Part IV

Intracranial Extra-Axial Primary Tumors

11

Meningiomas

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In 1614, the Swiss physician Felix Plater provided the first documented account of a meningioma (Netsky and Lapresle, 1956). In the eighteenth century, Antoine Louis, from France, presented a series of patients with "fungueuses de la dure-mere" (Louis, 1771) or "fungating mass of the dura matter." In the United States, W.W. Keen successfully resected a meningioma in 1887 (Bingham and Keen, 1986). Years later, Harvey Cushing coined the term "meningioma" to describe any primary discrete mass attached to the meninges (Cushing, 1922; Cushing and Eisenhardt, 1938).

The classic publication of Cushing and Eisenhardt's 32 chapter book in 1938 did much to bring together the classic neurology with which these tumors can present. Even today this book is an essential review for all those who deal on a regular basis with patients harboring these tumors. Cushing thought that meningiomas were a formidable problem and that the "prognosis hinges on the surgeon's wide experience with the problem in all its many aspects than is true of almost any other operation that can be named."

A recent update on the surgical management of meningiomas by Al-Mefty (1991) indicates that many of the challenges presented by these tumors cannot be overcome even with modern-day technology. Yet only in the last 15 years has the true long-term clinical problem of meningiomas come to be appreciated, largely because of the availability of magnetic resonance imaging (MRI). This imaging modality allows us to see with great detail small residual or recurrent tumors on the convexity and at the skull base.

Meningiomas can be found throughout the central nervous system, from the optic nerve sheath to the spinal cord but rarely, however, below the thoracic spine region. Their biologic behavior is almost always one of continuous slow growth, with metastases occurring only with the malignant form of the disease. These tumors affect women more commonly than men and are mostly found in the fifth and sixth decades of life (Burger et al., 1991; Martuza et al., 1985; Russell and Rubinstein, 1989). The expression of steroid hormone receptors on meningiomas has been used to try to explain this predilection for the female sex and has been the center of numerous studies (Carroll et al., 1997; Halper et al., 1989; Schwartz et al., 1984; Smith and Cahill, 1994).

Recently, new discoveries about the molecular biology of brain tumors have changed the way in which we view them; for example, techniques for their diagnosis have evolved and now include everything from minimally invasive image-directed biopsy to extensive craniofacial exposures for total removal of the tumor and dural attachments, aided by cytologic, chromosomal, genetic, and molecular studies. The insights provided by these sophisticated analytical laboratory tools provide the basis for the rapid translation of new discoveries from the bench to the bedside. This chapter reviews the current understanding of the basic biology of meningiomas and the current standards of clinical management.

INCIDENCE

Meningiomas account for 20% of all primary intracranial neoplasms and 25% of all intraspinal tu-

mors (Burger and Vogel, 1991; Carroll et al., 1993, 1995a,b, 1997, 1999). In the original surgical series of Cushing (1938), meningiomas accounted for 13.4% of more than 2000 brain tumor patients he had treated. The incidence of meningiomas in the general population varies between 2 and 15 per 100,000 people, the incidence increasing with age (Young, 1981; Kurland et al., 1982). The 1997 report of the Central Brain Tumor Registry of the United States shows that for the period 1990 to 1994, meningiomas accounted for 24% (4989) of primary brain tumors, with an incidence ranging from 0.08 (ages 0 to 19 years) to 13.72 (ages 75 to 84 years) per 100,000 population.

Two recent studies from the Kumamoto Prefecture in Japan (Kuratsu and Ushio, 1996a; Kuratsu et al., 2000) (population 1.85 million) have provided a longitudinal follow up from 5 to 7 years regarding the incidence of meningiomas. The first report (Kuratsu and Ushio, 1996a) found that the age-adjusted incidence of meningiomas in males and females was 1.56 and 3.95 per 100,000, respectively. Overall, meningiomas were the most common primary brain tumor in this population group, with an age-adjusted incidence of 2.76 per 100,000, with the highest incidence of 13.02 per 100,000 among women aged 70 to 79 years. A subsequent study from the same group, which included two more years of data, showed that meningiomas accounted for 32% of all primary tumors and that 39% of these tumors were asymptomatic (Kuratsu et al., 2000). Meningiomas tended to be asymptomatic most often in females and in particular those over the age of 70 years.

Other epidemiologic observations also note that intracranial and intraspinal meningiomas afflict women twofold and nearly ninefold as often as men, respectively (Earle and Richany, 1969; McDermott, 1996; Schmidek, 1991). Studies performed during the past two decades have demonstrated that meningiomas express estrogen (infrequently), progesterone, and androgen hormone receptors, leading to the hypothesis that steroid sex hormones may contribute to their growth, which could explain the higher incidence of meningiomas in women (Black et al., 1996; Black, 1993, 1997).

Race may also be important, as a higher percentage of all brain tumors are meningiomas in African countries. In one study of brain tumors in Los Angeles County, the male and female meningioma tumor rates were highest in the black population (Preston-Martin, 1989).

In children, meningiomas are uncommon, comprising only 1% to 4% of all brain tumors and with no female preponderance. In the recent review by Erdincler and colleagues (1998), 62% of pediatric patients presented between the ages of 10 to 15 years, and 41% had associated neurofibromatosis.

LOCATION

Meningiomas can occur anywhere along the course of the intracranial arachnoid and dura, but tend to cluster along sites where arachnoid granulations return cerebrospinal fluid to the venous system, that is, the convexity and basal venous sinuses. Larger clinical series with more than 500 patients document that the three most common locations for intracranial meningiomas are all supratentorial: parasagittal, convexity, and sphenoid wing. In the surgical series of Cushing (1922), 8% of meningiomas were in the posterior fossa, and they occurred along the tentorium, in the cerebellopontine angle, and at the foramen magnum, in decreasing order of frequency. A modern series that included patients treated surgically as well as those simply observed revealed convexity, falcine, sphenoid wing, and tentorium as the four most common locations. In the first two decades of life, Germano (1994) found that 67% of meningiomas were supratentorial and 14.4% were infratentorial. Intraventricular meningiomas are most commonly within the lateral ventricle (80%) near the atrium and most often on the left side of the brain. Three-fourths of the remaining 20% of intraventricular meningiomas occur in the third ventricle, and the rest occur in the fourth ventricle.

ETIOLOGY

Exogenous and Endogenous Factors Associated with Meningiomas

Meningiomas are thought to mainly arise from cap cells of the arachnoid layer around the major sinuses and large cerebral veins where arachnoid granulations are most prominent (Kida et al., 1988; O'Rahilly and Muller, 1986). Cushing pointed out that meningiomas are almost always attached to the dura even though they do not arise from it. Exogenous and en-

dogenous factors acting alone or in combination are thought to account for the tumorigenesis of meningiomas. Trauma, viral infection, and prior brain irradiation are some of the exogenous factors implicated in the development of meningiomas (Harrison et al., 1991; McDermott, 1996; Musa et al., 1995; Ron et al., 1988a,b). Presently, studies of radiation therapy for tinea capitis in childhood present the strongest and most convincing epidemiologic evidence linking ionizing radiation to the occurrence of meningiomas (Ron et al., 1988a,b). There are numerous other etiologic risk factors reported in the literature, including head trauma, cigarette smoking, nitrite consumption, and even elevated cholesterol levels (Longstreth et al., 1993).

Endogenous factors associated with meningiomas include progestins (McDermott et al., 1996), estrogen (Carroll et al., 1999), prolactin (Black, 1996), glucocorticoids (Carroll et al., 1993), dopamine, somatostatin (Black, 1993) and growth factors, including platelet-derived growth factor (PDGF) (Black et al., 1994) and epidermal growth factor (EGF) (Carroll et al., 1997).

The Role of Hormones and Growth Factors

The finding that meningiomas occur twice as often in females than in males raises the question of the possible role of estrogen and progestins in their growth (Black, 1997). Donnell and colleagues (1979) showed in the 1970s that estrogen binding sites were preserved in the cytosol of meningiomas. More recently, with highly sensitive detection methods, at least two isotypes of estrogen receptors have been found in meningiomas (Carroll et al., 1999). Many groups have investigated the potential role of estrogen, progesterone, and androgen on the growth of meningiomas (Carroll et al., 1993, 1999; Halper et al., 1989; Hsu et al., 1997; Martuza and Eldridge, 1988; Martuza et al., 1981; Martuza et al., 1981, 1985; Maxwell et al., 1990, 1993, 1998; Schwartz et al., 1984; Tilzer et al., 1982). The function of estrogen receptors in meningiomas, however, is still unclear (Table 11–1).

There appears to be a consensus in the literature that most meningiomas are progesterone receptor

Table 11–1. Tumor Suppressor Genes, Proto-oncogenes, and Receptors Identified in Meningiomas

Tumor Suppressor Genes	*Merlin* *p53 (rarely involved)*
Proto-oncogenes	c-myc
	N-myc
	c-sys
	IGF-I
	IGF-II
Receptors	Androgens
	Dopamine
	Endothelin A
	Epidermal growth factor
	Fibroblast growth factor receptor-1
	Glucocorticoids
	Interferon-α
	Interleukin 6
	Neurotensin
	Platelet-derived growth factor-β
	Progesterone
	Somatostatin
	Transforming growth factor-β_1

positive and some are estrogen receptor positive (Blankenstein et al., 1995; Bouillot et al., 1994; Carroll et al., 1999). In one study 33 meningiomas were examined for the presence of the progesterone receptor by Northern blot analysis, and 11 of these were analyzed by immunohistochemistry (Carroll et al., 1993). In this analysis the progesterone receptor mRNA was expressed in 81% of tumors and the progesterone receptor was found in the nucleus in 40% of meningiomas (Carroll et al., 1993). By transfecting a construct with a progesterone-responsive element and a reporter sequence into primary cultures of meningiomas, it was later shown that endogenously expressed progesterone receptors were activated in these tumors (Black, 1997; Carroll et al., 1993). The precise function of progesterone receptors in vivo is, however, unknown.

The antiprogesterone agent medroxyprogesterone acetate (MPA) has been used in an attempt to exploit the known positive progesterone receptor status of most meningiomas. MPA failed to decrease tumor size in four of five patients treated for 17 to 29 weeks (Markwalder et al., 1987; Olson et al., 1987). The antiprogesterone agent mifepristone (RU-486) has also been used with only modestly better results. Grunberg and colleagues (1991) studied the effects of long-term oral RU-486 therapy in 14 patients with unresectable meningiomas. Five patients showed some signs of reduced tumor measurement on computerized tomography (CT) scan, MRI, or improved visual field examination. Three patients experienced improved extraocular muscle function or relief from headache. Lamberts and colleagues (1992) examined mifepristone treatment of meningiomas. In this study, 6 of 10 patients were said to be responsive to the therapy, and 3 of them experienced tumor shrinkage. Although these studies suggest that long-term therapy with mifepristone may be effective in cases of unresectable benign meningiomas, the extremely small sample size and nonblinded methodology make the significance of the results difficult to determine.

In the mid-1980s, Weisman and colleagues demonstrated the enhancing effect of EGF on DNA synthesis and cell growth in primary cultures of meningioma cells (Weisman et al., 1986, 1987). Subsequently, they characterized the EGF receptor (EGFR) in meningiomas and suggested the involvement of this growth factor in the proliferation and/or differentiation of meningioma cells (Weisman et al., 1986, 1987). More recent studies demonstrate that the EGFR is expressed in human meningioma specimens and that the EGFRs are activated in some meningiomas (Carroll et al., 1997).

Several studies suggest that the growth of meningiomas may also be mediated by PDGF (Black et al., 1994, 1996; Shamah et al., 1997; Todo et al., 1996; Zhang et al., 1996). The PDGF ligand is found in two subunits, A and B, and there are two isoforms of the receptors, α and β. The role of PDGF has been evaluated in 20 meningiomas, and it has been observed that PDGF-A, PDGF-B, and PDGF-β-R are expressed in meningiomas (Black et al., 1994). This analysis suggests that the β-receptor is functionally involved in meningioma growth. When activated, c-fos levels were increased, and an increase in meningioma cell division was observed in response to addition of PDGF-BB. These findings support the hypothesis that PDGF acts as a growth factor in meningiomas (Black et al., 1994, 1996).

