800067), *MUTYH* (rs3219466), and *PCNA* (rs25406) genes [61].

Pathogenesis

The first report of a common chromosomal deletion was identified in 1967 and localized to the long arm of chromosome 22 in 1972 [62, 63]. Later molecular genetic studies found loss of heterozygosity on chromosome 22q in 40%–70% of meningioma cases, and up to 60% of sporadic cases were associated with mutations in the *NF2* gene, located on 22q12.2 [64–67]. Expression levels of the *NF2* gene product Merlin are lower in meningiomas having loss of heterozygosity of chromosome 22q [67]. Merlin belongs to the 4.1 family of proteins, involved in cytoskeletal functions as well as regulating cell growth and motility [68–70]. Current theory postulates that the quantitative loss of Merlin protein resulting from loss of heterozygosity is an early event in development of benign meningiomas but not evolution to higher-grade lesions [14]. The Dal-1 protein, another member of the 4.1 family of membrane-associated proteins, has tumor suppressive properties, and lower mRNA expression levels have been found in up to 76% of sporadic meningiomas [71, 72]. Although the etiology of lower mRNA expression is currently unknown, it is also thought to be an early event in the development of meningiomas [14, 72]. Interestingly, combined Dal-1 and Merlin losses are seen in 70% of anaplastic, 60% of atypical, and 50% of benign meningiomas, suggesting that concurrent losses confer a more aggressive type of lesion [72].

Table 2. Simpson grade

Simpson grade	Definition	10-yr recurrence rate
1	Macroscopic GTR with excision of dura, sinus, and bone	9%
2	Macroscopic GTR with coagulation of dural attachment	19%
3	Macroscopic resection without resection or coagulation of dural attachment	29%
4	Subtotal resection	40%
5	Biopsy	NA

Abbreviations: GTR, gross-total resection; NA, not available.

Progesterone and its receptor have also been implicated, and supporting evidence includes a higher incidence in women, higher levels of progesterone receptor expression, the location and biologic activity of progesterone receptors, and higher concentrations of progesterone receptors in recurrent meningiomas [73–76]. However, the level of progesterone receptors is inversely correlated with histologic grade and mitotic index in meningiomas, leading to the interpretation that progesterone receptors may be involved in formation of benign meningiomas but are either downregulated or not involved in the more aggressive histologies [72, 77–79].

Autocrine loops involving platelet-derived growth factor (PDGF)-BB, epidermal growth factor (EGF), endothelin-1, and insulin-like growth factor II may also play a role in the development or progression of meningiomas [80–83]. Other associations that may be involved in progression of a benign meningioma to a more aggressive form include losses of function on chromosome 1p, 6q, 9p, 10, 14q, and 18q, gains of function on chromosome 1q, 9q, 12q, 15q, 17q, and 20q, a higher expression level of vascular endothelial growth factor (VEGF), and greater telomerase activity [15, 84–89].

Prognostic Factors

Despite most meningiomas being classified as benign, survival times are shorter in patients with meningiomas than in matched controls. In Finland, survival analysis of a cohort of 1,986 patients with meningioma followed from 1953 to 1984 found the 10-year relative survival rate to be 86% when compared with a matched population [90, 91]. Data from the Swedish Cancer Registry found the 5-year relative survival rate estimate to be 92.0% for patients diagnosed with meningioma in 1989–1996 and the 10-year relative survival rate estimate to be 79.6% for those diagnosed in 1979–1991 [92]. In the U.S., in 1978–1988, 581 patients had an overall survival rate at 8 years of 82.4% after initial resection, which is lower than that of an age- and sex-matched cohort ($p = .002$) [93].

