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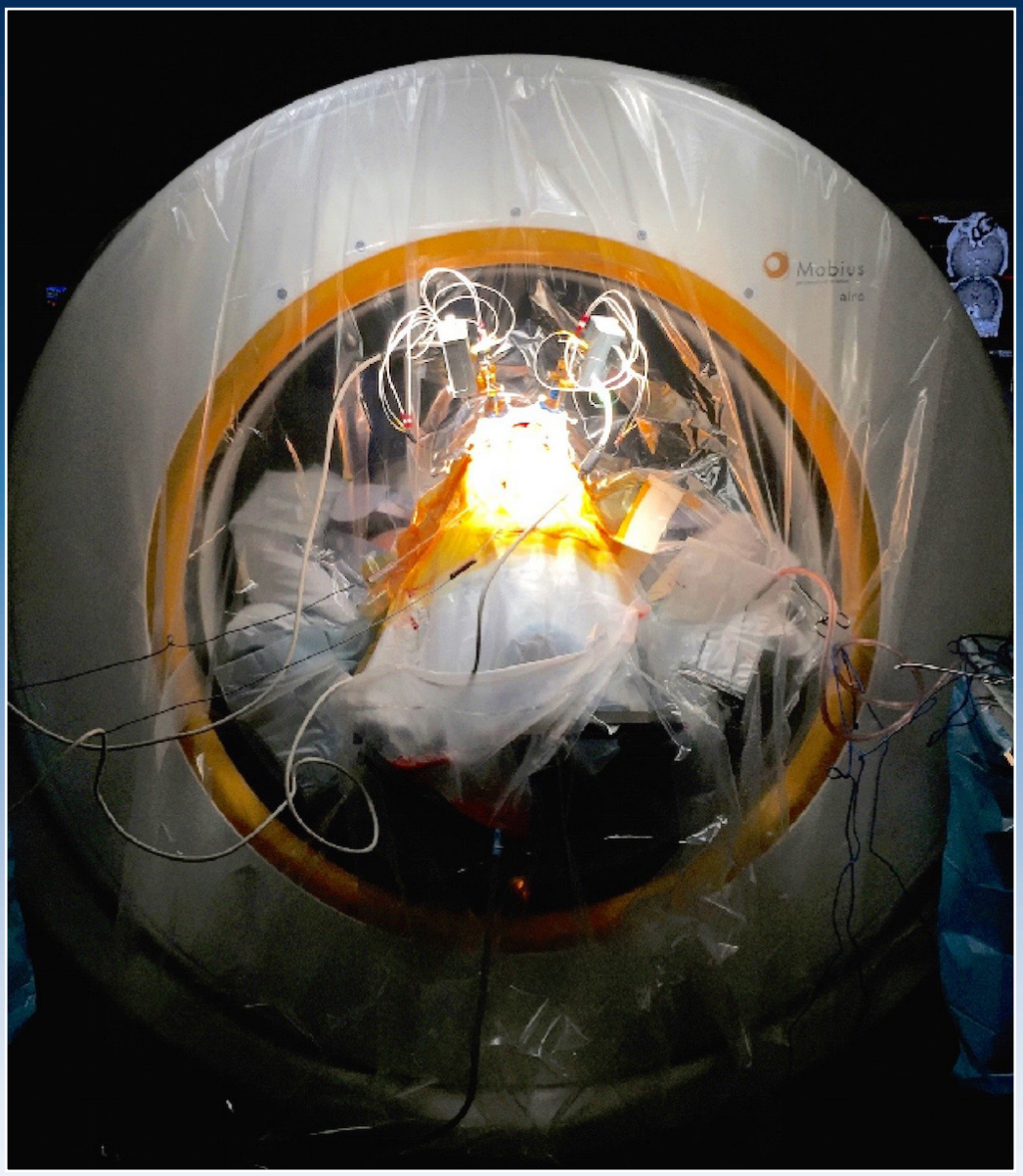

SPECIAL SECTION

RECENT ADVANCES *in* NEUROSURGERY

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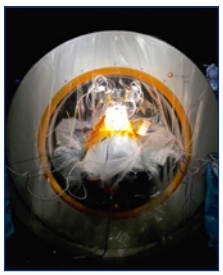

On the cover:
Deep brain simulation procedure with bilateral simultaneous micro-electrode recordings, performed with an intraoperative CT scanner at Rhode Island Hospital. Photo by Julie Guerin, Brown University neuroscience graduate student.