Meningioma and Pregnancy

Some have noted that the growth of meningiomas is accelerated during the luteal phase of the menstrual cycle and during pregnancy (Narayansingh et al., 1992; Roelvink et al., 1987; Saitoh et al., 1989; Wan et al., 1990). A literature review of 62 cases of pregnancy-related symptomatic meningiomas by Roelvink and colleagues (1991), however, failed to support a cause and effect relationship between pregnancy and meningiomas. They indicated that that if a causal relationship between pregnancy and meningiomas existed, the number of cases reported in the literature up to 1991 should have been greater than 62 with a higher incidence in the reproductive years. In reality, however, the incidence of meningiomas is highest during the fifth, sixth, and seventh decades of a woman's life (McCarthy et al., 1998), when progestins and estradiol are low, if not absent. Interestingly, it has been noted that while progestins and estradiol are no longer being produced by the female reproductive system of older women, peripheral tissues such as adipose cells are still producing progesterone.

Relationships with Breast Cancer

A positive correlation between meningiomas and breast cancer has been reported (Rachlin et al., 1991; Rubinstein et al., 1989; Schoenberg et al., 1975, 1977). This finding, however, has since been called

into question. In a study of 238 patients with meningiomas, after a person-year method from age- and sex-matched cancer incidence, Jacobs and colleagues (1992) found that the number of breast cancers in the meningioma group was not significantly higher than predicted for age and sex.

In direct support of the correlation between meningiomas and breast cancer, Sulman and colleagues (1998) found that 34% had a loss of heterozygosity in the short arm of chromosome 1p32 region. Loss of heterozygosity in the same region, 1p32, has been reported for breast carcinoma, melanoma, and other cancers (Sulman et al., 1998). Other studies, however, have failed to find a genetic link between meningiomas and breast cancer. For instance, the putative tumor suppressor genes *BRCA1* and *BRCA2,* associated with familial and sporadic forms of breast and ovarian cancer, do not appear to share a common pathogenic pathway with meningiomas (Kirsch et al., 1997). Lauge and colleagues (1999) searched for germline mutations in the *PTEN* gene, known to be affected in Cowden's disease, a genetic condition associated with increased risk of breast cancers, but found no evidence for germline *PTEN* mutations in families with breast cancer and meningiomas. The issue of the responsiveness of meningiomas to hormones, in analogy to breast cancer, is still unresolved.

ANGIOGENESIS

Meningiomas, while most often benign, can grow to a large size before being detected, can encircle critical structures, and can even be accompanied by peritumoral edema (Bitzer et al., 1997; Bradac et al., 1986; New et al., 1980). Any of these occurrences can cause distortion of local structures and, if left untreated, can cause life-threatening mass effect. Meningiomas can also cause diffuse elevation of intracranial pressure, with a subsequent decrease in cerebral blood flow, leading to a slowing of metabolism in nearby cells (Al-Mefty, 1991; Al-Mefty et al., 1994; Black, 1993). A small subset of meningiomas exhibits very aggressive behavior and can invade and destroy adjacent brain; these rare tumors are malignant.

Several groups have studied the role of peritumoral vasogenic edema in meningiomas and its complications (Bitzer et al., 1997, 1998; Black, 1993; Bradac et al., 1986; Kalkanis et al., 1996; Kondziolka et al., 1998; Park et al., 2000; Provias et al., 1997; Tsai et al., 1999; Vuorinen et al., 1996). The source of such edema is not well known but is thought to result from increased microvascular permeability and extravasation of proteinaceous and plasma fluid into the adjacent peritumoral space (Bradac et al., 1986; Kalkanis et al., 1996). Several studies have confirmed the importance of vascular endothelial growth factor (VEGF) production, a 40 to 46 kDa protein that is 10,000 to 50,000 times more potent than histamine in increasing vascular permeability (Guha, 1998), in tumorigenesis, neovascularization, and edema production of some tumors (Bielenberg et al., 1999; Cao et al., 1996; Folkman and Shing, 1992; Goto et al., 1993; Kenyon et al., 1996; Miller et al., 1994; Rosenthal et al., 1994; Shima et al., 1995), including meningiomas (Bitzer et al., 1998; Kalkanis et al., 1996; Park et al., 2000; Provias et al., 1997; Tsai et al., 1999).

To demonstrate the strong link between VEGF mRNA expression and peritumoral edema in meningiomas, 31 meningioma specimens were subjected to Northern blot analysis, hybridization with a complementary DNA VEGF probe, and laser densitometry to determine the relative levels of VEGF mRNA expression (Kalkanis et al., 1996). Magnetic resonance imaging was used in a double-blind fashion to correlate the neuropathologic tissue samples with the presence of preoperative peritumoral edema. Of 31 patients studied, 14 exhibited no edema and 17 exhibited some level of peritumoral fluid accumulation. The results demonstrated that meningiomas with peritumoral edema exhibited 3.4 times the level of VEGF mRNA as those without edema. These data indicate that VEGF expression is an important factor in the etiology of edema around meningiomas (Kalkanis et al., 1996).

Regulation of the expression of VEGF by meningiomas has been studied by means of an enzyme-linked immunosorbent assay of CH-157MN meningioma cell supernatants (Tsai et al., 1999). Tsai and colleagues (1999) demonstrated that epidermal and basic fibroblast growth factors similarly induce VEGF secretion by CH-157MN meningioma cells to 160% above baseline constitutive secretion. The sex hormones estradiol, progesterone, and testosterone did not stimulate or inhibit VEGF secretion in CH-157MN meningioma cells. Dexamethasone in this study was shown to decrease VEGF secretion to 32% of baseline constitutive secretion, thus providing a potential explanation for the effect of corticosteroids in allevi-

ating peritumoral brain edema in meningiomas. The results from this study suggest that growth factors and corticosteroids, but not sex hormones, may regulate VEGF secretion (Tsai et al., 1999).

Recent evidence suggests that both mitogenic signals and angiogenic signals (via induction of VEGF) share a common link by activation of the ras signaling pathway (Feldkamp et al., 1999a,b; Guha, 1998). Consequently, inhibition of ras activity may lead to control of both tumor cell and tumor angiogenic growth. The relevance of the ras pathway in meningioma proliferation was recently studied by Shu and colleagues (1999) using nine primary meningioma cell cultures infected with the recombinant adenovirus Ad-rasN17, encoding the dominant negative ras protein or control adenovirus Ad-pAC. Ras-N17 is a ras mutant protein that inhibits function of all endogenous cellular ras proteins. The results demonstrated that infection of meningioma cells with AdrasN17 increased the expression levels of the ras-N17 mutant protein and inhibited phosphorylation of the mitogen-activated protein kinases. Suppression of ras proteins inhibited proliferation of all exponentially growing and growth-arrested meningioma cells stimulated with serum, suggesting that proliferation of primary meningioma cells depends on the presence of functional ras proteins. Inhibiting the ras pathway may be of great value in preventing growth factor–stimulated meningioma proliferation (Shu et al., 1999).

APOPTOSIS

Studies with 20 different low passage meningioma cell cultures and the addition of hydroxyurea resulted in a decrease in cell proliferation and arrested cell growth in the S phase in vitro. Characteristic signs of apoptosis, including DNA fragmentation, detected by in situ DNA strand break labeling, and discrete oligonucleosomal fragments (DNA ladder) were observed (Schrell et al., 1997). In vivo studies showed that when tissues from five different meningiomas were transplanted into mice followed by treatment with hydroxyurea, in situ DNA fragmentation was observed in all hydroxyurea-treated meningioma transplants, providing evidence that hydroxyurea can cause apoptosis in tumor cells (Schrell et al., 1997).

Recent reports indicate that preoperative embolization of intracranial meningiomas, used for selected patients to reduce tumor vascularity and blood loss during surgery, may produce ischemic changes consistent with apoptosis (Matyja et al., 1999; Nakasu et al., 1997, 1998). Alterations of *p53, bcl-2,* and *bax* expression, genes involved in an apoptotic death pathway, have been observed in embolized meningiomas (Nakasu et al., 1998). *p53* and its downstream effector p21 accumulated mainly in perinecrotic areas, where apoptosis was also observed (Nakasu et al., 1997, 1998). *bcl-2* was often expressed in the areas distant from necrosis, whereas *bax* was immunostained more intensely in the perinecrotic areas (Nakasu et al., 1998). Matyja and colleagues (1999), in addition to finding similar results in four biopsy specimens of embolized meningiomas with *p53* and *bcl-2,* also found that the anti-CD-68 immunostained cells were distributed around or within the necrotic foci. These results are consistent with the hypothesis that cell injury by preoperative tumor embolization correlates with the expression of apoptosis-related proteins (Matyja et al., 1999).

Apoptotic cell death in some meningiomas and schwannomas has been associated with the use of gamma knife radiosurgery. Indeed, radiation-induced apoptosis is thought to contribute to the low-dose effects of gamma knife radiosurgery (Tsuzuki et al., 1996).

CYTOGENETICS AND MOLECULAR GENETICS

As early as the 1960s, monosomy of chromosome 22 was reported in meningiomas (Zang and Singer, 1967), a feature found in 40% to 80% of these tumors (Collins et al., 1990; Dumanski et al., 1990). There also seems to be an association with partial or total loss of chromosomes 14 (Katsuyama et al., 1986) and 17 (Maltby et al., 1988) and with the Y chromosome (Maltby et al., 1988). Abnormalities of chromosomes 1, 3, 6, 7, 8, 10, 12, 18, and X have also been reported in meningiomas (Arnoldus et al., 1992; Smith and Cahill, 1994; Vagner-Capodano et al., 1993).

In the mid-1980s, several groups described partial losses such as the terminal deletion of chromosome 22 (Dumanski et al., 1987, 1990; Seizinger et al., 1987a–d). With restriction fragment-length polymorphisms (RFLP), a tumor suppressor gene involved in meningiomas has been narrowed to a locus

on the long arm of chromosome 22 (Dumanski et al., 1987, 1990; Lekanne Deprez et al., 1991; Rouleau et al., 1987; Seizinger et al., 1987a–d) between the myoglobin locus and the 22q12.3-qter (Dumanski et al., 1990; Leon et al., 1994; Peyrard et al., 1999).

TUMOR SUPPRESSOR GENES PROTO-ONCOGENES

The concept of tumor suppressor genes originated in the late 1960s when Harris and colleagues (1969) demonstrated that normal cells contain genes that can suppress neoplastic growth via inhibition of cell division and cell proliferation. In meningiomas, the *p53* tumor suppressor gene has been studied for point mutations, but such mutations were rarely found (Mashiyama et al., 1991; Ohgaki et al., 1993). In contrast, the putative tumor suppressor gene mapping to chromosome 22 has more often been implicated in the tumorigenesis of meningiomas (Arnoldus et al., 1992; Black, 1993; Collins et al., 1990; Dumanski et al., 1987; Gutmann et al., 1997; Kazumoto et al., 1990; Merel et al., 1995a,b; Parry et al., 1996; Rouleau et al., 1987, 1989; Ruttledge et al., 1994; Seizinger et al., 1987a,b; Sulman et al., 1998; Trofatter et al., 1993; Twist et al., 1994).

The *NF1* gene resides on chromosome 17. Its product, neurofibromin, is a large protein of 2818 amino acids. The protein acts as a negative regulator in the ras signal transduction pathway and might also act downstream of ras (Sundaram et al., 1997; Zwarthoff, 1996). A 360 amino acid region of neurofibromin shows significant homology to the catalytic domain of the mammalian p21 ras-specific 120 kDa GTPase-activating protein. In the cell types that are affected in NF1 patients, the absence of neurofibromin leads to increased proliferation, resulting in benign, and in some cases malignant, tumors. A study by Sundaram and colleagues (1997) analyzed the expression and functional status of neurofibromin in established human leptomeningeal LTAg2B cells, in 17 sporadic meningiomas, and in a meningioma from a patient affected by NF2. The expression of neurofibromin was determined via immunoblotting and immunoprecipitation with antineurofibromin antibodies, whereas its functional status was determined through its ability to stimulate the intrinsic GTPase activity of p21 ras. This study showed for the first time that neurofibromin is expressed at high levels in leptomeningeal cells and in sporadic meningiomas, and diminished GAP activity of neurofibromin was found in approximately 28% of the tumors analyzed. These results suggested also for the first time that decreased levels of neurofibromin in these tumors might contribute to their tumorigenesis (Sundaram et al., 1997).

