PENFIELD LECTURE

Hormones, Radiosurgery and Virtual Reality: New Aspects of Meningioma Management

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ABSTRACT: The understanding and management of meningiomas is changing significantly today. One of the most striking features of their pathophysiology is their predominance in women. In a series of 517 patients with meningiomas seen by the Brain Tumor Group at Brigham and Women's Hospital, the female:male ratio was 2.4:1. The progesterone receptor appears to be the major candidate to explain this difference. Although meningioma cells variably express receptors for estrogen, androgen, platelet-derived growth factor, epidermal growth factor, and somatostatin, these molecules do not explain the differences because they are not differentially expressed or are not activated. Progesterone receptor can be shown to be expressed in 81% of women and 40% of men with meningiomas; it can also be shown to be activated by transfecting a construct with the progesterone responsive element and a reporter in it and using the cell's own receptors to activate this construct. Surgery remains the mainstay of meningioma management. At the Brigham and Women's Hospital three-dimensional reconstruction techniques have markedly improved the ability to visualize the tumor as well as its relation to vascular structures. With MRI reconstruction, it is possible to know the tumor's relation to the sagittal and other sinuses, to identify feeders and proximity to major arteries, and to establish its location and relation to cortex by frameless stereotaxis. These techniques can be used in a virtual reality format are some of the most powerful in neurosurgery both for teaching and for the surgical procedure itself. External beam radiation has been shown by others to be an effective adjunctive treatment to prevent meningioma recurrence. Recently, linear accelerator radiosurgery and stereotactic radiotherapy have changed the pattern of radiation at our institution. In a series of 56 skull base meningiomas, for example, 95% were controlled (i.e., showed no growth) over a four year period. Fractionated focal radiation potentially offers the same control rate with fewer complications. With increasing understanding and treatment possibilities, meningiomas remain one of the most intriguing and challenging tumors in the nervous system.

RÉSUMÉ: Hormones, radiochirurgie et réalité virtuelle: aspects nouveaux du traitement du méningiome. La compréhension et le traitement des méningiomes changent beaucoup actuellement. Leur prévalence plus élevée chez les femmes est une des caractéristiques les plus frappantes de leur pathophysiologie. Dans une série de 517 patients atteints de méningiome, évalués par le Brain Tumor Group au Brigham and Women's Hospital, la proportion femme:homme était de 2.4:1. Le récepteur de la progestérone semble être le meilleur candidat pour expliquer cette différence. Bien que les cellules de ces tumeurs expriment de façon variable des récepteurs des oestrogènes, des androgènes, du facteur de croissance plaquettaire, du facteur de croissance épidermique et de la somatostatine, ces molécules n'expliquent pas les différences observées parce qu'elles ne sont pas exprimées de façon différentielle ou ne sont pas activées. On peut démontrer que le récepteur de la progestérone est exprimé chez 81% des femmes et 40% des hommes qui ont un méningiome; on peut également démontrer qu'il est activé par la transfection d'un gène chimère contenant un élément sensible à la progestérone et un rapporteur, et en utilisant les récepteurs de la cellule pour activer ce gène chimère. La chirurgie demeure la base du traitement du méningiome. Au Brigham and Women's Hospital, les techniques de reconstruction tridimensionnelles ont amélioré sensiblement la capacité de visualiser la tumeur ainsi que ses relations avec les structures vasculaires. Avec la reconstruction par RMN, il est possible de connaître la position de la tumeur par rapport au sinus sagittal et aux autres sinus, d'en identifier les vaisseaux nourriciers et la distance par rapport aux artères importantes, et d'établir sa localisation et sa relation au cortex par la stéréotaxie sans cadre. Ces techniques, qui peuvent être utilisées dans un format de réalité virtuelle, sont parmi les plus puissantes en neurochirurgie tant pour l'enseignement que pour la chirurgie elle-même. Il a été démontré que la radiothérapie peut être un traitement d'appoint efficace pour prévenir la récidive d'un méningiome. Récemment, la radiochirurgie utilisant l'accélérateur linéaire et la radiothérapie stéréotaxique ont changé la façon d'utiliser l'irradiation dans notre centre. Sur une série de 56 méningiomes de la base du crâne, par exemple, 95% ont été contrôlés (n'ont pas progressé) sur une période de quatre ans. L'irradiation focale fractionnée offre le même taux de succès avec moins de complications. Avec des connaissances et des possibilités de traitement sans cesse croissantes, les méningiomes demeurent une des tumeurs les plus intriguantes du système nerveux.

