Meningiomas: Science and Surgery

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Meningiomas are perhaps the most fascinating brain tumors in neurosurgery.[3,6,8,10–12,32,52] Although "benign" in most cases, they create major problems for patients and doctors in decision making and management. Biologically, they raise important questions regarding hormonal dependence, genetic predispositions to tumors, and radiation. Studies into their biology and treatment are sparsely funded by government agencies, and patient advocacy has become very important in their care. Attitudes to their management range from observation through radiation to very aggressive attempts to remove the entire tumor.

This paper will discuss science and surgery for meningiomas. The science will include meningioma models, molecular epidemiology, and new treatments. It will primarily reflect work performed in the Meningioma laboratory at the Brigham and Women's Hospital (BWH) in the past 10 years and the emerging Meningioma Project supported by the Brain Science Foundation at the BWH. The references cited in this paper will be almost completely from our group and our collaborators—they are not meant to be a comprehensive list. In surgery for meningiomas, we will discuss outcome from one surgeon's (PB) surgical series of 733 patients with meningioma surgery.

Meningiomas aptly reflect the themes of this issue of Clinical Neurosurgery and of the 2006 CNS meeting—transcendent leadership in science, patient care, and mentorship. They also reflect three important subthemes—history, globalism, and patient advocacy.

HISTORY

In neurosurgery, we owe a great deal to our predecessors. We, therefore, start by paying tribute to some of the giants who paved the way for studies in meningiomas. Chief of these is Harvey Cushing, the surgeon-in-chief at the Peter Bent Brigham Hospital from 1913 to 1933. In 1922, and then in his 1938 classic book with Louise Eisenhardt, *Meningiomas, Their Regional Behavior, Life History, and Surgical End Results*, Harvey Cushing gave full expression to his understanding of meningiomas.[30,31] He describes how he

decided to group a number of previously disparate tumors under the designation "Meningioma" "…it seemed highly desirable to draw them together into single designation which would be brief and convenient; the simple and noncommittal designation "meningioma" as a catch word sought to be suitable and all embracing." Cushing took dural epitheliomas, fibromas, etc. and put them together under one heading. It is not yet clear that this was the right thing to do pathogenetically, but he thought that they were one tumor and that "meningiomas are unmistakably direct descendants of the same mesothelial mother-cells, the meningocyte." He also made beautiful sketches of the surgical approach to these tumors.[9]

Cushing thought that "it was apparent that some varieties of meningiomas because of their differences in behavior would have to be distinguished." He proposed a grouping by histology, which turned out to have little prognostic significance. Today the World Health Classification has created three major grades, which have major prognostic significance.[45]

Grade 1: Benign meningiomas (85–90%), which include meningothelial, fibrous (fibroblastic), transitional, psammomatous, angiomatous, microcystic secretory, lymphoplasmacyte-rich, or metaplastic. Most of the categories within the benign group have no prognostic significance but are merely descriptions of different histology.

Grade 2: More aggressive types (5–10%), including clear cell, choroidal, and atypical histological types.

Grade 3: The malignant group (3–5%), including papillary, rhabdoid, and anaplastic meningioma.

This histological classification has major implications for invasion and recurrence, phenomena not appreciated in many earlier reports that aggregated all meningiomas together.

Subsequently, many others have contributed to meningioma surgery: Leo Davidoff in the early 20th century; and, more recently, Gazi Yasargil, Robert Ojemann, Leonard Malis, Madjid Samii, Jacques Brotchi, Shigeki Kobayashi, Laligham Sekhar, Takeshi Kawase, Rudolph Fahlbusch, Edward Laws, Michael McDermott, John Tew, Necmettin Pamir, Vinko Dolenc, Osama Al-Mefty, and many others. Dr. Black would like to pay particular homage to his own

teachers, Robert Ojemann, Nicholas Zervas, and Jay Loeffler, in their mentoring on the management of these fascinating tumors.