Another tumor suppression gene, known as *NF2,* merlin, or schwannomin, is found to be mutated in most sporadic meningiomas, and it has been recently implicated in their tumorigenesis (Gutmann et al., 1997; Kimura et al., 1998; Lee et al., 1997). Schwannomin is a member of the band 4.1 superfamily of proteins that have been shown to play important roles in linking cell membrane proteins with the cytoskeleton, a site of activation of tumor suppressor genes in humans (Rouleau et al., 1993). Lee and colleagues (1997) used immunoblotting and immunoprecipitation experiments to determine the size and subcellular distribution of normal schwannomin in rabbit and human brain tissue, and established human leptomeningeal LTAg2B cells. Subsequently, they used similar techniques to determine the expression level of schwannomin in 14 human sporadic meningiomas. Their results showed that schwannomin is a protein of approximately 66 kDa predominantly expressed in the Triton X-100–insoluble fraction of the brain and LTAg2B cells. The expression of schwannomin was severely reduced in almost 60% of primary sporadic meningiomas, which raises the issue that this may be an important factor in the tumorigenesis of meningiomas. The development of meningotheliomatous meningiomas is probably linked to alterations in other oncogenes or tumor suppressor genes as results showed that all six tumors with normal schwannomin expression were of this type (Lee et al., 1997).

Proto-oncogenes, or genes that stimulate cell division, can become oncogenes when mutated. Oncogenes encode proteins that stimulate proliferation and sometimes mediate biologic activities that contribute to invasion. In a study of 19 meningiomas, Kazumoto and colleagues (1990) found that there was at least a fivefold expression of the *sis* oncogene and of the *c-myc* oncogene in a great percentage of these tumors. The *n-myc* gene has also been found to be involved in meningiomas (Detta et al., 1993; McDonald and Dohrmann, 1988; Tanaka et al., 1989). IGF-I and IGF-II have been found in a large number of meningiomas and may play an important role in tu-

mor growth and cell division of meningiomas (Antoniades et al., 1992; Friend et al., 1999; Glick et al., 1997; Nordqvist et al., 1997).

PATHOLOGY

In the classic monograph by Cushing and Eisenhardt (1938), meningiomas were divided into 9 major morphologic types; 7 of these categories were further divided into a total of 20 subtypes. Subsequent recognition of the lack of associated prognostic significance for most of these subtypes led to a widely adopted simplified scheme of three commonly encountered "classic" patterns: meningothelial, fibrous (fibroblastic), and transitional (mixed) (Fig. 11–1). In addition to these three basic patterns, the newly revised World Health Organization (WHO) classification (Kleihues and Cavenee, 2000) includes six additional morphologically distinct variants of low-grade meningioma (WHO grade I): psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte rich, and metaplastic. There is no prognostic difference between these morphologic variants and those that exhibit a "classic" pattern; the formal codification and morphologic description of these entities is provided in acknowledgment of the importance of recognizing them as meningiomas despite their unusual phenotypic appearance.

Four specific meningeal tumor morphologies recognized by the WHO classification are associated with a greater likelihood of recurrence and/or aggressive behavior and thus warrant brief comment: the clear cell, chordoid, rhabdoid, and papillary variants. Clear cell and chordoid meningiomas are classified as WHO grade II tumors, and rhabdoid and papillary meningiomas are classified as WHO grade III. Papillary meningiomas were originally described as an aggressive variant characterized by a high rate of recurrence and distant metastases (Ludwin et al., 1975). This description was subsequently confirmed by other investigators (Pasquier et al., 1986) and is currently recognized in the WHO classification (Fig. 11–2). Any discussion of aggressive meningeal tumors includes the issue of meningeal hemangiopericytoma. The meningeal hemangiopericytoma is a morphologically distinct neoplasm (Fig. 11–3) that historically has been variously considered as either an aggressive variant of meningioma (Russell and Rubinstein, 1989) or as the meningeal equivalent of systemically occurring hemangiopericytomas (Burger et al., 1991). The current WHO schema classifies meningeal hemangiopericytoma as a malignant mesenchymal neoplasm of nonmeningotheliomatous origin. It is agreed by all investigators that these tumors exhibit a generally more aggressive behavior than "typical" meningiomas and therefore must be distinguished from them.

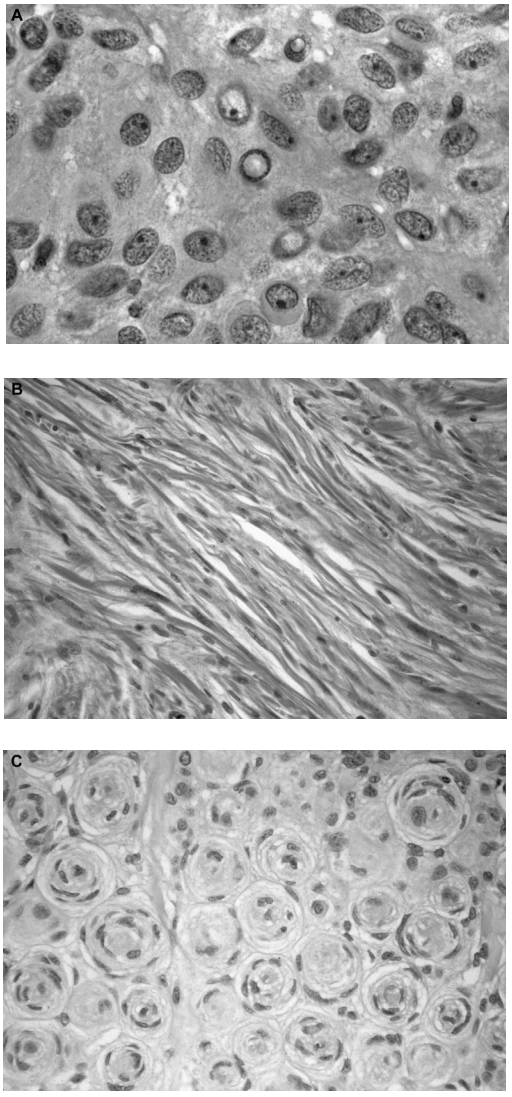

Figure 11–1. Meningioma. The three "classic" histologic patterns of meningioma are meningothelial **(A),** fibrous **(B),** and transitional **(C).**

Any of the various subtypes of meningiomas discussed above may exhibit morphologic features asso-

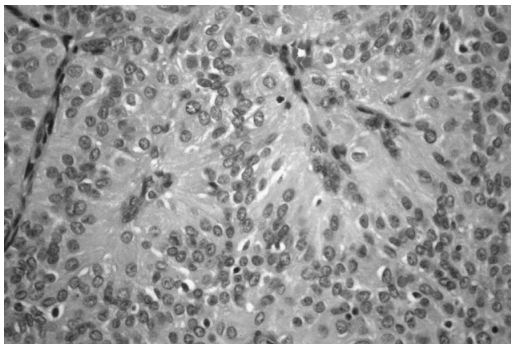

Figure 11–2. Papillary meningioma. This unusual variant is characterized by prominent perivascular arrangement of meningothelial cells, often with distinctive perivascular anuclear zones that resemble the perivascular pseudorosettes of ependymoma. Separation of adjacent angiocentric phalanges gives rise to the pseudopapillae that typify the lesion.

ciated with aggressive clinical behavior and warrant upgrading to either atypical (WHO grade II) or anaplastic (WHO grade III) meningioma. Morphologic criteria for atypical meningioma include either increased mitotic activity (defined as greater than or equal to 4 mitoses per 10 high power fields), brain invasion (invasion of the dura and cranial bone does not by itself constitute an indication of atypicality), or at least three of the following five features: dense cellularity, small cell formation, prominent nucleoli, patternless or sheet-like growth, and foci of tumor necrosis. Criteria for anaplastic meningioma (WHO grade III; WHO terminology prefers the term *anaplastic* over *malignant*) include either a very high mitotic rate (defined as 20 or more mitotic figures per 10 high power fields) or morphologic features far in excess of those seen in atypical meningiomas, which would include appearances similar to sarcoma, carcinoma, or melanoma. Frank brain invasion may be seen in low-grade, atypical, or anaplastic meningiomas. When present in an ordinary low-grade meningioma, this feature was previously used as a criterion that warranted a diagnosis of anaplastic (or malignant) meningioma; however, recent studies have shown that the clinical behavior of otherwise ordinary meningiomas that show brain invasion is much closer to that of atypical meningiomas than to truly anaplastic (malignant) meningiomas (Perry et al., 1999), and current WHO criteria recommend classification as such. Much research effort is currently directed toward the evaluation of proliferation markers, such as MIB-1 (a monoclonal antibody that recognizes the Ki-67 antigen in routinely processed formalin-fixed, paraffin-embedded tissue), as potentially powerful prognostic indicators of aggressive behavior.

CLINICAL PRESENTATION BY LOCATION

In general, meningiomas present with the usual triad of symptoms of brain tumors in an adult patient, namely, headache, seizures, progressive focal neurologic deficit, and/or change in personality. Given that many of these tumors grow slowly, the onset of symptoms can be insidious. Those symptoms caused by delayed effects of chronic increased intracranial pressure, such as deteriorating vision from papilledema, or double vision from sixth nerve palsies, are uncommon today.

Supratentorial Meningiomas

Olfactory groove meningiomas arise in the midline adjacent to the crista galli and the planum sphenoidale. As they enlarge, they compress the inferior frontal lobe, elevating it, and posteriorly displace the

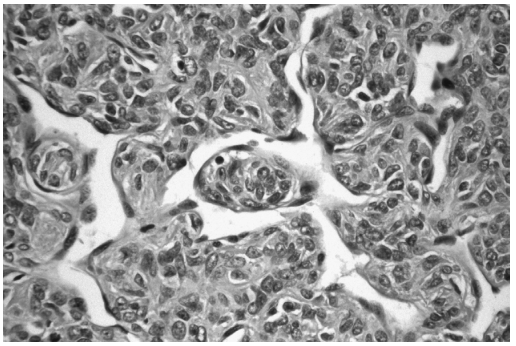

Figure 11–3. Meningeal hemangiopericytoma. Distinctive features of this aggressive tumor include the densely packed, disorganized cellularity and characteristic angular, branching vasculature ("staghorn" pattern). Meningeal hemangiopericytomas also differ from meningiomas immunohistochemically (lack of epithelial membrane antigen expression), ultrastructurally (presence of basement membrane-like material and lack of abundant intercellular desmosomal attachments), and in incidence between the sexes (equal frequency for hemangiopericytomas compared with a definite female predilection for meningiomas).

optic apparatus. Typically these patients have slow onset of change in mental status, depressed mood, and impaired insight, judgment, and motivation. It is rare for patients to complain of a loss of the sense of smell. Family members usually notice a change in personality first; late in the course of their disease, patients may complain of headaches and reduced vision. The rare syndrome described by Foster and Kennedy of anosmia, unilateral optic atrophy, and contralateral papilledema was originally attributed to tumors in this location.

Immediately behind the olfactory grove is another location where meningiomas develop, the *tuberculum sellae.* This is the bone on the anterior aspect of the sella turcica, and most patients with tumors in this location have progressive visual loss, which is usually asymmetric. Changes in personality and mental status are uncommon because the patients come to medical attention with their visual disturbance before their tumors become large. They occur more commonly in women than in men and typically present in the fifth and sixth decades of life. Visual field findings may resemble those of pituitary adenoma with a bitemporal field defect.

The *sphenoid wing* is one of the most common locations for an intracranial, supratentorial meningioma. These tumors typically arise anywhere along the course of the sphenoid wing, from the anterior clinoid medially to the pterion laterally. Symptomatology is related to location along the sphenoid wing. Those patients with medial clinoid meningiomas usually have slow progressive unilateral visual loss, headaches, and seizures. Middle-third sphenoid wing meningiomas present with headaches, seizures, and mild proptosis, without prominent visual disturbance. Lateral sphenoid meningiomas present with headaches, seizures, and swelling in the region of the temporal fossa. A type of meningioma in this location that occurs much more commonly in women is the hyperostosing "en plaque" meningioma. The typical chronology is "a middle-aged women who for long periods has slowly had increasing unilateral exophthalmos with ultimate impairment of vision and with palpable swelling in the temporal region," as described by Cushing and Eisenhardt (1938). Edema of the inferior lid may be prominent in these patients. An impairment of lateral gaze may also be present due to involvement of lateral periorbital and/or lateral rectus muscle.