To better understand prognosis, studies have investigated clinical factors, the extent of surgery, radiographic findings,

and laboratory markers to help predict the aggressiveness of meningiomas. Age at diagnosis and surgical resection were both clinical predictors for survival in two separate large cohorts. Both studies observed a longer survival time in the group of patients who underwent surgery and an inverse relation between age at diagnosis and survival [90, 94]. The Simpson grading system is a predictive model for meningioma recurrence correlating with extent of resection (Table 2) [95]. Location of tumor origin is an important predictor of resectability and prognosis. Tumors of the convexity can be cured by surgical resection, whereas skull-based tumors, especially in the petroclival region or with involvement of the cavernous sinus or orbit, often have a more unfavorable outcome [14]. Histology predicts mortality and recurrence, with atypical and malignant meningiomas having higher recurrence rates and shorter survival times than those with benign histologies. Five-year recurrence rates have been reported at 38% for atypical and 78% for malignant meningiomas [96]. Five-year survival rates were estimated at 70.1% for benign meningiomas and 54.6% for malignant lesions [94]. A multivariate model including clinical, surgical, and pathologic factors found that age <40 years, male gender, less than gross-total resection, intracranial involvement of the optic nerve, and a high mitotic index were independently associated with a shorter progression-free survival interval [93].

Certain findings on computed tomography scans may help delineate if the tumor is more likely to be a benign or malignant meningioma. Homogeneous enhancement and calcification are more frequently seen in benign tumors, whereas nonhomogeneous enhancement and "mushrooming" are more concerning for malignant tumors [97]. Brain single-photon emission tomography using ^{99m}Tc-tetrofosmin may also be of value in predicting the aggressiveness of meningiomas based on data showing correlations with tumor grade and recurrence in a small cohort of 18 cases [98].

Biologic and genetic markers may also have a role in predicting aggressiveness of meningiomas. The proliferative markers MIB-1 and Ki-67 generally have labeling indices that increase with higher WHO grade and risk for recurrence [99–101]. Progesterone receptors are more frequent in benign meningiomas and correlate with a lower frequency of recurrence and better overall prognosis [77, 102]. Telomerase activity is detected more frequently in higher grades of meningiomas and predicts a poor outcome in benign meningiomas [103]. VEGF expression levels are greater in anaplastic and atypical meningiomas and are predictive of a higher risk for recurrence in benign meningiomas [104]. Although several genetic deletions are associated with tumor progression, two studies have demonstrated deletion of 14q to be an independent prognostic marker for tumor recurrence [85, 105]. Gene-expression profiling and multivariate interaction models may differentiate tumor aggressiveness but have not been validated in larger cohorts [77, 106].

Treatment

Treatment of meningiomas is dependent on the tumor size, tumor location, associated symptoms, age, and health status. Asymptomatic lesions can be observed with close monitoring of clinical and disease status. A tentative diagnosis of meningioma can be made on classic radiographic findings (with MRI scans preferred) of a dural-based mass, homogeneous contrast enhancement, the presence of a dura tail, or a cerebrospinal fluid cleft. Octreotide scintigraphy can be used as an adjunct when there is uncertainty in the diagnosis. This is especially true for skull-based tumors, optic nerve sheath tumors, and for identifying recurrent tumors versus scar tissue [107, 108].

For symptomatic or progressively enlarging meningiomas, complete surgical excision, when feasible, of the tumor bulk, surrounding dural attachment, and involved bone is recommended [95]. Most convexity, spinal, and falcine meningiomas are amenable to complete excision. In contrast, meningiomas involving the cavernous sinus, petroclival region, posterior region of the superior sagittal sinus, or optic nerve sheath and parasagittal meningiomas involving the sinus posterior to the coronal sinus have a much higher morbidity rate [13, 109–111]. If complete excision is not possible, options include definitive external-beam radiation and partial excision followed by adjuvant radiotherapy. Long-term data using definitive external-beam radiation have demonstrated prolonged tumor control comparable with that observed with surgery followed by adjuvant radiation [112]. Recurrence-free survival rates after partial resection were found to be 63% at 5 years, 45% at 10 years, and 9% at 15 years [91]. Retrospective data from 140 patients demonstrated an 89% 5-year and a 77% 10-year progression-free survival rate in patients receiving adjuvant radiotherapy after partial resection of benign meningiomas. With improved imaging modalities after 1980, the 5-year progression-free survival rate improved to 98%, with a low morbidity rate of 3.6% [113]. Radiotherapy is also recommended for recurrent disease or aggressive tumor histology [113–115].