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Wilder Penfield and The Harvard Medical School

It is a great honor to acknowledge Dr. Penfield's legacy in this paper. In considering this legacy, it is worth noting that he had strong links to Harvard and to the Peter Bent Brigham Hospital, the institutions in which I presently work. In 1914, he took a tutorial in human anatomy and Greek at The Harvard Medical School with Dr. Robert Green.[1] He later felt that this had been a remarkable opportunity to work with a man who was

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completely devoted to both scientific and classical pursuits. He returned to the classics in his second career, that of a writer, when he wrote fiction about Hippocrates and his world.[2] In 1918-19, he was an intern at the Peter Bent Brigham Hospital. Harvey Cushing was the Surgeon-in-Chief at that time. Penfield worked with Cushing in the year 1918-19, but did not warm up to him. He says of this time, "I visited the Peter Bent Brigham Hospital in Boston where I had my surgical internship and sought out Dr. William Quinby. He was the Urologist-in-Chief of that hospital. I admired him greatly and have felt closer to him than to the Chief Surgeon, Dr. Harvey Cushing." (1, p. 55). It is interesting that, in spite of his differences with Cushing, Penfield sent his sister to be operated on by him when she developed a recurrent glioma[3]

Cushing and Penfield shared Sir William Osler, a McGill graduate and Ontario native, as a hero. Osler was the most famous physician of his time, having been chief of medicine at Johns Hopkins before he became Regius Professor of Medicine at Oxford. Cushing wrote the definitive biography of Osler, for which he received a Pulitzer prize.[4] Penfield considered Osler one of his best friends and created an environment at McGill that led Osler to donate his magnificent medical library to that institution.

While in Boston, Dr. Penfield also became best friends with Dr. Stanley Cobb, then the head of Neurology and Psychiatry at the Massachusetts General Hospital. They shared the same interests in the relationship between brain, mind and soul and the friendship remained strong until Dr. Cobb's death.

Penfield was given to philosophy and speculation. His interest in the spiritual and intellectual side of neurosurgery will remain an enduring part of his legacy. He explicitly recognized the importance of role models. For him, these included: Conklin the scientist, Finney the surgeon, Green the physician-classicist, and Osler the friend. He also felt very strongly that he had an important mission in life, a concept perhaps encouraged by his mother. In 1913, for example, he wrote that his objective in life was to "support myself and my family and somehow make the world a better place to live."[1] He certainly did this: the restless urge to do something truly important characterized his life.

As much of this paper will be about brain tumors, it is appropriate to note that these lesions were important to Penfield's development early in his life. He was drawn to medicine initially because of his work with a scientist named Conklin who was studying how cells multiplied. As a young surgeon in New York, he had an experience with brain tumors that was not unusual in those days. On page 71 of *No Man Apart*, he writes, "it was about this time that I carried out my first major brain operation at last. It was followed by a second before the week was out. Although each operation was long and agonizing, each was followed by death."[1] He also wrote an early paper about meningiomas, the topic of this scientific discourse today.[5]

Like many other trainees at McGill, I came under Dr. Penfield's spell. It was while reading "Speech and Brain Mechanisms" one day as a Harvard undergraduate in the Harvard Biological Laboratories, that led me to consider neurosurgery as a field.[6] While I was a medical student at McGill, I went to visit him at the Montreal Neurologic Institute. On my first visit, I mentioned that I might be interested in neurosurgery as a career. He asked me to show him my hands. He looked at them, compared them with his, and approved. He said he thought that a neurosurgeon should have functional hands, not long slender, elegant appendages. We had several subsequent discussions about neurosurgery; the opportunities for understanding the mind and soul that this field provides were uppermost in his conversation. It seems to me that these remain the ultimate goals of neurosurgery.