GLOBALISM

Any contemporary list of meningioma surgeons and investigators will be an international one. Surgeons and scientists in Germany, Japan, France, Belgium, and many other countries have made important contributions. There is an international society of Meningioma and Cerebral Veins, which holds regular meetings. The last was held in Mt. Fuji, Japan, and this important meeting will be held in 2008 in Boston, Massachusetts (www.TheMeningiomaConference2008.org).

PATIENT ADVOCACY IN MENINGIOMAS

Meningiomas beautifully demonstrate the importance of patient advocacy in a field. Until a few years ago, they were not included in cancer registries; we, therefore, had little idea of their incidence and prevalence. It was patients who demanded a change in this situation, and the result was The Benign Brain Tumor Act of 2003 that required government-run cancer registries to include meningiomas. Nancy Conn-Levin, a meningioma survivor, and Carol Krutchko of the Central Brain Tumor Registry were particularly important in this initiative. It soon became clear that meningiomas were much more prevalent than was previously thought.

In 2000, a visionary executive named Stephen Haley created the Brain Science Foundation, a support organization for meningioma care and research at BWH. It would have been impossible to carry out these studies without his help because funding agencies generally do not support benign tumor research. Patient advocacy groups, such as Meningioma Mommas (meningiomamommas.org), led by Elizabeth Holzemer, created websites and other systems for sharing information regarding these tumors. Groups such as the Brain Science Foundation, a support group for research in tumors that particularly focuses on meningiomas, allow important research to be performed—without their support, there would be little meningioma science because it is difficult to get the National Institutes of Health (NIH) funding since these tumors are not "Cancer."

MENINGIOMA SCIENCE

Causes of Meningiomas, Including their Epidemiology

We know more about the causes of meningiomas than about most brain tumors. There are at least four factors that seem to be important in their development: genes, radiation therapy, hormone receptors, and perhaps environmental factors.[29]

Genes

Genetic abnormalities, particularly deletions on chromosome 22 in the neurofibromatosis (NF)-2 tumor suppressor gene, are important in many meningiomas.[43] Part of this gene is lost both in meningiomas that are associated with NF and in sporadic meningiomas. The *NF2* tumor suppressor gene encodes a protein called merlin, which may have to do with cell-cell interactions. Cells that have defective merlin tend not to recognize their neighboring cell and, therefore, continue to grow one on the other to create tumors.

Sometimes the degree of meningioma growth with NF can be quite striking (see *Fig. 16.1*, the magnetic resonance imaging (MRI) scan of a patient with NF. Note the extensive dural involvement including orbit, cavernous sinus, cerebellopontine angle, and convexity dura).

We can begin to dissect out the contribution of a particular gene to meningioma formation by creating meningioma models that knock out that specific gene in mice. Our laboratories have worked for several years with Marco Giovannini and Michel Kalamarides in Paris to create a knock-out mouse in which the *NF2* gene has been inactivated.[39] In this model, the knock-out vector is injected at birth in the retroorbital area of the mouse (*Fig. 16.2*). In 9 months, the mouse begins to develop tumors along the base at the site of the injection, the tumors are histologically identical to meningiomas. A paper describing the imaging in this model is in currently in preparation.
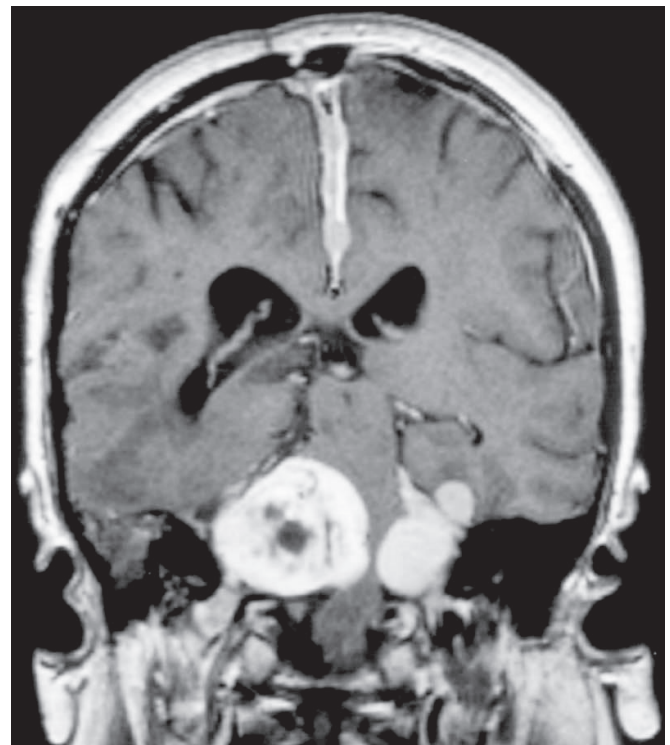