Introduction to Recent Advances in Neurosurgery

ZIYA L. GOKASLAN, MD
GUEST EDITOR

It is absolutely my pleasure to share with you in this issue some of the recent advances in treating a variety of neurosurgical conditions at the Department of Neurosurgery of Rhode Island Hospital and Brown University.

The following contributions are included in this special focus section of the *Rhode Island Medical Journal*:

Current Treatment of Metastatic Spine Tumors – Surgery and Stereotactic Radiosurgery by Jared S. Fridley, MD; Jaroslaw T. Hepel, MD, and Adetokunbo A. Oyelese, MD, PhD, describes our multidisciplinary approach to patient care and the incorporation of stereotactic radiosurgery as well as other minimally invasive procedures into our surgical treatment paradigm in caring for patients with metastatic spinal tumors.

The Role of Radiation Therapy in the Treatment of Metastatic Brain Disease by Sohail Syed, MD, and Deus Cielo, MD, is a comprehensive review which describes the use of a variety of radiation treatment modalities in managing patients with single and multiple brain metastases.

Current Strategies in the Surgical Management of Ischemic Stroke by Cody A. Doberstein, BS; Radmehr Torabi, MD; Sandra C. Yan, BS, BA; Ryan McTaggart, MD; Curtis Doberstein, MD, and Mahesh Jayaraman, MD, summarizes the transformation we have witnessed over the last several years in treating patients with major cerebral vessel occlusion via emergency endovascular thrombectomy, resulting in truly amazing restoration of neurological function for patients who would have otherwise been left with devastating permanent neurological deficits. Our multidisciplinary team of physicians is leading the field in this very exciting area with some of the best outcomes in the world.

Rhode Island Hospital's Contribution to the Field of Endoscopic Spine Surgery by Albert E. Telfeian, MD, PhD; Adetokunbo A. Oyelese, MD, PhD, and Ziya L. Gokaslan, MD, is a description of the groundbreaking work by Dr. Albert Telfeian, the Director of the Center for Minimally Invasive Endoscopic Spinal Surgery at Rhode Island Hospital and Brown University, which allows outpatient endoscopic surgical treatment of spinal cord and painful nerve root compression, using pencil-tip size incisions. We are truly among the world leaders in this very exciting field, which has dramatically shortened the recovery time from surgery while drastically improving patient outcomes.

Updates On Chimeric Antigen Receptor-Mediated Glioblastoma Immunotherapy by George Mao, MD; Prakash Sampath, MD, and Sadhak Sengupta, PhD, is again amazing work, outlining how the patient's own immune system, specifically his/her own killer T-cells can be conditioned to recognize tumor- specific chimeric antigens in patients with glioblastoma. We are about to start clinical trials to translate this groundbreaking discovery to the care of our patients.

A Comprehensive Approach to Deep Brain Stimulation for Movement Disorders by Umer Akbar, MD, and Wael F. Asaad, MD, PhD, is a description of the multidisciplinary approach that our physicians employ in evaluating patients with movement disorders such as Parkinson's disease and the state-of-the art surgical methods and technology they use in the operating room, with intraoperative, image-guided navigation, and electrophysiological recordings for precise placement of the deep brain electrodes used for stimulation.

Recent Advances in the Treatment of Gliomas – Comprehensive Brain Tumor Center by Steven A. Toms, MD, MPH, and Nikolaos Tapinos, MD, PhD, is a comprehensive review of the whole spectrum of treatment options including radiation, chemotherapy and immunotherapy in patients with gliomas. The article also describes the multidisciplinary approach employed by the Comprehensive Brain Tumor Center at the Lifespan Cancer Institute of Rhode Island Hospital and exciting ongoing translational research projects in our Brain Tumor Research Laboratories.