Meningiomas

This paper will discuss three aspects of meningiomas that illustrate contemporary advances in neurosurgical technique and care: the increased understanding of the molecular biology of these tumors; the development of focused radiation techniques for their treatment; and the use of virtual reality for surgical management. These would have been close to Dr. Penfield's heart: the development of better neuropathological understandings of a lesion; the use of new techniques to achieve a desired goal; and the incorporation of brain imaging into the operating theater as a method of improving patient care.

Hormones and Meningiomas

A striking feature of meningiomas is the predominance in incidence of women over men. In the Brain Tumor Center at the Brigham and Women's Hospital and Dana Farber Cancer Institute, we have seen 369 women with intracranial meningiomas and 148 men, a ratio of 2.4:1.

The most prominent feature of the molecular genetics of this tumor, a deletion on the long arm of chromosome 22 in the majority of patients, does not explain this sex difference. This deletion occurs apparently equally in men and women. This paper will suggest that the difference is very likely a result of the expression of progesterone receptor by meningioma cells.[7] This makes them particularly susceptible to circulating progesterone and they are therefore, like breast carcinomas, tumors that are hormonally driven.

What are the receptors found in meningiomas? Initial experiments with competitive binding suggested that estrogen receptor may be expressed in these tumors but molecular studies by our laboratories and others have shown that it is not an important stimulatory molecule; it is expressed in very small amounts and is probably not active. (Black and Carroll, unpublished data). Androgen receptor is expressed in 69% of women and 31% of men, but its role in tumor growth is unclear.[8] Meningiomas also express receptors for other compounds including platelet-derived growth factor,[9] prolactin (Black and Carroll, unpublished data), glucocorticoids,[7] epidermal growth factor,[11] dopamine and somatostatin.[12] They express messenger RNA for all members of the platelet-derived growth factor family including PDGF A, PDGF B, and PDGFR-ß, the beta form of the PDGF receptor. Activation of the *ras* oncogene as an intermediate messenger occurs when PDGFR-ß is activated:[9] this oncogene has little direct role in meningioma pathophysiology, however. EGFR and PDGFR are expressed equally in men and women. Prolactin receptor is expressed in meningiomas and addition of prolactin to meningioma tissue increases growth rate.[10]

Our laboratory believes that the hormone receptor of most importance expressed in meningiomas is the progesterone receptor. We have demonstrated using Northern Blot Analysis and immunohistochemistry that this receptor is expressed in 81% of women and 40% of men with meningiomas.[7] It is also expressed in normal arachnoid cells. Immunostaining demonstrates that it is nuclear in its binding, and through a fairly complicated mechanism it can be

demonstrated that it is also active in the sense of being able to activate downstream sequences in the cell.[7]

The mechanism to demonstrate receptor activity uses an indirect approach since progesterone receptor does not act through a simple intermediary transcription cascade such as *ras*. This system uses the progesterone responsive element, a sequence which is activated by progesterone receptor and is necessary for progesterone to exert its effects.[7] 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 acetyl-transferase (CAT) can be used to determine activation of the progesterone responsive element. This was done in a series of meningiomas in culture and the results are shown in Figure 1. Progesterone receptor in the cell was used to activate its own CAT in cells exposed to exogenous progesterone. The fact that tumors with progesterone receptors express CAT indicates that the receptor is active in the sense of being able to activate the progesterone responsive element.

The potential role of hormone receptors is particularly interesting in view of some recent 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.[13] These findings raise the possibility that meningiomas develop from altered arachnoid cells that can be stimulated by steroid hormones.

Linear Accelerator Radiosurgery and Radiotherapy for Meningiomas

Meningiomas have recurrence rates which vary from 9 to 40% at 10 years.[14,15] External beam radiation therapy lessens this rate of recurrence. In a retrospective series, Barbaro et al. reported that 60% of patients with residual meningioma had continued growth if they were denied radiation therapy compared with 32% of patients with irradiation.[16] The time of recurrence was 66 months in non-irradiated patients and 125 months in irradiated patients ($p < 0.0007$). For Taylor et al., there was a local control rate of 82% in patients with subtotal excision coupled with radiation versus 18% for subtotal excision alone.[17]

These and other papers demonstrate the effectiveness of radiation in controlling meningioma growth;[18-20] however, one of the concerns in such treatment has been the radiation of surrounding brain as well. Recent advances in radiation technology have allowed the delivery of focused radiation to these lesions in the form of stereotactic radiosurgery or stereotactic radiotherapy. Radiosurgery is a single application of a highly focussed radiation beam; stereotactic radiotherapy is the use of fractionated treatments to a highly focal area.