FIGURE 16.1. Meningiomas in a patient with NF2. Note the diffuse involvement of the falx and the combination of meningioma and schwannoma that is quite common.

A second way of looking at the factors leading to meningioma formation is to look at either deoxyribonucleic acid (DNA) or messenger ribonucleic acid (RNA). We have just completed a microarray analysis on these tumors and find that there is overexpression of genes associated with growth, blood vessels, and cytoskeletal proteins. We know that some genes important for other tumors are not important for meningioma initiation. The *p18INK4c* gene, important in glioma pathogenesis, has a limited role in meningioma formation.[53] The *BRCA1* and *BRCA2* genes, which are in important in breast cancer seem to have no role in meningioma development.[44]

Perhaps the most interesting recent development in the molecular dissection of these and other tumors is the analysis of susceptibility genes as part of molecular epidemiology.[29] Susceptibility genes in themselves do not cause a tumor but make it more likely that a tumor will develop if a cell is exposed to other injury, such as radiation, cigarette smoke, or lead. Some of the genes that seem to be important in susceptibility are DNA repair genes, cell cycle genes, and genes involved in hormone metabolism. These are the subjects of considerable molecular epidemiological interest because they may define susceptibility to a particular environmental stress. They may also explain the fact that children of parents with cancer of any kind have at least twice the potential risk of meningioma formation as children without parental cancer.[36]

A very important issue in the biology of these tumors is whether they change their histological type. Cushing felt very clearly that they did not. We have collected several cases in which transformation occurred unequivocally. The Black laboratory, one of the components of the Meningioma Project, is presently engaged in a molecular analysis of the changes that occur in this transformation.

Radiation

Radiation has a very important role in meningioma formation. Approximately 4% of all meningiomas are radiation induced.[12] Interestingly, these are not usually accompanied by the *NF2* gene mutation. Often, these tumors come from the periphery of the radiated field. Evidence for radiation comes from at least four sources[29]:

1. Survivors of childhood tumors who have had radiation to the eye or to the neck have a significant incidence of meningioma formation in these sites 20 years later.