Current Concepts in the Pathogenesis, Diagnosis, and Management of Type I Chiari Malformations by Cody A. Doberstein, BS; Radmehr Torabi, MD, and Petra M. Klinge, MD, is an excellent review of the topic on this rare and often poorly understood condition and its neurosurgical treatment. Dr. Klinge is a worldwide expert and leads the Center for CSF Disorders of the Brain and Spine, where we at Rhode Island Hospital and Brown University offer state of-the-art care to our patients.

This is just a brief summary of some of the very exciting work we are doing here at the Department of Neurosurgery of Rhode Island Hospital, the Norman Prince Neurosciences Institute and Brown University, on a daily basis.

We are also pleased to share with you that we have just moved into a dedicated neuroscience floor at Rhode Island Hospital, which also houses an 18-bed Neuro Intensive Care Unit and highly specialized physician and nursing teams. Similarly, we have a dedicated spine floor with specialized nursing staff where we care for our patients with the whole spectrum of spinal disorders.

Author

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Current Treatment of Metastatic Spine Tumors – Surgery and Stereotactic Radiosurgery

JARED S. FRIDLEY, MD; JAROSLAW T. HEPEL, MD; ADETOKUNBO A. OYELESE, MD, PhD

ABSTRACT

There has been significant progress and innovation in the treatment of patients with metastatic spinal tumors over the last two to three decades that has impacted our ability to provide individualized care that improves a patient's quality of life and degree of neurologic impairment. Advances in surgical techniques and radiation delivery modalities have dramatically improved our ability to decrease local tumor recurrence rates, improve pain control, and provide more durable spinal stability. Modern day spine tumor resection and reconstruction techniques have been shown to improve and prolong patients' ability to ambulate, maintain continence, and reduce the need for pain medications. Spinal radiosurgery, the focused delivery of radiation to a target in the spine, has significantly enhanced the ability to provide a high degree of local tumor control in a non-invasive manner, even for tumors that are deemed radioresistant by conventional radiation therapy standards. In most patients, a combination of treatment modalities, including both surgery and radiation, is the mainstay of any comprehensive treatment plan for metastatic spinal tumors.

KEYWORDS: spine metastases, separation surgery, spinal radiosurgery, spine tumor, spine decompression

INTRODUCTION

Metastases are the most common spine tumor, with up to 40% of cancer patients developing spinal metastases, and 5-10% developing symptomatic epidural spinal cord compression.[1] The spine is the most common site of skeletal metastases, with the thoracic spine being the most frequently involved spinal segment, followed by the lumbar and cervical spine. Advances in the treatment of cancer has led to improved patient survival, but also a higher incidence of patients with spinal metastases. The treatment of these patients has evolved substantially over the past several decades, with dramatic advances in both surgical and radiation therapies. In this paper, we summarize some of the more important advances in these respective fields.

SURGICAL ADVANCEMENTS

For many years, patients with metastatic spine tumors causing epidural spinal cord or nerve root compression were treated with simple posterior spinal decompression followed by fractionated external beam radiotherapy. While some patients did improve in terms of ability to ambulate and bowel/bladder function,[2] the results weren't encouraging. When compared to radiation alone the addition of a simple posterior decompression was not found to add any significant benefit in terms of pain, sphincter function, or improved ambulation.[2] The disheartening results of such studies led to a decline in surgical intervention.