Cavernous sinus meningiomas are a difficult clinical problem. Typically, patients with these tumors present with double vision, facial numbness, and, later in their course, headache and reduced visual acuity. Seizures are uncommon and usually occur only if there is a large exophytic middle fossa component to the tumor. These symptoms make sense anatomically given the presence of the third, fourth, fifth, and sixth cranial nerves within the cavernous sinus compartment.

Parasagittal meningiomas fill the angle between the convexity dura and the midline falx. The classic clinical presentation is a patient with a headache and focal motor or sensory seizures, beginning with symptoms in the lower extremity progressing up into the body, arm, and face. Frequently these patients will have unilateral upper motor neuron signs or cortical sensory disturbance. Papilledema is relatively uncommon except in the largest tumors.

Meningiomas that arise truly from the *falx* are covered on their superior aspects by cortical tissue of the frontal, parietal, or occipital lobes. Clinical signs or symptoms depend partly on where along the falx these tumors grow. Anatomically these tumors are defined as occurring in the anterior, middle, or posterior third of the falx. Anterior-third falx meningiomas may present with headache, seizure, and mental status change. Middle-third falx meningiomas present with headache, seizures, and focal motor sensory deficit. Posterior-third falx meningiomas present with headache and visual loss, or irritative visual phenomenon with visual hallucinations. It is rare for a large bilateral dumbbell-shaped falx tumor to present with a spastic paraparesis.

Convexity meningiomas arise in the dura over the frontal, temporal, parietal, or occipital lobes. Frequently these tumors are asymptomatic and are discovered on imaging carried out for another reason. However, when the tumors are large, they present with headache, seizures, and focal neurologic deficit depending on whether the tumor is on the right or left side and over speech, motor, sensory, or occipital cortex. These tumors are the most favorable for surgical treatment.

Patients with *intraventricular* meningiomas have protean manifestations. In the series of Cushing and Eisenhardt (1938), tumors within the atrium of the lateral ventricle typically presented with headache, nausea, vomiting, seizures, and speech disturbance. Patients with large tumors may also have a hemianopsia and unilateral sensorimotor deficit. Third-ventricular meningiomas present with nonspecific

symptoms, which are predominantly from increased intracranial pressure.

Posterior Fossa Meningiomas

Tentorial meningiomas present most often with headache, extremity or gait ataxia, nausea, and vomiting. Seizures and mental status changes are uncommon because of their posterior fossa location. Common clinical findings include evidence of cranial nerve III, IV, V, and VI deficits and appendicular cerebellum disturbance. The more medial and anterior the location of the tentorial meningioma, the more likely the patients are to have extraocular muscle disturbance. Tentorial meningiomas that have a significant component extending up into the inferior temporal or occipital lobes may cause seizure or visual disturbance. A peculiar and surgically unfavorable type of meningioma involving the tentorium is the falcotentorial meningioma, which involves the junction of the falx cerebri and tentorium, usually including the straight sinus. These patients typically present with symptoms of increased intracranial pressure without focal neurologic deficit.

Petroclival meningiomas usually have an insidious onset of headache, gait disturbance, double vision, reduced hearing, and vertigo. Common clinical signs include cranial neuropathy, particularly involving nerves IV, V, VI, and VIII, along with papilledema, ataxia, and cerebellar dysmetria. For meningiomas that arise along the posterior petrous bone within the CP angle, Sami and Ammarati (1988) distinguished symptoms of those tumors arising anterior to the internal auditory canal (IAC) from those arising posterior to it. Anteriorly placed lesions usually present with facial pain, facial numbness, and reduced hearing. With tumors posterior to the IAC, cerebellar signs are predominant and gait disturbance is common. It is not infrequent for a tumor in this location to be confused with a vestibular schwannoma. Meningiomas of the *cerebellar convexity* usually present with symptoms and signs of increased intracranial pressure, hydrocephalus, or cerebellar dysfunction ipsilateral to the tumor. Papilledema, appendicular, and truncal ataxia are common.

Foramen magnum meningiomas are difficult to diagnose clinically and, before MR imaging, were frequently confused with demyelinating disorders. Most patients have a history of neck and suboccipital pain that is worse with flexion and Valsalva maneuvers. Motor and sensory deficits usually develop first in the arm and then in the legs and may involve all extremities to the point of spastic quadraparesis. The so-called crural palsy, with atrophy in the intrinsic muscles of the hand, trapezius, and shoulder, can be particularly confusing for the clinician. Secondary damage from increased venous pressure in the cervical spinal cord may be the cause for some of these symptoms and signs. In a clinical series from the Mayo Clinic, 94% of patients complained of upper extremity dysesthesia; 75% of suboccipital or neck pain; 49% of upper extremity weakness; 47% of gait disturbance; and 42% of clumsiness of their hands. Problems with lower cranial nerve function may lead to complaints of dysarthria and dysphasia. Differential diagnosis in these patients can also include syringomyelia and intramedullary cervical spinal cord tumors.

Meningiomas occurring near the *torcular of Herophilus,* or confluence of the superior sagittal, straight, transverse, and occipital sinuses, present with symptoms of increased intracranial pressure. The patients of Cushing and Eisenhardt (1938) complained of visual impairment related to papilledema, headaches, and neck pain. The authors noted that lower quadrants of the visual field appeared to be affected before the upper quadrant of the visual field, and recovery of these fields postoperatively proceeded in a reverse direction. The last location for meningiomas of the posterior fossa is the fourth ventricle. Despite the abundance of critical nuclei immediately below the pial surface of the floor of the ventricle, these tumors usually present only with symptoms of obstructive hydrocephalus and increased pressure.

IMAGING STUDIES

Plain X-Rays

For the most part the use of plain radiographs for the diagnosis of intracranial meningiomas is of historic interest only. In the past, evidence of intracranial calcification, hyperostosis of the sphenoid wing or calvarium, displacement of the pineal gland or enlarged vascular channels were used as indirect supportive evidence of the presence of a long-standing, vascular tumor attached to the dura and/or invading the bone. Computed tomography followed by MR imaging have

become standards of imaging for the diagnosis and follow up of intracranial meningiomas. Sometimes, when only MR imaging has been done and the patient has a history of prior craniotomy or craniectomy, plain X-rays are helpful in delineating the extent of bone removal, which may assist with preoperative planning and intraoperative cranial pin fixation.

Computed Axial Tomography

Computed tomography is inferior to MRI for delineating soft tissue details of both the meningioma under investigation and the surrounding brain. It is superior to MRI for defining the extent of bony hyperostosis, a key point in the consideration of basal and convexity meningiomas with associated hyperostosis. Pathologic studies have demonstrated that hyperostotic bone contains meningiothelial cells, and failure to remove this involved bone may lead to later recurrence of a soft tissue tumor or progression primarily within bone. Thin-cut CT imaging may now be used with image-guided surgical systems primarily for the purpose of helping the surgeon define the bony margins of tumor intraoperatively. In these circumstances, image fusion technologies allow the surgeon to use MRI data to determine the soft tissue margins of the tumor adjacent to brain (e.g., determining the distance to the medial or deep aspect of the tumor) and then switch to CT-based images for the resection of tumor-involved bone.

On non-contrast CT imaging, meningiomas appear isodense to slightly hyperdense. Calcification within the tumor can be punctate or confluent and is easily seen. Optic nerve sheath meningiomas may show the traditional "tram track" linear calcification outlining the orbital course of the optic nerve. When hyperostosis of the calvarium is extensive the bone can have a mottled to radiating starburst appearance. Meningiomas along the sphenoid wing produce dense sclerotic hyperostosis of the greater wing and pterion producing associated exophthalmos. These tumors are characteristically seen in women. With the administration of iodinated contrast, meningiomas usually enhance homogenously and intensely. The "dural tail" so often referred to with MRI is not well visualized with CT as it is thinly opposed to the underlying bone.

Mantle et al. (1999) reported on the use of quantifying peritumoral brain edema on CT scanning for predicting the probability for meningioma recurrence. Between 1980 and 1998, 135 patients were evaluated. Edema grade was linearly related to edema volume by digitizing the CT scans. The completeness of resection was the most powerful predictor of recurrence, followed by edema grade and brain invasion. The chance of recurrence within 10 years after complete resection was exponentially related to the maximum linear dimension of surrounding peritumoral edema. The chance of recurrence increased by approximately 10% for each centimeter grade increase in the amount of edema. The authors also found that the histopathologic documentation of brain invasion increased by 20% per centimeter of edema thickness on the actual CT scan. Thus, valuable information can be derived by this simple imaging study, which may influence treatment and outcome. Furthermore, Kuratsu and colleagues (2000) in evaluating the clinical features of asymptomatic meningiomas found that patients with evidence of tumoral calcification on CT scans had a significantly lower likelihood of tumor growth after longer than a 1 year follow up ($p = 0.008$).

One disadvantage of CT is that multiplanar imaging is limited. Direct coronal imaging without much artifact is limited to the anterior and middle cranial fossa. Direct sagittal images cannot be achieved. On the other hand, bony foramina within the skull base are clearly seen, and three-dimensional reconstructions available from image-guided system workstations give bony spatial resolution and detail superior to that obtained from MRI.

Magnetic Resonance Imaging

As originally described by Cushing, meningiomas are typically dural-based lesions when seen on MR scans. Approximately 60% of these tumors are isointense and 30% hypointense on T_1-weighted images (Fig. 11–4A,B). On T_2-weighted imaging studies, intensities may vary anywhere between hypointense to hyperintense, and there may be a correlation between pathologic type and T_1/T_2 imaging features. On the T_2-weighted images, a hypointense signal that surrounds the edge of a meningioma may represent the compressed, but preserved arachnoid plane between brain and tumor (Fig. 11–4C).

Hypointensity within the tumor may relate to cystic change or intratumoral calcification, such as is seen with psammomatous meningiomas. The so-called "dural tail" is an imaging feature thought to be