2. A cohort of patients followed in Israel who had low-field radiation of the scalp for ringworm have developed multiple meningiomas 20 and 30 years later.
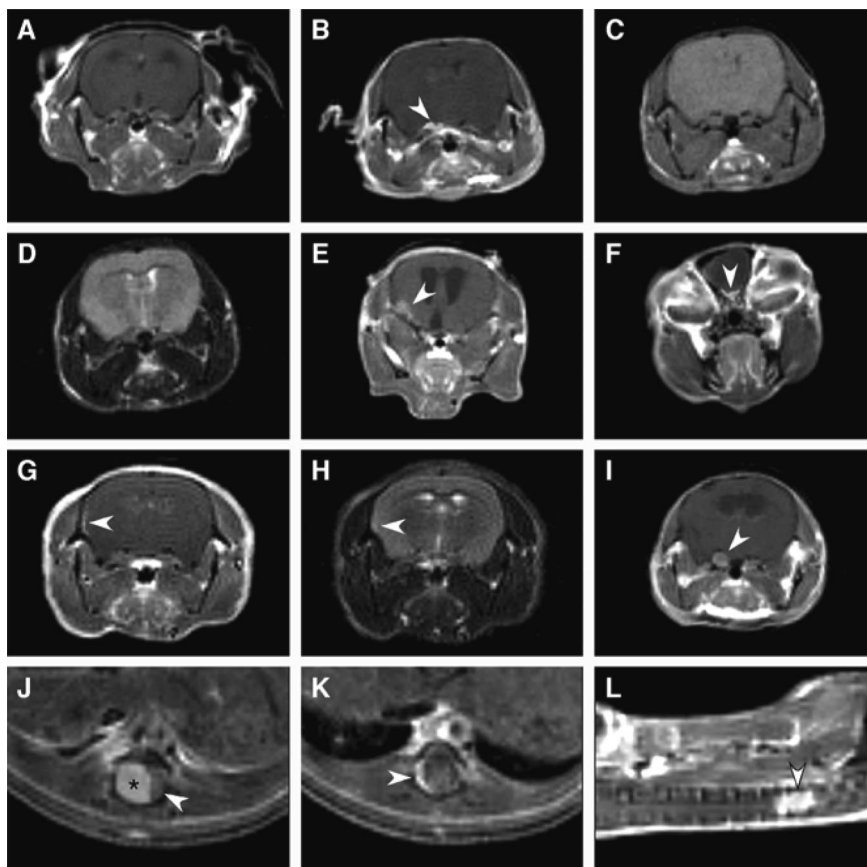

FIGURE 16.2. Meningiomas in mice with *NF2* knockout. The arrows show the sites of spontaneous tumor formation. Courtesy of Dr. Rona Carroll.
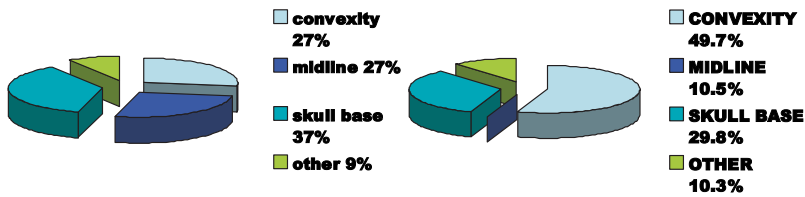
FIGURE 16.3. Meningioma location in Cushing (313 patients) and in Black (807 patients).

3. Survivors at the periphery of atomic bomb explosions have meningiomas as delayed effects of radiation many years later.

4. Epidemiological evidence suggests that full-mouth dental x-rays are associated with a greater incidence of meningiomas.

There needs to be more work on the precise effects of radiation on the formation of meningiomas.

Hormones and Meningiomas

An intriguing aspect of meningiomas is their relation to sex.[2,8,36] They are known to occur more often in women than in men, with a 5-to-2 ratio for cranial meningiomas and a 10-to-1 ratio for spinal meningiomas. They may increase in size during pregnancy; they have an increased incidence in patients with carcinoma of the breast; and their cells have progesterone and estrogen receptors, although their role is not known.[2,15,54]

Progesterone receptors are robustly expressed in meningiomas. Using immunochemistry, our laboratory found that 80% of women and 34% of men with meningiomas had expression of the progesterone receptor.[20] Using a very complex system, we were able to demonstrate that it was active.[22] We had to use an indirect approach because the progesterone receptor does not act through a simple intermediary transcription cascade, such as *ras*. This system uses the progesterone responsive element, a sequence that is activated by progesterone receptor and is necessary for progesterone to exert its effects. This sequence is also activated by the glucocorticoid receptor. It can be transfected into a meningioma cell and activated by the cell's own endogenous progesterone or glucocorticoid. A reporter sequence such as choline acetyltransferase (CAT) can be used to determine activation of the progesterone responsive element. For our experiments, progesterone receptor in the cell was used to activate its own CAT in cells exposed to exogenous progesterone. CAT expression indicates that the receptor is active in the sense of being able to activate the progesterone responsive element. We also showed that the receptor was lost after two or three passages in culture, making it inadvisable to use culture studies to assess possible antiprogesterone drugs.[22] This limits the use of meningioma cultures to predict therapeutic response, although cultures can still be useful to evaluate morphological features, including whorl formation, in meningiomas.[13]

Initial experiments with competitive binding suggested that the estrogen receptor is expressed in these tumors, as are steroid cofactors that allow it to be active.[2,24] However, the role of estrogen receptor is unclear and anti-estrogen drugs have had little therapeutic value.