Intensity-modulated radiation therapy (IMRT) is being investigated in a phase II Radiation Therapy Oncology Group (RTOG 0539, NCT00895622) study. Patients with meningiomas are being stratified into three recurrence risk groups based on WHO grade, extent of resection, and recurrence status. Group I patients have a low risk for recurrence, with newly diagnosed WHO grade I meningioma that has been either subtotally or gross totally resected. Group II patients have an intermediate risk, with a newly diagnosed WHO grade II meningioma after gross resection or recurrent WHO grade I meningioma. Group III patients have a high risk and include those with WHO grade III meningiomas, recurrent WHO grade II meningiomas, and newly diagnosed subtotally resected WHO grade II meningiomas. Group I patients will be observed, group II patients will receive 50 Gy of IMRT, and group III patients will receive 60 Gy of IMRT.

Stereotactic radiotherapy (SRS) has become an alternative option to external-beam radiation for recurrent or partially resected meningiomas <35 mm in diameter and for patients in whom surgery is not an option because of the tumor's location or patient comorbidities [117–120]. A series of 190 patients with recurrent or residual meningiomas treated with gamma knife SRS demonstrated 93% and 68% 5-year control rates

with low treatment-related morbidity in benign and atypical meningiomas, respectively [121]. In a larger cohort of 972 patients with meningiomas, tumor control using SRS was achieved in 93% of patients with low-grade histology, 50% of patients with WHO grade II histology, and 17% of patients with WHO grade III lesions [122]. SRS has been especially useful to treat skull-based meningiomas, with data demonstrating 98% tumor control rates, 58% tumor reduction, and 39% reduction in cranial nerve deficits [123]. Cyberknife surgery, a form of SRS designed to be accurate and expand treatment sites outside the head, is another effective modality, particularly for skull-based lesions, with data demonstrating 18.8% tumor reduction and 77.5% tumor stabilization in a cohort of 191 patients with either symptomatic or growing tumors [124]. Spot-scanning proton beam radiotherapy is a sophisticated modality wherein the proton beam scatters within the tumor volume, sparing surrounding tissue, and can be applied to complicated tumor volumes. Weber et al. [125] treated 16 patients (eight incomplete resections, five with disease progression, and three inoperable lesions) with spot-scanning proton therapy and demonstrated a 91.7% 3-year progression-free survival rate with a 75% 3-year toxicity-free survival rate [125]. Endovascular embolization is an alternative option for unresectable meningiomas. In a series of seven patients managed by embolization alone, after a mean follow-up of 20 months, six patients had tumor shrinkage and improved symptoms [126].

Alternative therapies have been investigated, especially for inoperable meningiomas, recurrent disease, and aggressive histologies. Based on the high prevalence of elevated progesterone receptor expression in meningiomas and promising results in smaller studies, mifepristone (RU486) was investigated in a prospective multicenter study with disappointing results [127–129]. However, more recent data with mifepristone demonstrated that eight of 28 patients had minor responses, with seven of the eight responders being either male or premenopausal females, suggesting a subset of patients that needs further investigation for hormonal therapy [130]. Other hormonal therapies that have been studied include tamoxifen and flutamide. In a phase II study of tamoxifen in 21 patients with meningioma, six had stable disease, two had a minor response, and one had a partial response [131]. Flutamide was used in six patients with recurrent meningiomas at Brigham and Women's Hospital in an unpublished study, and two patients had disease stabilization for almost 1 year [132].