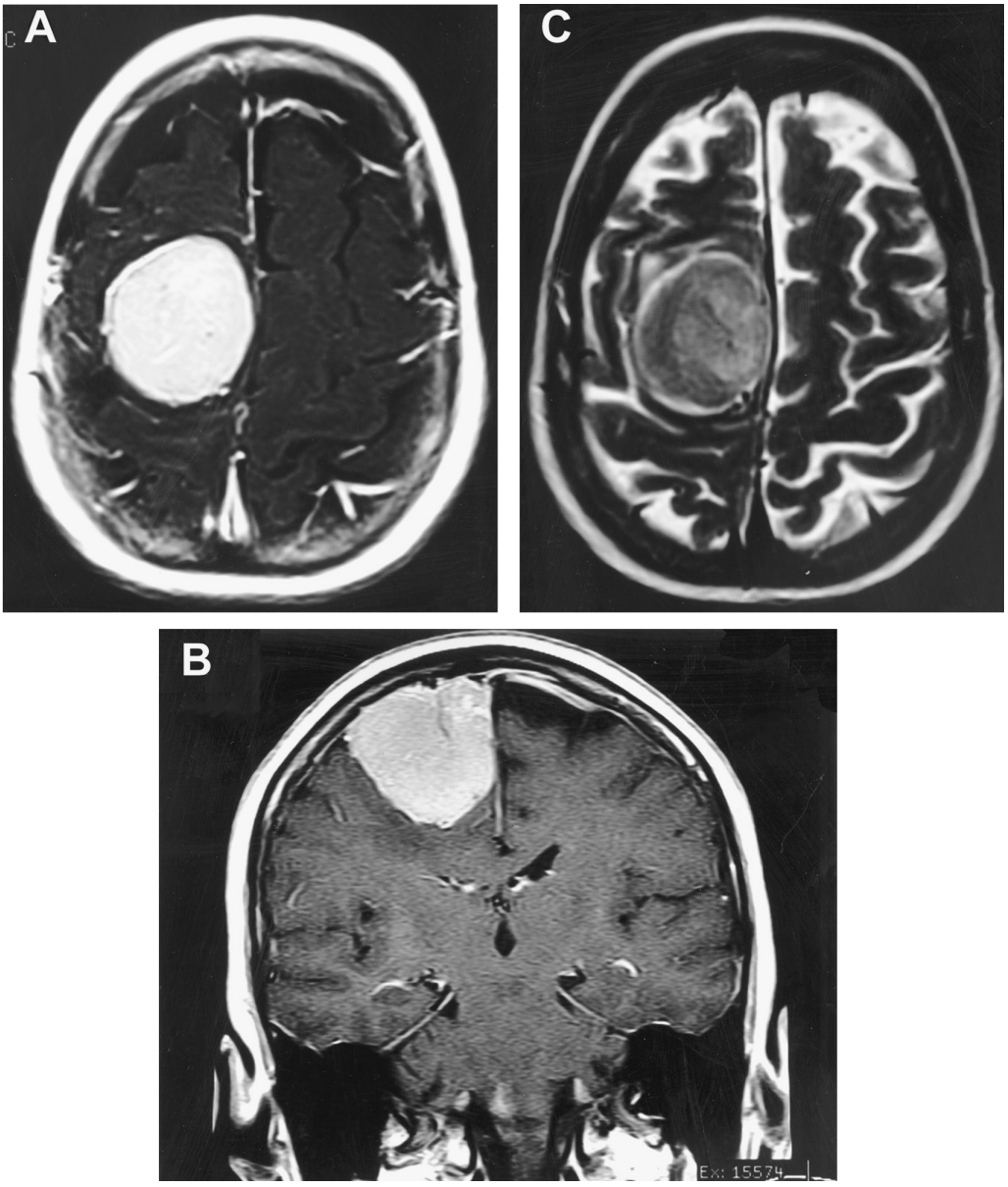

Figure 11–4. (A) Axial T_1-weighted MRI scan of right frontoparietal parasagittal meningioma with homogenous enhancement typical of benign meningioma. **(B)** Coronal T_1-weighted MRI showing meningioma filling the angle between falx and convexity dura, characteristic of parasagittal meningioma. Signal flow void near midline is consistent with patent superior sagittal sinus. Note relative lack of mass effect given large size of tumor, suggesting slow tumor growth over a long interval of time. **(C)** Axial T_2, second echo image showing no edema in surrounding brain and thin rim of hyperintensity between tumor edge and brain, consistent with preserved arachnoid plane.

characteristic of meningiomas. This tail typically extends several millimeters from the edge of the tumor and is thought to represent hypervascularity rather than tumor infiltration. Magnetic resonance imaging is the preferred modality for deriving a volumetric study for the use of image-guided surgical systems, and these systems help with planning skin flaps, bony openings, and extent of removal as surgery proceeds.

Paleologos et al. (2000) evaluated the use of image-guided surgical systems in 100 patients treated

surgically for meningiomas. This group was compared with 170 patients operated on without the use of intraoperative navigational systems. Although the study was not randomized, surgical times were shorter for the image-guided group, and blood loss and mean hospital days spent were less for the image-guided group. Importantly, surgical complications, either permanent neurologic deficit or those complications requiring an additional surgical procedure, were significantly less in the image-guided group. There are technical considerations with the use of image-guided systems for skull-based neoplasms, such as the type of imaging, imaging sequence, and convenience issues referable to the type of image guidance system, either light-emitting diode or passive mechanical arm, to be used. At our institution, The University of California, San Francisco, image-guided surgical systems are the standard for operations on large convexity or skull-based meningiomas, and we prefer an older passive arm system because it avoids problems with line of sight when the operating microscope is in position.

Magnetic resonance imaging has been reported to be of value in predicting the relationship between peritumoral edema as evidenced by hyperintensity on T_2-weighted images and the cleavage plane between tumor and surrounding brain. In the study by Ildan et al. (1989) increasing degrees of peritumoral edema on T_2 images correlated significantly with worsening of surgical cleavage plane between tumor and surrounding brain. On angiographic studies, those tumors with pial arterial supply were much more likely to demonstrate significant peritumoral edema. The authors proposed that MRI findings might predict the difficulty of microsurgical dissection for the surgeon before operation.

In another study of cystic meningioma, Zee et al. (1995) evaluated the MRI features of 15 cystic meningiomas classifying them into three different types. Type I cystic meningiomas were those with cysts wholly within tumor. Type II were those with cysts at the periphery, but still within margins of the tumor, and type III were cysts peripheral to the tumor in adjacent brain. Enhancement of cyst walls was seen in type II cystic meningiomas, but not in type III. The authors suggested that this pattern of enhancement required surgical excision of the enhancing wall. They also found that the pathology in these cystic meningiomas tended to be more aggressive.

Functional MRI techniques are also useful in predicting the location of visual, motor, sensory, and speech language cortex relative to meningiomas. Presuming that the meningiomas do not invade the adjacent brain, information about the adjacent cortex may nonetheless be important for predicting temporary neurologic disability that may result after removal of large meningiomas.

Cerebral Angiography

Conventional cerebral angiography is still useful in the management of patients with meningiomas despite the advent of MR angiography and MR venography. Whereas the blood supply for the variety of tumor locations is predictable based on anatomy, this information can still assist the surgeon with planning a surgical approach, and embolization of very hypovascular tumors may assist with surgical removal. Angiographic information about tumor blood supply and the displacement of major arteries and their positions relative to the margins of the tumor are important. On the venous phase of these studies, the positions of draining cortical veins are critical as well because these must be preserved. The later phase of angiography, which gives information about venous anatomy, is still the gold standard for determining whether or not a major venous sinus is still patent (Fig. 11–5).

Bendszus et al. (2000) recently tried to evaluate the benefit of preoperative embolization of meningiomas. Their perspective was drawn from a nonrandomized, noncontrolled study of 60 consecutive patients in two different neurosurgical centers who were operated on and followed up. In Center A, no embolization was performed. In Center B, all patients underwent embolization. Mean tumor sizes and mean blood losses with surgery did not differ between groups, but, in the subgroup of patients who had subtotal devascularization in more than 90% of the tumor, blood loss was significantly less than in patients who were not embolized ($p < 0.05$). There were no differences in surgeons' observations regarding hemostasis, tumor consistency or intratumoral necrosis. There was one new permanent neurologic deficit related to embolization (3%).

At our institution, preoperative embolization is reserved for the largest meningiomas even if the external carotid supply can be accessed easily during the opening (Fig. 11–6). A variety of embolic agents may

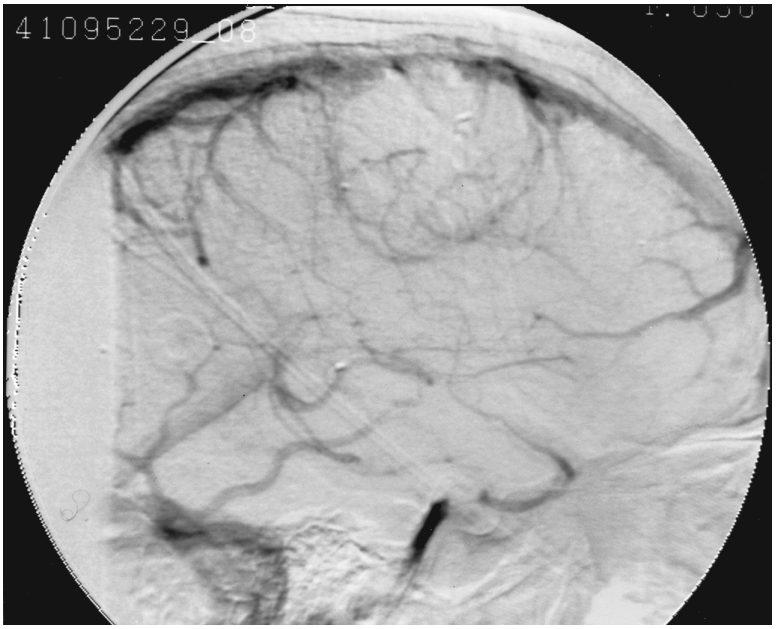

Figure 11–5. Sagittal, venous phase of cerebral angiogram in same tumor as in Figure 11–1. Study confirms patency of superior sagittal sinus and displacement of draining veins.

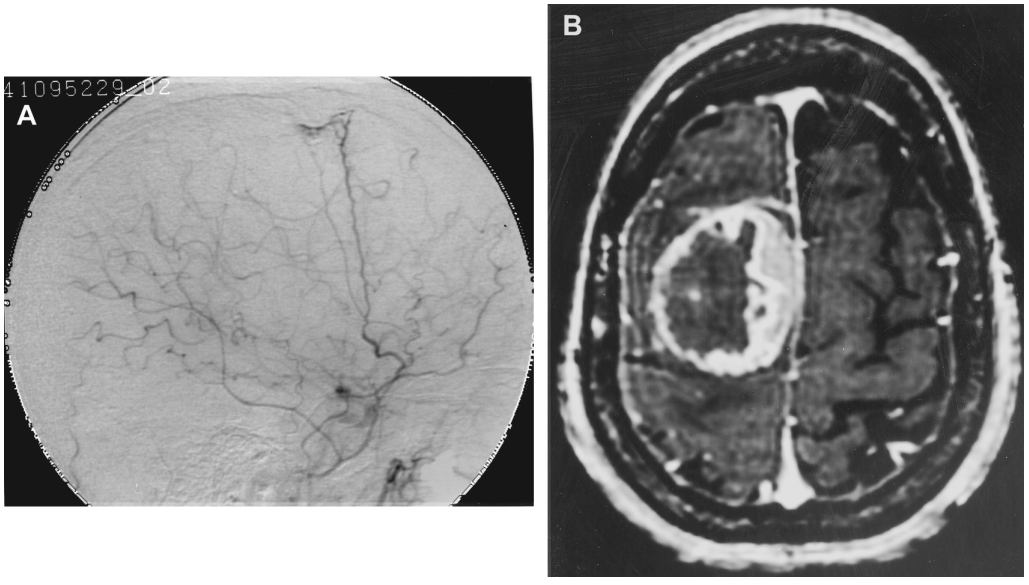

Figure 11–6. **(A)** Lateral external carotid injection of middle meningeal artery supplying tumor. **(B)** Preoperative T_1-weighted MRI with contrast (for image-guided system) showing dramatic effect of embolization on central blood supply to tumor. Persistent medial enhancement is due to supply from falcine artery originating off the anterior ethmoid arteries, not suitable for embolization.

get into the smallest blood vessels supplying tumors. We have used a combination of gelfoam powder, polyvinyl alcohol foam, and platinum coils. It has been our practice to embolize these large meningiomas the day before operation without waiting for further thrombosis to occur. In the principal author's experience there have been no problems with this approach in more than 100 surgical cases. If embolization is performed, a surgeon must remember that compromise of the blood supply to the scalp may have occurred and consider this when planning skin incisions.

OPTIONS FOR TREATMENT

Observation

Not every patient with an intracranial meningioma requires surgical intervention, and many factors, patient and tumor related, are involved in the decision to recommend surgery. One of the first questions to ask when a tumor is found on imaging studies is whether the imaged tumor is responsible for the patient's symptoms and signs. If not, and the imaging features are consistent with a benign tumor (homogeneous enhancement, smooth rounded margins, no associated brain edema, no satellite lesions), a period of observation is recommended. More and more asymptomatic meningiomas are discovered on imaging studies done for some other reason.

Olivero et al. (1995) followed 57 patients with symptomatic meningiomas over an average of 32 months (range 6 months to 15 years). None of the patients became symptomatic from their enlarging tumor during follow up, and tumor growth was observed in only 10 of 45 patients (22%) imaged. The average growth rate in these patients was a 0.24 cm increase in maximum diameter per year. In another study, Kuratsu et al. (2000) studied 109 patients. Of these, 63 (57.7%) had imaging follow ups of more than 1 year. Thirty-one percent of this subgroup showed tumor growth over an average follow-up period of 27.8 months (range, 12 to 87 months). While the average age in the two groups of patients, with and without tumor growth, was similar (67.5 versus 66.0 years), tumors that did not grow were more likely to be calcified on CT or hypointense on T_2-weighted MRI, consistent with intratumoral calcification. Clearly, then, not all tumors grow under observation, and it is our policy to recommend 6 month interval follow-up imaging with MRI for 2 years and then once a year if tumors are stable and the patient remains asymptomatic.