The androgen receptor is expressed in 69% of women and 31% of men, but its role in tumor growth is unclear.[25]

Meningiomas also express receptors for other compounds, including platelet-derived growth factor (PDGF),[17] vascular endothelial growth factor (VEGF),[41] glucocorticoids,[23] epidermal growth factor,[26] dopamine,[27] and somatostatin.[46] They express messenger RNA for all members of the PDGF family, including PDGF A, PDGF B, and PDGFR-β, the beta form of the PDGF receptor.[49] The receptors are active and the *ras* oncogene is an intermediate messenger when PDGFR-β is activated.[50] With present development of PDGF receptor blockers, such as Gleevec, this may have some relevance for medical therapy.

VEGF expression is important in growth and in edema formation. VEGF, rather than location, size, or venous compromise, is probably the most important feature in cerebral edema around meningiomas.[1]

Meningiomas secrete parathormone-related peptide, which may be responsible for their calcification.[28]

Prolactin receptor is expressed in meningiomas, and addition of prolactin to meningioma tissue increases growth rate.[27,38] Some integrins, which shape the extracellular matrix responses to cell penetration, are also important in meningioma growth.[5]

The potential role of hormone receptors is particularly interesting in view of data from our laboratory suggesting that some meningiomas are polyclonal; that is, that tumor cells of differing lineage may be recruited into the tumor phenotype.[58,59] These findings raise the possibility that meningiomas develop from altered arachnoid cells that can be stimulated by female hormones.

Trauma

Cushing noted that 101 of his 313 patients had a history of trauma, sometimes right over the tumor. Subsequent studies have not shown that trauma has a consistent relationship to these tumors (*Fig. 16.3*).

Electomagnetic Fields

There is considerable public concern that meningiomas are associated with cell phone use or other sources of electromagnetic fields. There are at least 10 epidemiological studies that have been completed to date, none show association with meningiomas. They have been discussed in a recent review by Claus et al.[29]

Important data come from a prospective case-controlled study of causative factors in brain tumors directed by Peter Inskip of the NIH section on cancer epidemiology.[37] Several important papers emanate from this study.[18,36,37] Many of these are in the epidemiology literature and, therefore, not read by most neurosurgeons. Their conclusion regarding cell phones, published in the *New England Journal of Medicine*, was that there was no relationship with meningiomas.[37]

There have also been studies from Germany, Denmark, and Sweden with the same conclusions. The most recent study was the Interphone Study from Sweden, which showed that there was no short-term effect of cell phones for meningiomas or gliomas. Acoustic neuromas did show an increase in incidence with a longer than 10-year use, with an odds ratio of 3.9 to 1.[29]

There is also some interesting data on electrical shaver use and hair dryers and meningiomas coming from the Inskip study. It has shown an odds ratio of 10.9 to 1 for meningiomas in men with electric shaver use, especially with nine or more years of use, and an increased incidence with hair dryers.[18]

The most comprehensive proposed program in understanding the role of environmental and hormone factors in meningiomas is a study directed by Elizabeth Claus, a neurosurgeon at BWH and an epidemiologist at Yale, which has just been funded by the NIH. This study includes five centers; the BWH in Massachusetts, Yale University in Connecticut, Duke University in North Carolina, University of California, San Francisco in California, and MD Anderson in Texas. It will collect 1600 cases and 1600 controls matched by age, sex, race, and geography, and will formally and comprehensively examine environmental, genetic, pathological, and clinical variables associated with meningioma risk. It will also consider quality-of-life issues. This study should be finished in 5 years and will be a major contribution to the understanding of these tumors.