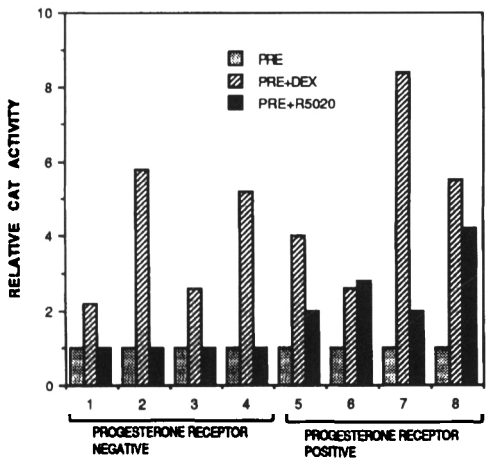

Figure 1: Transfection of the progesterone responsive element with a CAT reporter demonstrates the progesterone receptor is active. (See text; reprinted with permission from 8).

Our radiosurgery is done with a linear accelerator. The dedicated linear accelerator stereotactic radiosurgery suite at Brigham and Women's Hospital is an image-guided radiation oncology suite which uses a Varian linear accelerator dedicated to radiosurgery, the CRW stereotactic frame system (Radionics, Inc., Burlington, MA) and the XKnife Planning System (RSA, Inc., Boston, MA). Virtually all patients are treated as outpatients. This facility is part of the Brain Tumor Center at Brigham and Women's Hospital, Children's Hospital, Dana-Farber Cancer Institute, and the Joint Center for Radiation Therapy at Harvard Medical School. An extensive database keeps relevant data on all patients treated. Our experience with radiosurgery as well as that of others using either the linear accelerator or the gamma knife has demonstrated that a single-fraction of high dose radiation can be used safely and has a major role in controlling meningioma growth. This unit has treated over 200 patients with meningiomas with stereotactic radiosurgery or stereotactic radiotherapy over the last 5 years. This treatment was carried out by a team consisting of neurosurgeons from the Brigham and Women's Hospital and radiation oncologists from the Joint Center for Radiation Therapy. For most of these patients, the goal was to prevent recurrence after surgery, but approximately 15% had this treatment as the only intervention.

Our experience with 56 skull base meningiomas is indicative of our whole series. 41% of the tumors shrunk, 54% stayed stable and only 5% continue to grow with a 5 year follow-up after this single-dose treatment. Most of these had been operated on before radiosurgery. The mean radiation dose was 1500 cGy with a range of 1000-2000 cGy. The mean lesion volume was 4.1 cc, with a range of 0.2-3.6 cc. The median collimator size was 27.5 mm, with a range from 12.5-40 mm. 90% of treatments were normalized to the 80% isodose line.[21]

There are, however, local complications following radiosurgery. In this series there were 5 cases of cranial nerve problems or brain stem edema from this treatment. These resolved over a year but the cranial nerve deficits persisted. As a result of this experience, our group has moved to using fractionated radiation therapy techniques for the treatment of meningiomas that are against the brain stem, or greater than 2 cm in diameter.[22]

Using linear accelerator radiosurgery, with doses of 54-70 cGy and a mean follow-up of 25 months, the Heidelberg group found a 98% local control rate.[23] However, they also reported late complications in 42% of patients. These included transient neurological defects, edema, intratumoral necrosis, and visual loss. Based on the number of complications, this group has moved to conformal fractionated precision radiotherapy, a system that uses small fields in a fractionated system. Kondziolka et al. reported the results of radiosurgery using the gamma knife in 24 patients available for radiographic follow-up.[24,25] They found decrease in tumor volume in 13, no radiographic change in 9, and 2 with growth outside of treatment volume. They noted a number of complications including new neurological defects (6%), new cranial neuropathies (4%) and contralateral hemiparesis (4%). Later