Surgery

A discussion of the specific surgical approach for each tumor location is beyond the scope of this text, but some general comments can be made. First, for symptomatic meningiomas, surgery is the mainstay of diagnosis and is the first step in treatment. With surgical removal there is no delay in "tumor response" as with other forms of therapy. Symptoms related to increased intracranial pressure or those related to local compression of brain can be improved quickly. Chozick et al. (1996) found that 39.9% of 158 patients with meningiomas had preoperative seizures and 88.9% of these patients had complete control of seizures postoperatively following tumor removal.

The surgeon must consider the indications for, risks associated with, reasonable goals of, and projected outcomes for expected or unexpected pathologies associated with surgery. These issues must be reviewed frankly with patients but without frightening them. Patient factors such as age, life expectancy, neurologic condition, and associated medical conditions should be taken into account. A determination of the resectability of the tumor should also be made. In some skull-base locations, such as cavernous sinus, complete removal of all microscopic tumor tissue is very difficult, if not impossible. Larson et al. (1995), in their experience with 36 patients who had cavernous sinus meningiomas, documented microscopic invasion into cranial nerves by tumor. Sen and Hague (1997) examined six patients with benign meningiomas of the cavernous sinus at autopsy. There was a tendency for infiltration of the carotid artery, the pituitary gland, and the connective tissue between fascicles of nerves. The trigeminal nerve and ganglion were particularly prone to invasion. These pathologic studies, as well as clinical experience, have prompted a conservative surgical approach with these tumor locations, treating residual or recurrent disease with radiotherapy.

The degree of surgical removal is also related to the risk of recurrence. This was outlined in the seminal paper of Donald Simpson (1957) (Table 11–2). Tumor-infiltrated bone left behind increases the risk of recurrence as does simple coagulation rather than

Table 11–2. Simpson Grade by Extent of Tumor, Dura, and Bone/Venous Sinus Excision

	Tumor Removal			*Dural Attachment*		*Bone/ Sinus Excised*
Grade	*Complete*	*Partial*	*Biopsy*	*Excised*	*Coagulated*	
I	X			X		X
II	X				X	X
III	X					
IV		X				
V			X			

excision of the tumor's dural attachment (Fig. 11–7). Surgical decision-making during the operation with respect to the degree of tumor removal attempted and the length of the operation may also affect outcome. Condra et al. (1997) classified "total excision" (TE) as a Simpson grade I, II, or III excision and found that of the 174 of 229 (76%) patients with this degree of excision, local control rates were 93%, 80%, and 76% at 5, 10, and 15 years, respectively. In contrast, the "subtotal excision" (SE; Simpson grade IV) results for equivalent time periods were 53%, 40%, and 30%, with cause-specific survival results mirroring local control for the TE and SE groups. Condra et al. (1997) thought that SE alone was inadequate therapy. In contrast, Jung et al. (2000), in reporting their results for the removal of 38 petroclival meningiomas, found that the median progression-free survival (PFS) was 66 months after SE and that the growth rate was slow (0.37 cm/year). The mean tumor doubling time was 8 years. These authors thought that subtotal resection, with or without radiation, was an option for patients with petroclival meningiomas. Similarly, Couldwell et al. (1996) reported their experience with 109 patients with petroclival meningiomas, many of who had subtotal resection of the posterior cavernous sinus component. In 69%, gross total tumor resection was achieved with a recurrence rate of only 13% over a 6.1 year mean follow up. In the 20 patients with known subtotal resection of the cavernous sinus component, 12 (60%) demonstrated radiographic progression and went on to further treatment.

Whether complications result from surgery for meningiomas depends on a number of factors, with patient age and tumor location as major considerations. In the series of Kuratsu et al. (2000), asymptomatic meningiomas that underwent surgical removal had a perioperative morbidity of 23.3% for those over the age of 70 years and 3.5% for those younger. The neurologic, medical, and surgical morbidity rates in the entire group were 6.9%, 3.4%, and 2.3%, respectively. For supratentorial meningiomas, a parietal location is a risk factor for the development of postoperative seizures. Infratentorial and skull-base meningiomas present challenges for cranial nerve preservation. In the series of Couldwell et al. (1996), of 109 petroclival meningiomas, permanent new cranial nerve deficits developed in 33% and the mortality rate was 3.7%. Modern neurosurgical series also reveal that neurologic morbidity after operation is site dependent.

At open operation, meningiomas are attached to the dura, and displacing the adjacent arachnoid and brain maintaining the "arachnoid plane" assists the surgeon with dissection. Two common principles employed during meningioma surgery are *(1)* to debulk the tumor centrally, first folding the thinned-out walls back into the cavity created rather than retracting brain to define the tumor margin; and *(2)* to respect the arachnoid membranes, which help separate tumor from the adjacent brain, blood vessels, and cranial nerves. A variety of instruments are now used routinely to assist with the surgical removal of these tumors, including the operating microscope, neurophysiologic monitoring, image-guided surgical navigation systems, ultrasonic aspirators, and, more recently, intraoperative MRI. For many of the complex skull-base tumors, especially those in the middle and posterior fossa, a team approach is taken, combining the skills of neurosurgeons and neuro-otologists. For very long operations this method allows co-surgeons to share the workload, with a rest between operative sessions of 2 to 4 hours helping to maintain their concentration and stamina. Without going into

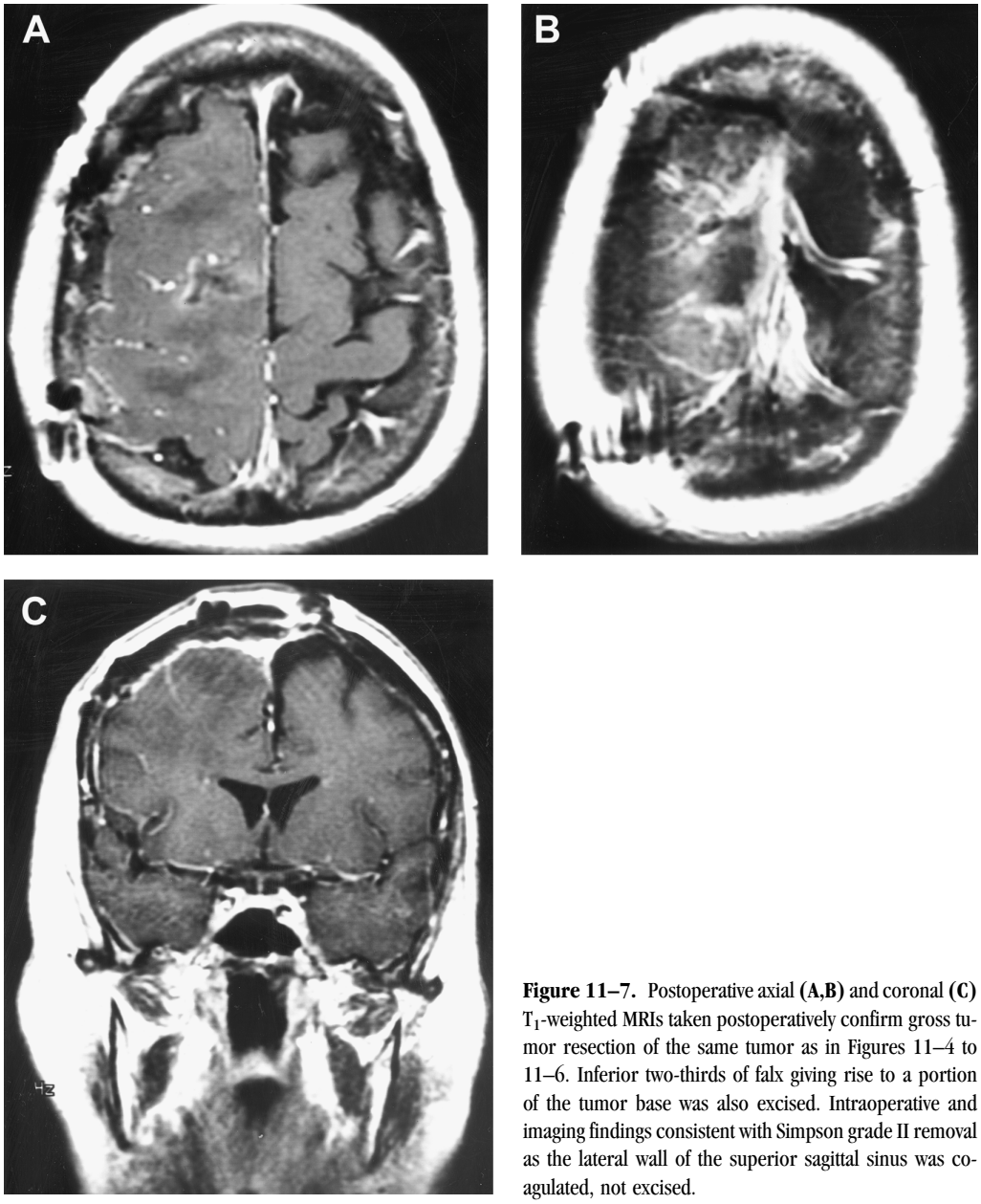

Figure 11–7. Postoperative axial **(A,B)** and coronal **(C)** T_1-weighted MRIs taken postoperatively confirm gross tumor resection of the same tumor as in Figures 11–4 to 11–6. Inferior two-thirds of falx giving rise to a portion of the tumor base was also excised. Intraoperative and imaging findings consistent with Simpson grade II removal as the lateral wall of the superior sagittal sinus was coagulated, not excised.

exhaustive detail, a few specific comments can be made about the most common tumor locations.

Supratentorial

Common locations in the supratentorial compartment include convexity, falx/parasagittal, sphenoid wing, and parasellar. Convexity meningiomas, when small, are straightforward. Image-guided surgical systems can be used to map out the location of the tumor and then to plan a margin of normal dural excision. Al-Mefty (1991) has coined the term "grade zero" excision for tumors in these locations to include a cuff of 2 cm of normal dura around the tumor base. When the tumors are very large, the most medial surface may have a poor brain–tumor interface even with benign pathology.

For falx/parasagittal meningiomas, preoperative assessments of the venous sinuses and parasagittal draining veins with MR venography or angiography will help the surgeon decide whether total excision is possible and which is the best route for avoiding important veins. Use of surgical navigational systems has become almost routine for the approach to these tumors. When the superior sagittal sinus is occluded on the preoperative angiogram, the point along the sinus where flow is present or not can be determined with a small intraoperative Doppler probe.

For sphenoid wing and parasellar tumors, the increased use of skull-base approaches limits the amount of brain retraction needed, reducing early and late complications. Orbitozygomatic osteotomies, combined with removal of the roof, lateral walls of the orbit, and the pterion, can be performed before the dura is opened for tumor removal. Similarly, for large olfactory groove, planum sphenoidale, and tuberculum meningiomas, a bifrontal, extended frontal (bilateral supraorbital osteotomy) craniotomy provides excellent exposure with the least brain retraction. Microdissection of the olfactory nerves back to the optic nerves can be done to preserve smell.

Infratentorial

Medial anterior tentorial tumors with extension into Meckel's cave or the posterior cavernous sinus and petroclival tumors are best approached with a retrolabyrinthine petrosal craniotomy. An incision in the dura along the temporal floor, crossing the superior petrosal sinus and then down in front of the sigmoid sinus, is combined with incision of the tentorium to its medial free edge. Care is taken to avoid injury to the vein of Labbe entering the tentorium and to the fourth nerve at its free edge. This provides the shortest route to the center of the tumor without significant cerebellar retraction and, when combined with physiologic monitoring, hearing is not inadvertently affected.

For foramen magnum meningiomas, the far lateral transcondylar approach provides a corridor to the tumor without spinal cord or brain retraction. After suboccipital craniotomy and C-1 hemilaminectomy, the posterior one-third of the occipital condyle is drilled off and the dura is opened in a curvilinear fashion just medial to the entry of the vertebral artery into the posterior fossa dura. With intraoperative monitoring of cranial nerves IX to XII, internal debulking of the tumor allows displacement of the capsule away from the nerves, brain stem, and upper spinal cord. Arnautovic et al. (2000) reported gross total resection in 12 of 18 patients using this approach.