MENINGIOMA SURGERY

Treatment Options for Meningiomas

Treatment options for meningiomas include observation, surgery, and radiation therapy. Medical treatment has not been helpful to date in these tumors.

Observation

Ojemann and Black[50] presented some of the difficult decision making in the approach to these tumors. Observation is often the first treatment modality suggested. A small convexity meningioma in an elderly person may best be managed with a repeat scan in 6 months. If there is growth, surgery or radiation may be considered. With our surgical planning laboratory, we are presently developing automated systems for performing volumetric assessment of these tumors.

At the BWH, we take into account the following in deciding whether to observe a tumor. The ultimate decision, however, is a joint process among patient, family, and tumor board:

- *Symptoms:* progressive symptoms other than seizures are generally an indication for surgery.
- *Age:* in patients older than age 65 years, tumors are usually observed as the first step.
- *Imaging appearance:* tumors with size smaller than 3 cm, lack of edema, and smooth margins can usually safely be observed.
- *Morbidity of surgery or radiation:* associated structures and their relationships to tumor.
- *Patient preference.*
- *Need for definitive diagnosis:* e.g., in a patient with a breast carcinoma.

Surgery for Meningiomas

Assessing Surgical Risk

There is considerable work now being performed on the stratification of patients in considering risks of surgery.[47,51] Lee and his group at the Cleveland Clinic have proposed a "Class" decision algorithm, which includes both risk and benefit factors. This includes[47]:

- Comorbidity (-2 to 0)
- Location (-2 to 0)
- Age (-2 to 0)
- Size (0 to 2)
- Symptoms and signs (0 to 2)

They found, retrospectively, that they could divide patients into three groups. Those in Group 1, with a CLASS score of $+1$ or higher, had the most favorable outcome; with a good outcome in 98.1% of cases. Those in Group 2 had a score of had 0 or -1 and had a poor outcome in 4% of cases. Those in Group 3 had scores of -2 or less and had a poor outcome in 15% of cases. Other systems are also being developed to predict surgical risk.

Surgical Techniques

Surgery is the most important therapeutic modality for definitive meningioma management. For Cushing, the factors that led to success in meningioma surgery were: 1) "increasing familiarity with behavior of tumors in different regions;" 2) improved methods of clinical, anatomical, and pathological diagnosis; and 3) refinements in operative technique.

These factors continue to be important today. We have begun to learn about how different types of meningiomas behave and how that may relate to their treatment; to use imaging including functional MRI and diffusion tensor imaging to gauge the safety of surgery; we have improved imaging, neuropathology, and molecular techniques for these tumors; and our surgery has become increasingly expert (and uniform) for managing these lesions.

Cushing's mortality changed from 53% in the first 4 years to 11.8% in the last 5 years of his practice. Presently, our mortality at BWH for all meningiomas is less than 1% and morbidity is 2 to 4%, depending on the meningioma location.

Although our surgery is improving, however, we must develop science along with surgery. In *Meningiomas*, Cushing presents three cases that illustrate how difficult these tumors can be.[29] The first is General Leonard Wood, one of the major military figures in the US Army who was rescued from hemiparesis for 20 years by removal of a parasagittal meningioma. At a second operation, however, General Wood succumbed to blood loss and intraventricular clot. The second case was Edith Mindes, a woman who had her first resection of tumor when 25 years old and during the next 20 years gradually continued through her life being able to give music lessons despite more than 10 tumor surgeries for recurrent meningiomas at different sites. She also had radiation therapy for these tumors. She ultimately died from an inoperable third ventricular recurrence. The third case was Mr. Timothy Donovan, who had a similar story.

These cases illustrate the problem of trying to attack biology with surgery. Surgery and science must go hand in hand in managing these remarkable tumors.