Chemotherapeutic agents have been investigated and most have failed to show consistent efficacy with the possible exceptions of hydroxyurea and a multidrug regimen of cyclophosphamide, doxorubicin, and vincristine (CAV). Hydroxyurea induces apoptosis in meningioma cell cultures, and several smaller studies have shown stabilization of disease in patients with unresectable or recurrent tumors [133–136]. A recent phase II trial treated 29 patients with progressive tumors or neurologic deficits with hydroxyurea (20 mg/kg per day). Although there was no decrease in tumor size, 71% had stable disease, with a median progression-free survival interval of 27 months [137]. The CAV regimen was studied in 14 patients with malignant meningiomas. After surgical resection (four gross total, 10 subtotal) followed by 2–4 weeks of involved-field radiotherapy (median dose, 60 Gy), all patients were treated with either three cycles (after gross-total resection) or six cycles (after subtotal resection) of CAV. The median time to tumor progression was 4.6 years and the median survival time was 5.3 years, demonstrating a modestly better result than in historical controls [138].

Interferon-α and somatostatin analogs are among the biologic agents showing responses in patients with recurrent meningioma. Six patients with recurrent and unresectable meningiomas that had been previously irradiated were treated with interferon-α2B at 4 mU/m^2 per day, 5 days per week. Four patients had disease stabilization and one patient had a slight regression; responses lasted 6–14 months [139]. Another study of 12 patients treated with interferon-α demonstrated stable disease in nine patients, with three having prolonged responses [140]. A more recent study of interferon-α in 35 patients with recurrent grade I meningiomas showed no radiographic responses, 74% of patients with stable disease, and a median progression-free survival interval of 7 months [141]. Because somatostatin receptors are present on most meningiomas and in vitro studies show inhibition of growth, a long-acting somatostatin analog, sandostatin, was studied in 16 patients with recurrent meningiomas [142, 143]. Five patients had partial responses and five had stable disease, with seven maintaining progression-free survival at 6 months [144]. Another somatostatin analog with broader and higher affinity to somatostatin receptors, pasireotide, is currently under investigation in patients with recurrent or progressive meningiomas in a multicenter phase II trial [145].

Newer molecular targets including the PDGF, VEGF, EGFR, phosphoinositide 3-kinase/Akt, and Ras/Raf/mitogen-activated protein kinase pathways are being evaluated in meningiomas. Although initial studies with imatinib, a PDGF inhibitor, in recurrent meningiomas have not shown significant activity, a phase II study combining imatinib with hydroxyurea has closed with results expected to be released shortly [146]. Recently, 25 patients with recurrent meningiomas were treated with erlotinib or gefitinib in a phase II trial with disappointing results. There were no objective responses and the 6-month progression free survival rates were 25% for benign and 29% for atypical or malignant meningiomas [147]. Sorafenib and sunitinib have multiple tyrosine kinase effects and are currently being evaluated for efficacy in recurrent or inoperable meningiomas. An interim analysis of sunitinib showed promising results with a 6-month progression-free survival rate in WHO grade II and grade III meningiomas $>$50% [148]. Another promising agent targeting the PDGF and VEGF pathway is vatalanib, which also showed a 6-month progression-free survival rate $>$50% in patients with WHO grade II and grade III meningiomas [149]. At this time, there are 47 phase II and phase III trials under investigation for meningiomas in the ClinicalTrials.gov database, 36 of which are active. The National Comprehensive Cancer Network recently updated their practice guidelines for central nervous system cancers in the

2010 version, newly incorporating current diagnostic and treatment algorithms for meningioma.

SUMMARY

As a result of the recent Public Law 107–260, which requires registration of benign brain tumors, updates on epidemiology are expected to demonstrate an increase in the incidence of meningiomas, especially added to the current trend of an aging population and longer female life expectancy. Exposure to high doses of ionizing radiation is the only known modifiable risk factor for meningioma development. Treatment is indicated for symptomatic lesions or when neurologic problems are pending. Surgery is often the treatment of choice, but in anatomically inaccessible locations, SRS can also be curative. Adjuvant radiation therapy should be considered for WHO grade II and grade III lesions. Systemic therapies are reserved until after surgical and radiation options have been exhausted, because they have limited efficacy. Investigational trials should be offered when possible.

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