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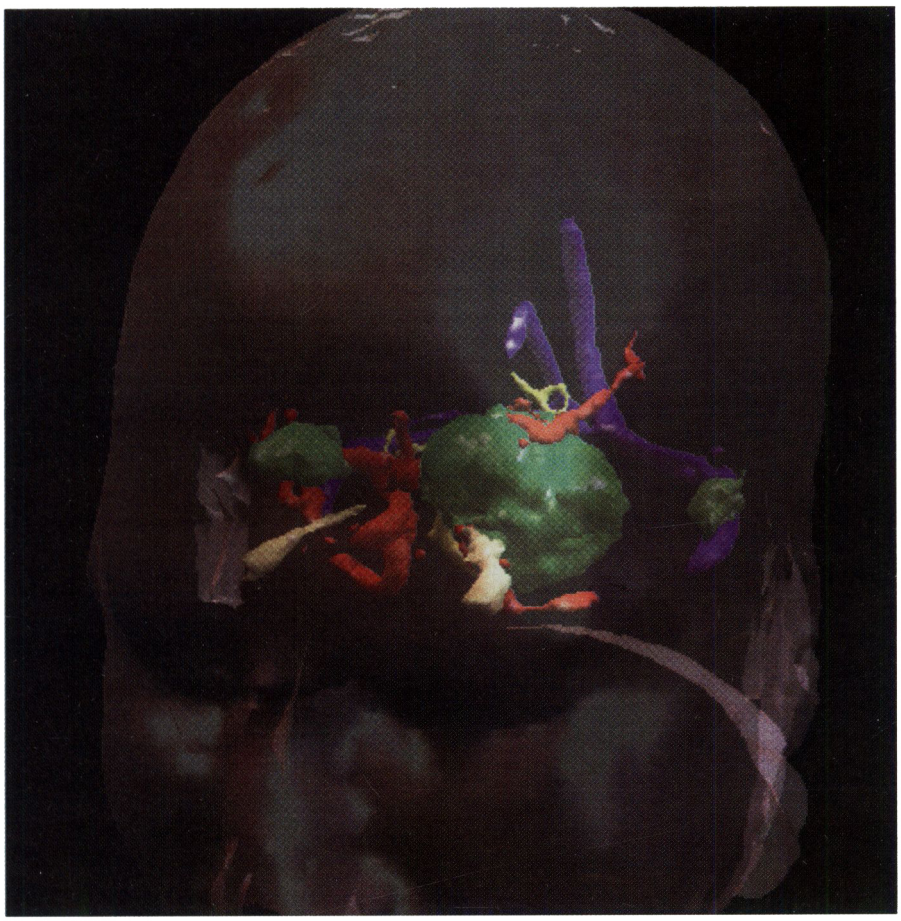

Figure 2: *Three-dimensional reconstruction of a meningioma. This is created from MRI scans.*

series from this group have had fewer of these complications.[26]

We believe that the severe edema we found was a result of endothelial damage to the vessels of the tumor, leading to a significant leakage of fluid into the interstitium. The complications associated with large tumors has led to use fractionated linear accelerator radiotherapy in patients whose tumors are larger than 2 cm or are close to brain stem or cranial nerves.[27] Stereotactic radiotherapy using the Gill-Thomas-Cosman repeat fixation stereotactic system has been associated with no deficits or other complications now in over 130 patients with meningiomas. Linear accelerator delivery systems provide a major advantage over multiple source systems such as the gamma knife in that they allow fractionated technique.

We presently believe that indications for postoperative radiotherapy in meningiomas include; residual tumor after surgery in a young person, growing residual tumor in an older person, or atypical or malignant histology in a patient who has had complete resection. Indications for radiotherapy as primary treatment include a tumor in an inaccessible location, medical disease such as anticoagulation, severe heart or renal disease contraindicating surgery in a patient with a symptomatic tumor; and patient preference. If the lesion is greater than 2 cm in diameter or is within 5 mm of the brain stem or optic apparatus we will use stereotactic radiotherapy rather than radiosurgery. If it involves a tumor diameter that is greater than 5 cm we will recommend standard external beam therapy.