The BWH Series

The results presented here are from one surgeon (PB) from July 1, 1989 to September 1, 2006. In that time, he has operated on approximately 5000 patients with brain tumors. Of these, 733 had meningiomas. For Cushing, meningiomas comprised 15.7% of all tumors. For Black, they were 14.7%. This is not a significant difference in proportion; the slight decrease is likely a result of the increased detection of other tumors, such as vestibular schwannomas, pineal region tumors, ventricular tumors, and metastases that were not part of the neurosurgery of Cushing's time.

The Black series has 520 women (71%) and 213 men (28%); Cushing had 191 women (61%) and 122 men (39%). Our median age was 58 years; Cushing's average age was 46.6 years. In our series, 89% of meningiomas were Grade 1, 8.5% were Grade 2, and 2.5% were Grade 3. It is impossible to compare this with Cushing's series because this grading scheme was not used in Cushing's time. Repeat surgery was performed in 7% of patients. The median time to the first reoperation was 22 months, primarily in patients with atypi-

cal meningiomas; the median time to the second was 58.5 months.

Our mortality was 0.4%; Cushing's was 5.3%; this is primarily a reflection of improved anesthesia and surgical technique. Mortality in other series varies: one recent Finnish series had a 7% mortality. Investigating the potential source; they found that poor preoperative clinical condition, compressive symptoms from the tumor, old age, incomplete tumor removal, pulmonary embolism, and intracranial hematoma were factors that increased mortality.[42]

If we evaluate the location of tumors, it seems clear that the greatest difference today is in convexity tumors, often identified only by MRI scanning.

General Principles of Surgery

For meningiomas, it is important to begin with a clear idea of the goals of the surgery. Complete resection is the usual goal for meningiomas that occur in the convexity, olfactory groove, anterior third of the sagittal sinus, and tumors of the posterior fossa dura. Deliberately incomplete resection is more appropriate for medial sphenoid wing, posterior parasagittal, orbital, tentorial, and clivus tumors. Cavernous sinus meningiomas are probably best treated by radiation alone.[7] Above all, however, the goal should be to end with an intact patient. Even a VIth nerve palsy from aggressive manipulation in the cavernous sinus can be a completely disabling problem

Morbidity

Complications of meningioma surgery include general medical complications and complications of the specific tumor site. Medical complications include pneumonia, heart disease (including infarction and arrhythmia), deep venous thrombosis, and pulmonary emboli. Deep venous thrombosis is especially problematic; meningiomas may produce a hypercoagulable state.

Complications related to the tumor include hemorrhage, new neurological defect, and infection. With resection by any technique, cortical deficits may occur when the plane between arachnoid and pia is adherent to the tumor and there is loss of pial vasculature with subsequent cortical microinfarction. Cranial nerve deficits may also occur in cranial base meningiomas. Specific complications related to specific tumor locations are discussed below.

MENINGIOMAS IN THE ELDERLY

Meningiomas are often found in patients older than 70 years old, and management in these cases may be problematic. Black et al.[14] found that surgery was not riskier in patients older than 70 years than in patients younger than 70 years. They reported a 1% mortality rate for patients either older than or younger than age 70 years in groups matched for tumor size and location. Morbidity was 9% for the elderly group and 6% for the younger group, not a significant

difference. This was very different than a population-based survey, however, which found that, in general, morbidity and mortality were considerably higher in elderly patients.[4]

QUALITY OF LIFE IN MENINGIOMAS

Kalkanis et al.[40] used the Functional Assessment Of Cancer Therapy—Brain questionnaire, a general quality-of-life questionnaire for cancer patients modified for brain tumor patients, in 164 patients with meningiomas to assess quality of life; patients were aged 23 to 87 years, with a median follow-up of 28 months. Of the patients, 86% reported that they could write, read, drive, and return to work at their premorbid level.

SPECIFIC LOCATIONS

For purposes of this paper, meningiomas will be classified into three groups by location: convexity (including lateral sphenoid wing); midline (parasagittal and falx); and cranial base. Cranial base meningiomas are those arising in the olfactory groove, cavernous sinus and medial sphenoid wing, clivus and petroclival region, tentorium, and foramen magnum.