RADIATION THERAPY

External Beam Irradiation

It seems somewhat paradoxical that a form of treatment implicated in the development of meningiomas would be recommended for benign residual or recurrent disease. Radiation therapy for residual benign meningiomas is still somewhat controversial, although there is good evidence that subtotal excision plus radiotherapy produces local control and overall survival that is superior to subtotal removal alone. For surgeons the problem of arachnoid scarring created by radiotherapy makes reoperation for recurrence much more difficult. This concern needs to be balanced against the risk of earlier recurrence. Modern series of external irradiation (XRT) using three-dimensional treatment planning limits the amount of dose delivered to surrounding normal brain compared with bilateral opposed fields. The advent of intensity-modulated radiation therapy (IMRT) provides for even greater dose conformity, although clinical experience with this technology is in its early stages.

Radiation affects tumor cells (reproductive and apoptotic cell death) and tumor vasculature by both direct and indirect means. The indirect form of DNA damage that results from the ionization of water and production of free radical species accounts for approximately 80% of the observed clinical effect. This effect is observed following a latent interval characterized by slowly proliferating tumors, which take longer to shrink after radiation than quickly proliferating tissues (e.g., lymphoma). Several studies since 1990 document the effectiveness of this treatment (Table 11–3). McCarthy et al. (1998), in an evaluation of factors associated with meningioma patient survival from the National Cancer Data Base, found that radiation was a significant factor associated with improved survival for both benign ($N = 8891$; $p < 0.0001$) and malignant ($N = 771$; $p < 0.001$) meningiomas. No details about treatment were given.

Table 11–3. Results of External Irradiation for Meningiomas Since 1990

Author	*Pathology*	*No. Patients*	*Dose (Gy)*	*Control Rate*
Glaholm et al. (1990)	Benign	177	50–55 (range)	84% 5 yr 74% 10 yr
Miralbell et al. (1992)	Primary	17	54 (median)	88% 8 yr
	Recurrent	16	54 (median)	78% 8 yr
Goldsmith et al. (1994)	Benign	117	54 (median)	89% 5 yr 77% 10 yr
	Malignant	23	54 (median)	48% 5 yr
Maire et al. (1995)	Mixed*	91	50.9 (mean)	91% 5 yr† 72% 10 yr
Milosevic et al. (1996)	Atypical	17	50 (40–60)	51%†
	Malignant	42		27%†
Condra et al. (1997)	Benign	21	53.3 (median)	87% 15 yr 86% 15 yr†
Maguire et al. (1999)	Mixed*	28	53.1 (median)	81% 8 yr
Nutting et al. (1999)	Benign	82	55–60 (range)	92% 5 yr 83% 10 yr

*Majority of cases benign; see reference for details.

†Cause-specific survival.

At the University of California, San Francisco, the 5 and 10 year PFSs for residual benign meningiomas treated with XRT were 89% and 77%, respectively (Goldsmith et al., 1994). Frontal and olfactory locations had slightly higher recurrence rates, and the risk of recurrence increased 2.2-fold for every 100 cm^2 increase in tumor size. A dose–response effect on tumor control was observed for benign and malignant tumors: For benign tumors doses >52 Gy and for malignant tumors doses >53 Gy were associated with significantly improved local control.

Condra et al. (1997) analyzed the experience with 262 patients at the University of Florida, dividing them into treatment groups of total excision (TE), subtotal excision (SE), and subtotal excision plus radiotherapy (SE + RT). The median follow up for the entire group was 8.2 years, and in this time no radiation-induced malignancy was reported as a complication of treatment. Of the 25 patients with SE alone who recurred, salvage therapy of any type was less successful in regaining long-term tumor control. Local control (LC) and cause-specific survival (CSS) at 15 years were significantly reduced after SE alone (30% LC/51% CSS) compared with TE (76% LC/88% CSS) or SE + RT (87% LC/86% CSS) ($p = 0.0001$ LC; $p = 0.0003$ CSS). Multivariate analysis confirmed the prognostic importance of treatment selection, with SE alone inferior to others ($p = 0.0001$). Atypical pathologic features and Karnofsky performance score were also predictive of CSS.

Radiosurgery has been used most often for small, well-defined meningiomas, residual or recurrent, that are commonly seen in skull-base locations. Nutting et al. (1999) published their results with fractionated XRT, proposing these as a baseline for the evaluation of new treatment strategies such as radiosurgery and skull-base surgery. There were 82 patients with histologically confirmed benign meningiomas, with a median follow up of 9 years included in the study. The 5 and 10 year rates of freedom from progression were 92% and 83%, respectively. Sphenoid ridge tumor locations had a higher recurrence rate than parasellar locations (31% versus 10%). There were no cases of secondary tumor development, and only one patient had radiation retinopathy.

Complications of XRT with current delivery methods are few. Toxicity is usually described in terms of the time interval from treatment as acute (hours to days), early delayed (weeks to months), and late delayed (months to years). Goldsmith et al. (1994) provided a detailed account of complications in their series. Of 140 patients, 5 (3.6%) had permanent

(late-delayed) complications of treatment. Three patients had sudden blindness 20 to 22 months after the completion of radiation therapy, and 2 patients developed cerebral necrosis at 13 and 30 months after treatment. In the series of Nutting et al. (1999) of cavernous sinus meningiomas, 61 of 82 patients were available for long-term follow up. Six patients had visual impairment (9.8%), five due to cataracts and one due to retinopathy. Three patients developed hypopituitarism (4.9%), and four had impairment of short-term memory (6.5%).

Radiosurgery

The technique of radiosurgery delivers a high dose of radiation to a defined intracranial target using stereotactic methods in a single treatment session. Typically, a stereotactic frame is applied to the patient's skull under local anesthesia. Relocatable frames using straps and dental bite blocks are used for fractionated stereotactic radiotherapy. Radiosurgical treatments can be delivered with a specially adapted linear accelerator or gamma knife unit. Each relies on a steep dose gradient outside the edge of the target to limit normal tissue effects. Published results are now maturing, and there appear to be good data that this treatment is an effective form of therapy for small, well-defined tumors that are more than 4 mm from the optic nerve or chiasm (Table 11–4).

For meningiomas located outside the cranial base, complete excision of the tumor and dural attachments is the goal. For parasagittal meningiomas, achieving this goal is problematic due to involvement of the superior sagittal sinus and draining veins. Kondziolka and colleagues (1998) in a multicenter study of radiosurgery for benign parasagittal meningiomas collected 203 cases with a median follow up of 3.5 years. The mean tumor volume was 10 cc. The 5 year overall tumor control rate was 67% ± 8.77% for the entire series. Considering just the "in-field" control rate for the targeted lesion, it was 85% ± 6.2% at 5 years. Patients who had radiosurgery as the primary mode of therapy had a better control rate than those who had undergone prior resection (93% versus 60%; $p = 0.08$). In multivariate analysis, predictors of tumor progression were pre-existing neurologic deficit and tumor volume greater than 7.5 cc. A marginal dose of 15 Gy or greater, or the maximum dose, did not improve tumor control. The 3 and 5 year actuarial rate of symptomatic edema was 16% ± 3.8%. This is similar to the 14.8% rate of symptomatic edema reported by Singh et al. (2000). Outcomes were also dependent on neurologic status at the time of treatment. For those with deficit before radiosurgery 65% were improved or stable compared with a rate of 83% for those without deficit before treatment. A follow-up article on perspectives of 99 patients who underwent radiosurgery for meningiomas

Table 11–4. Radiosurgery Results for Meningiomas Based on Selected Series Published Since 1990

Author	*Pathology*	*No. Patients*	*Min./Max. Dose (Gy)*	*Control Rate*
Engenhart et al. (1990)	Benign	17	29 (mean max.), LN	76% at 3.3 yr
Kondziolka and Lundsford (1992)	Benign	50	16.9 (mean marginal), GK	96% at 2 yr
Duma et al. (1993)	Benign	34	16 (median marginal), GK	100% at 2.2 yr
Valentino et al. (1993)	Benign	72	37 (median max.), LN	94% at 2.5–8 yr
Chang et al. (1998)	Benign	55	18.3 (median marginal), LN	98% at 2 yr
Kondziolka et al. (1998)	Benign	185	15 (median marginal), GK	85% at 5 yr
Hakim et al. (1998)	Benign	106	15 (median marginal), LN	89% at 5 yr
Subach et al. (1998)	Benign	62	15 (mean marginal), GK	87% at 8 yr
Shafron et al. (1999)	Benign	38	12.7 (mean marginal), LN	100% at 2 yr
Iwai et al. (1999)	Benign	24	10.6 (median marginal), GK	100% at 1.5 yr
Morita et al. (1999)	Benign	88	16 (median marginal), GK	95% at 5 yr
Roche et al. (2000)	Benign	92	15 (median marginal), GK	93% at 5 yr
Ojemann et al. (2000)	Malignant	22	15.5 (median marginal), GK	48% at 2 yr

LN, linear accelerator; GK, Gamma knife

revealed that 5 to 10 years after treatment 96% of those surveyed believed that radiosurgery provided a satisfactory outcome and 93% had required no further treatment (Kondziolka et al., 1999).

Hakim et al. (1998) reported similar results in 127 patients with 155 meningiomas treated using a linear accelerator, 52.9% of which were categorized as being located in the skull base. Their median tumor volume was 4.1 cc, and median follow up was 31 months. Of the tumors studied, 106 were benign, 26 atypical, and 18 malignant. The 1, 2, 3, 4, and 5 year tumor control rates for benign meningiomas outside versus within the cranial base were 100/100%, 92.0/93.8%, 92.0/88.9%, 92.0/88.9%, and 92.0/88.9%, respectively. The median time to progression for atypical and malignant meningiomas was 24.4 and 13.9 months, respectively. When death from intercurrent disease was excluded, the 2 and 4 year survivals for benign, atypical, and malignant meningiomas following radiosurgery were 94.8/91%, 83.3/83.3%, and 64.6/21.5%, respectively. Six patients (4.7%) developed permanent complications, including two deaths, one from cerebral infarction and a second from hypothalamic dysfunction.

For many skull-base meningiomas with extension into the cavernous sinus complete surgical removal would seem to be the exception rather than the rule. Radiosurgery for residual or progressive disease is effective and with acceptable risks. Conformal treatment plans are a must to keep complication rates low. Chang et al. (1998) reported preliminary results with radiosurgery for 55 patients with skull-base meningiomas. The 2 year actuarial control rate was 98%, with 29% of tumors decreasing in size and 69% remaining stable. Twenty-seven percent of patients had improvement in neurologic status, and 22% (12) developed new cranial nerve deficits 6 to 12 months after treatment (transient in 10, permanent in 2). Roche et al. (2000) reported the largest series of 80 cavernous sinus meningiomas treated with radiosurgery with a minimum 1 year follow up. The mean patient age was 49 years, and mean tumor volume was 5.8 cc (range 0.9 to 18.6 cc). The mean maximum prescription dose was 28 Gy (range 12 to 50 Gy) delivered with a median planning isodose line of 50% (range 30% to 70%). With a median follow up of 30.5 months (range 12 to 79 months) the actuarial 5 year PFS was 92.8%. No new oculomotor deficit was observed.

Morita et al. (1999) reported that in their series of 88 skull-base meningiomas treated with radiosurgery, the risk of trigeminal neuropathy was associated with doses of 19 Gy or more, and the optic apparatus appeared to tolerate doses greater than 10 Gy. If lower doses to cranial nerves are associated with reduced side effects, the question is what effect lowering the dose will have on tumor control rates. Iwai et al. (1999) achieved similar control rates to other series over a shorter term of follow up (median 17.1 months) with a much lower marginal median prescription dose of 10.6 Gy. Only one patient in their series (1/24) developed worsening of a preexisting cranial nerve deficit, and no patient had any new deficit.

Brachytherapy

Interstitial brachytherapy is an irradiation technique that is not commonly used for newly diagnosed or recurrent meningiomas. Permanent ^{125}I-sources can be implanted either at open craniotomy or stereotactically. These low-activity implants have a half-life of 60 days and produce low-energy photons (27 to 35 keV) with a half value in tissue of 20 mm. Continuous low-dose irradiation has many theoretical biologic advantages for tumor control and protects the surrounding normal brain tissue. One additional method of protecting the brain stem from high doses is to place a small amount of sterile gold foil between the implant site and surrounding neural tissue.