Virtual Reality

Three-dimensional reconstruction of the brain is important because it allows accurate estimation of the volume and location of cerebral lesions and precise analysis of cortical surface topography. Work being done by our group in the Surgical Planning Laboratory uses virtual reality to facilitate the correlation of imaging with brain structures in the patient. The Surgical Planning Laboratory is a joint venture between the divisions of neuroradiology and neurosurgery at Brigham and Women's Hospital. It has the general goals of making computer computation rapid and transparent to the user and developing a rapid and satisfactory system of fitting anatomical contour to the MRI.[28] This allows the surgeon to work in three-dimensional space and essentially use the MRI as his or her visual system in planning a surgical procedure.

MRI acquisition is done with 3 mm sections which are processed by a physician who outlines the structures to be reconstructed. This reconstruction takes approximately 4 hours. The images are displayed on a SUN workstation and manipulated using a connection supercomputer.

In preparation for surgery, a virtual reality headset may be used to display the three-dimensional image through the scalp contour and the lesion is marked on the shaved scalp. Alternatively, the scalp and the three-dimensional reconstructed image can be superimposed in a video display using a mixing board. In the operating room, the same mixing board is used to mix the three-dimensional image with the real-time two-dimensional video of the patient's shaved head. The lesion is marked out and the incision and bone removal required can also be marked. Recently, a navigation system has also been used within this three-dimensional shell.

This system has been used in a number of cases in which its strengths are apparent. It is useful both for localization of the lesion itself and for defining its edges as it is resected (Figure 2). It is also important in establishing its relationship to surrounding structures such as blood vessels, cranial nerves, and brain stem. As one example, a healthy middle-aged man had a right temporal extra-axial mass thought to be a meningioma. Initial MRI imaging was done, to be certain there was no encasement of the carotid artery. Reconstructed MRI confirmed this and also showed the relation to medial temporal structures; at surgery it was possible to get complete resection of this meningioma without difficulty. A second patient had a tumor with a diffuse margin around the motor strip; the difficulty was defining the margin, which was problematic because of its lack of difference from the brain tissue itself. In this case the superimposed MRI allowed very precise determination of the margin. This method can be used for spinal as well as cranial abnormalities. For example, a middle-aged woman had neck pain and sensory loss. Her scan showed a large clivus meningioma which

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compressed the brain stem. It was possible to navigate well within the space in removing this from an anterior approach.

There remain three major problems in the adoption of three-dimensional planning and brain imaging to neurosurgery. The first is making the system work smoothly and quickly; the second is getting an automated segmentation system; the third is merging image with reality accurately.

Advances are steadily being made in all three areas. With adequate help and the use of supercomputers, the system is now able to do the reconstructed planning in approximately six hours. The segmentation is now half automated. For merging the reconstructed image with the real image, there are now several alternative techniques. In the system described here, the contours of the scalp themselves are used and are particularly important to get oriented correctly at the beginning of the surgical procedure. New techniques of laser scanning make this even more accurate. These techniques allow more precise localization of a tumor, essentially being frameless stereotaxis; for intrinsic tumors they can also describe the tumor margin in a sophisticated way. Recently, the cortical veins have also been used as important landmarks.[29]

A major problem with this and all other navigational techniques using preoperative images however, is the fact that the brain contents shift. We have developed at Brigham and Women's Hospital an intraoperative MRI that allows visualization of the lesion during scanning and surgery in the MRI scanner. This revolutionary new device will bring true image-guided surgery to the management of meningiomas. It will be possible to evaluate residual tumor, drainage to surrounding brain, and other real-time changes. Thus far, I have done 60 craniotomies in this device and find it a remarkable advance.

Summary

Wilder Penfield believed in the use of science to improve the understanding and treatment of neurosurgical lesions. The contemporary ability to understand meningioma receptor function, to realize the potential importance of radiation in meningioma treatment, and to use modern three-dimensional imaging in surgical management is in keeping with his legacy.

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