Convexity Meningiomas

Complete removal is our goal. In the Black series of 163 convexity meningiomas, the operative mortality was 0.4% and neurological morbidity was 3% (Morokoff and Black, submitted). Navigation techniques are proving extremely valuable in the management of these tumors, and more than half of these surgeries are performed with navigation in the traditional operating room. We have not found intraoperative MRI scanning to be particularly useful, because there is little brain shift and the challenge is just identifying the tumor. Once the tumor is identified, its texture allows for dissection and removal from the surrounding brain.

Midline Meningiomas

These tumors tend to invade the sagittal sinus and it is unlikely that they can be completely removed. There are two general approaches to these tumors—to be radical in their removal, an approach recently advocated by Sindou et al.,[52] or to remove that segment not in the sinus and use radiation to treat the remaining fragment if it grows, the approach that we and others have used.[16] Reconstruction or partial resection of the sinus has a substantial risk of sinus thrombosis. Our policy has been to take out tumor that can easily be removed and to observe the rest.

For parasagittal meningiomas with a median follow-up of 54 months, we had a mortality of 0%, and a morbidity of 2%; 16 of 17 preoperative deficits resolved or improved. The recurrence rate was 10% at 5 years (Zauberman and Black, submitted).

Cranial Base Meningiomas

Our management principles have changed considerably via using a combination of aggressive surgery with stereotactic radiosurgery for these tumors.[16,19,33,34] We have increasingly moved away from the concept of radical surgical removal because of the deficits associated with this approach. Using these principles, we found that, in 100 cranial base meningiomas, mortality was 0.5% and morbidity was 6%. Of the patients, 46% had complete resection, but only 7% required radiosurgery within 5 years of their surgery. Stereotactic radiotherapy may also be used if the tumor is particularly close to cranial nerves or brainstem.[57] These data suggest that a modest resection followed by observation with radiation held in reserve can be an important approach to these tumors.

RECURRENCE

The pioneering work of the Australian neurosurgeon, Simpson, began the analysis of meningioma recurrence.[56] He classified resection as follows: Grade 1, complete removal including resection of dura and bone; Grade 2, complete tumor removal with coagulation of dural attachment; Grade 3, complete tumor removal without resection or coagulation of dural attachments; Grade 4, subtotal removal; Grade 5, decompression. In his series, Grade 1 tumors had a 9% recurrence at 10 years, Grade 2 had a 19% recurrence, Grade 3 had a 29% recurrence, and Grade 4 had a 40% recurrence.

Several other groups have extended this analysis of completeness of surgery in analyzing features that may lead to recurrence. Kallio et al.[42] found that coagulation of the tumor base, invasion of bone, and soft consistency of tumor were risk factors; 34% of tumors with two of these factors, 15% with one, and 11% with none recurred at 20 years. However, these and similar series may neglect the role of aggressive (atypical) phenotype in these tumors.

THE MENINGIOMA PROJECT AND MENINGIOMA CENTER AT BWH

To emphasize the importance of these tumors and to create a matrix from which their science can be better understood, we created a Meningioma Center at BWH, which has the components of patient care, imaging research, and molecular research. Further information can be obtained through the Brain Science foundation website (www.brain-sciencefoundation.org) or blacklab.org. In patient care, the Center has created a patient-oriented high-technology meningioma clinic that includes computers and internet access in the waiting room, patient coordinators, individual check-in and check-out, electronic records; along with a teaching meningioma fellowship in meningioma biology and white papers on meningioma clinical care and research. There are four main areas:

1. Epidemiology and molecular genetics—Elizabeth Claus, Mark Johnson, and Peter Black.

2. Meningioma model using the *NF2* knock-out—Rona Carroll and Michel Kalamarides (Paris, France).

3. New therapies including slow-release polymers with anti-invasive agents—Rona Carroll, Marcelle Machluf (Haifa, Israel).

4. Image-guided surgery and brain mapping—Alex Golby and Peter Black.

This is an exciting time in the science and surgery of meningiomas and, hopefully, the next decade will increasingly advance their treatment.

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