Gutin et al. (1987) reported one of the first series of interstitial brachytherapy for recurrent skull-base tumors, six of which were meningiomas: three benign and three malignant. Five to 36 sources were implanted at open operation, delivering 80 to 150 Gy to the periphery of the tumors over the lifetime of the sources. Two patients recurred outside the implanted volume, surviving only 8 and 9 months, respectively. The remaining four patients were stable at follow up from 2+ to 54+ months. At last review, 13 patients had been treated in a similar manner, with 8 stable at a median follow up of 10.5 months (range 5 months to 6.5 years). Kumar et al. (1993) treated 15 patients with primary and recurrent skull-base meningiomas using stereotactic implantation of ^{125}I-sources with a median follow up of 29 months. They reported an impressive 73% complete radiographic response rate and stabilization of tumors in the remaining patients (100% control). No patients were

reported to have developed early or late delayed radiation toxicity.

Vuorinen et al. (1996) published the largest experience with interstitial brachytherapy for 25 parasellar-clival meningiomas and 19 globoid meningiomas in elderly patients. The dose to the margin of the tumors ranged from 100 to 150 Gy, with sources implanted using stereotactic methods. In 2 of the 44 cases, sources were found on postoperative imaging studies to lie on the surface of the tumor. In the parasellar-clival group, studied for a median of 19 months, 16% were moderately smaller, 52% slightly smaller, and 20% were stable in size. Of the 17 patients with III, V, VI cranial neuropathy before treatment, 36% showed improvement. One patient suffered a third nerve injury with the implant procedure, and facial numbness developed or increased in 47% of patients. There was no serious bleeding and no procedural mortality. Even this small amount of data may indicate a role for brachytherapy for recurrent meningiomas undergoing reoperation where the residual tumor, or involved cranial base dura, can be implanted at the same sitting.

CHEMOTHERAPY

Cytotoxic Chemotherapy

The treatment of recurrent benign or malignant meningiomas with standard alkylating agents, while used in a number of cancer centers since the 1980s, did not appear in the medical literature until the mid-1990s. Wilson (1994) reported an experience with cyclophosphamide, adriamycin, and vincristine for malignant meningiomas recurrent after surgery and radiation therapy. In 11 patients, 73% had progression at 1 year and 100% at 2 years. Chamberlain (1996) reported prospective results giving the same agents to 14 patients. Patients who had gross total tumor resection received three cycles of chemotherapy, and those with subtotal removal received six cycles of treatment. Four patients required dose reductions for neutropenia, and for three the planned course of treatment could not be completed. There were 3 partial responses, and 11 patients had stable disease. The median time to tumor progression was 4.6 years, and the median survival was 5.3 years.

Other reports documenting the use of intra-arterial or intravenous use of drugs such as cisplatin, doxorubicin, and/or dacarbazine have not produced dramatic results. Schrell et al. (1997) reported on four patients with 15% to 74% reductions in tumor volumes who received 1000 to 1500 mg per day of hydroxyurea over a period of 5 to 24 months. Despite this report, there are no other published data documenting a similar experience, and so the search for a well-tolerated, effective form of therapy is ongoing.

Biologic Therapy

The largest series of immunomodulatory therapy for recurrent benign and malignant meningiomas involves the use of interferon-α_{2B}. This leukocyte-produced cytokine may have two mechanisms of action: one tumor antiproliferative effect and a second antiangiogenic effect. Kaba et al. (1997) reported on the use of this agent by six patients at a dosage of 4 mU/m^2 per day, 5 days per week. Patients were treated for 4 to more than 14 months, and side effects were limited. Five of six patients showed radiographic response, four had stabilization of disease, and one had slight tumor reduction. One of the responding patients had progression of his tumor on two occasions after stopping treatment. Further investigations with this agent and other biologic response modifiers seem to be indicated.

Hormone Receptor Antagonists

As previously mentioned, because meningiomas are more common in women than in men, and some tumors become symptomatic during pregnancy, a role for female sex hormones has been suggested in their development. Laboratory work has shown that estrogen receptors are present at reduced levels compared with progesterone receptors. Clinical trials of the antiestrogen agent tamoxifen have not been encouraging. Markwalder et al. (1987) studied six patients with recurrent inoperable meningiomas treated with tamoxifen over a 6 to 12 month period. One patient appeared to show an initial tumor response; two had stabilization of tumor; and three others had disease progression at follow up.

The Southwest Oncology Group (Goodwin et al., 1993) studied 21 patients, and, after a median follow up of 15.1 months, 32% of patients had no tumor growth and 53% had disease progression on

imaging studies. In subsequent studies with the antiprogestational agent medroxyprogesterone acetate (MPA), the drug could reduce the level of tumor progesterone receptor compared with historic controls, but it did not reduce tumor size in four of five women who took the drug once a week for 17 to 29 weeks. As noted at the beginning of this chapter, another antiprogestational drug, RU-486, mifepristone, was given to 14 patients with recurrent and unresectable meningiomas, and 4 had a minor decrease in tumor size on imaging studies. Another patient had an improved visual field examination. Lamberts et al. (1992), using the same dosage of 200 mg per day, noted that of 12 patients 3 had transient tumor regression and 1 had a sustained regression (70% volume reduction). A recent case report by Oura et al. (2000) also showed a volume reduction (73%) in a presumed meningioma after 2 years of treatment with MPA. Clearly, there may be some role for the treatment of benign recurrent meningiomas with antiprogesterone agents, and it is hoped that responses can be correlated with progesterone receptor status derived from surgical specimens.

MALIGNANT MENINGIOMA

Malignant meningiomas generally account for less than 10% of all meningiomas and deserve separate mention as they are one of the most difficult primary brain tumors to control. Survivals from a number of clinical series range from 2 to 9 years (Table 11–5). In the recent series of Palma et al. (1997), 8.6% of intracranial meningiomas were atypical or malignant, and in the personal series of Wilson (1994) the incidence was 12%. Unlike benign meningiomas, there does not appear to be the same predominance of female sex, and, in fact, the ratio may be reversed. Younis et al. (1995) found that 67% of malignant meningiomas occurred in males.

The most common presenting symptoms are headache, seizures, personality change, and painless subcutaneous scalp lumps. The duration of symptoms is shorter than with benign meningiomas. Spread of tumor outside the nervous system has been documented in as many as 24% of patients before death, and common sites for metastases are lung, liver, and bone. On imaging studies, these tumors reflect their aggressive nature with irregular borders, surrounding

Table 11–5. Malignant and Anaplastic Meningioma Recurrence Rates and Survivals in Selected Series Since 1990

Author	*Pathology*	*No. Patients*	*Recurrence Rate*	*Survival*
Maier et al. (1992)	Anaplastic	14	73%	na
Mahmood et al. (1993)	Atypical	20	50% at 5 yr	5.95 yr
	Anaplastic	5	33% at 5 yr	8.75 yr
Goldsmith et al. (1994)	Malignant	23	52% at 5 yr	58% at 3.3 yr
Wilson (1994)	Malignant	24	na	2.0 yrs. (median)
Younis et al. (1995)	Atypical	6	67% at 2 yr	50% at 5 yr
	Malignant	12	44% at 2 yr	62% at 5 yr
Milosevic et al. (1996)	Atypical	17	66%	28% at 5 yr
	Malignant	42	(all patients)	(all patients)
Palma et al. (1997)	Atypical	42	52% at 5 yr	95% at 5 yr
	Malignant	29	84% at 5 yrs.	64.3% at 5 yr
Hakim et al. (1998)	Atypical	26	24.4 mo. PFS	83.3% at 4 yr
	Malignant	18	13.9 mo. PFS	21.5% at 4 yr
Hug et al. (2000)	Atypical	15	62% at 5 yr	93%
	Malignant	16	48% at 5 yrs.	38% (mean 59 mo.)
Ojemann et al. (2000)	Malignant	22	68% at 2 yr	75% at 2 yr
			74% at 5 yr	40% at 5 yr

na, Not available; PFS, progression-free survival.

edema, and nonhomogeneous contrast enhancement. "Mushrooming" is also a feature of these tumors, where the main body of the dural-based tumor pushes off nodules of tumor into the dura adjacent to it. In one series where both CT and MRI had been used in diagnostic imaging, 50% of tumors showed indistinct margins, 41% "mushrooming," 33% had soft tissue involvement, and none exhibited intratumoral calcification.

The mainstay of therapy for these tumors is surgical removal. As expected, time to recurrence and overall survival are shorter in those with partial resections versus complete resection. Palma et al. (1997) found that for atypical meningiomas, those with a Simpson grade I excision did significantly better than those with Simpson grade II or III ($p < 0.0071$). Tumor location in the convexity was strongly related to grade I surgical excision ($r = 0.75$). For malignant meningiomas, even though a grade I excision was not significantly associated with improved survival versus grade II resection, patients with tumors of the convexity did significantly better than those with basal/parasagittal malignant tumors. In multivariate analysis, convexity location proved to be a positive factor for survival.

Radiotherapy has been shown in most series to lengthen time to recurrence and survival. Goldsmith et al. (1994) found a dose–response relationship for XRT with a 5 year PFS of 63% for those receiving a dose of ≥53 Gy versus 17% for those whose dose was <53 Gy. Milosevic et al. (1996) also found a significant relationship between cause-specific survival and dose above or below 50 Gy ($p = 0.0005$). Boosting the tumor site with additional photon or proton radiation may improve local control. At the Harvard proton therapy unit, significantly improved local control was achieved for both atypical and malignant meningiomas with the addition of a proton boost for total doses ≥60 Gy. Actuarial 5 and 8 year survival rates for malignant meningioma were significantly improved with proton over photon therapy and doses >60 Gy.

Radiosurgery has been used to treat malignant meningioma immediately following XRT as a boost, but more often for recurrent disease. Hakim et al. (1998) treated 26 atypical and 18 malignant meningiomas with radiosurgery in an overall series of 127 patients of whom 51% were being treated for recurrence. The median time to progression (TTP) for atypical and malignant meningioma was 24.4 and 13.9 months, respectively. Five year disease-free survivals were 83.3% and 21.5% for atypical meningiomas and malignant meningiomas. Ojemann et al. (2000) recently reported the results of radiosurgery for malignant meningioma in 22 patients, 3 of whom were treated in a boost setting. The median prescription dose was 15.5 Gy (range 12 to 18 Gy), and the median target volume was 7.35 cc (range 0.59 to 35.0 cc). Nineteen patients were treated for recurrence and had 37 lesions treated in 30 sessions. For the 31 malignant meningioma tumors treated, the 2 and 5 year PFS rates were 48% and 34%, respectively. On multivariate analysis of factors affecting time to progression, age <50 years ($p = 0.0003$) and tumor volume <8 cc ($p < 0.05$) were significant. A number of patient and treatment factors were also analyzed for effect on overall survival, but no significant relationships were found. Five of the 22 patients treated (23%) developed radiation necrosis as a complication of treatment with a median time to onset of 77 weeks after treatment (range 15 to 120 weeks). Given its effectiveness for recurrent malignant meningioma, the role and timing of radiosurgery in the management of malignant meningioma requires further evaluation.

CONCLUSION

Despite their benign histology in the majority of cases, meningiomas located around the venous sinuses and base of the skull can be difficult to control and at times impossible to eradicate. Whereas selected series reporting the results of specific therapies show favorable outcomes, population-based data have suggested otherwise. The availability of cytogenetic and molecular techniques for the identification of exogenous and endogenous factors associated with meningiomas will improve our understanding of the basic mechanisms involved in tumorigenesis and provide for new methods of treatment. At present, it is not clear what roles hormones, growth factors, and oncogenes, as well as tumor suppressor genes, play in the development of meningiomas. These tumors remain a clinical problem to be best solved by the combined approaches of basic scientists and those clinicians who treat patients suffering from these tumors. Cushing and Eisenhardt (1938) were correct more than 60 years ago when they said that "the ultimate prognosis hinges more on the surgeon's wide experience

with the problem in all its many aspects than is true of almost any other operation that can be named."

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