The primary problem with a simple posterior decompression of the spinal cord, which is typically done via laminectomy, is that in many patients, epidural compression is ventral to the spinal cord, not dorsal. This means that many patients continue to have ventral spinal cord compression despite a posterior decompression. Following the disappointing outcomes of earlier studies examining laminectomy and radiation for tumor treatment,[2] surgeons began developing techniques to directly decompress the spinal cord with ventral tumor resection. The hope was that circumferential decompression of the spinal cord with instrumented stabilization of the spine might lead to improved outcomes. This was confirmed in a landmark randomized, prospective trial published in 2009 by Patchell et al. comparing radiation alone to radiation plus circumferential surgical decompression in patients with a single spinal metastasis compressing the spinal cord.[3] The authors found that 84% of patients treated with both circumferential decompression and radiation were able to ambulate after treatment versus 57% patients who underwent radiation alone. In the group of patients unable to walk before treatment, 62% in the surgery group regained the ability to ambulate versus 19% in the radiation only group. This contrasts with the results of performing a laminectomy alone with radiation in the study by Young et al. in which 45% of patients were able to ambulate after treatment.[2] The surgery plus radiation group was also able to walk for a longer period of time after treatment versus the radiation only group (122 days vs. 13 days). This study provides the best evidence to date that circumferential spinal cord decompression can significantly improve patient quality of life.

Pathologic fractures in patients with metastatic spine

tumors without epidural compression often present with significant back pain. When unstable these fractures tend to be managed via surgical instrumentation. However, when neither gross instability nor significant epidural spinal cord compression exist, percutaneous vertebral body cement augmentation is a non-invasive method that can provide back pain relief. There are two primary methods of cement augmentation: balloon kyphoplasty and vertebroplasty, both of which have been shown to be effective for treating pain from pathologic fractures.[4] These procedures involve injection of polymethylmethacrylate (PMMA) through the percutaneous insertion of a small metal trocar into the vertebral pedicle, followed by injection of cement under fluoroscopic guidance. With balloon kyphoplasty, a small inflatable balloon is inserted into the vertebral body and inflated to augment vertebral body height prior to injection of cement. Even in patients with significant vertebral body collapse, cement augmentation can be an effect option for pain relief, with a low overall complication rate.[5]

ADVANCES IN RADIATION TREATMENT

Radiation delivery for spinal metastases has evolved substantially since the end of the 20th century. Traditional external beam radiation therapy (EBRT) consists of radiation delivered in a fractionated dose, typically 30 Gy over 10 fractions, and using simple one to two portal configurations that encompasses the area of disease with a wide margin of 1 vertebral level above and below. EBRT has been shown to be effective in treating very radiosensitive tumors such as multiple myeloma and lymphoma as well as moderately radiosensitive tumors such as breast and prostate cancer.[6,7] However, EBRT has been shown to not be as effective in the treatment of more radioresistant tumors, such as sarcoma, melanoma and renal cell carcinoma.[6,7] To maximize the dose of radiation delivered to a tumor target and minimize radiation toxicity to surrounding healthy tissues, advances in both computing hardware and radiation planning software were incorporated into treatment planning. This led to the development of conformal radiotherapy such as intensity modulated radiation therapy (IMRT), which utilizes sophisticated 3D planning and multi-leaf collimators that focus radiation to the intended tumor target and minimize dose to adjacent normal tissues. However, the radiation sensitivity of the spinal cord and its intimate location to metastatic disease in the vertebra, limits the safe delivery of only moderate doses of radiation (45-50Gy in standard fractionation) with this technique.[8]

The next significant advance in radiation therapy was the development of stereotactic radiosurgery to be delivered to spine lesions akin to stereotactic radiosurgery for brain metastases in the late 20th century. Radiosurgery consists of a single or hypo-fractionated dose of radiation delivered with extreme precision to the tumor target. Unlike cranial stereotactic radiosurgery, spinal radiosurgery has unique technical obstacles. This includes dose limitations due to proximity of the spinal cord and spinal motion during radiation delivery. Unlike the head, which can be fixated in place using a stereotactic frame, the spine is more difficult to constrain. To overcome the problem of motion, immobilization devices coupled with real-time image guidance during treatment have been developed which allow for targeting accuracy to 1mm or less. The extreme precision combined with sophisticated dose modulation allows for the delivery of high doses of radiation while still relatively sparing the spinal cord. This results in safe delivery treatment that is effective even for radiation-resistant histologies. Using single fraction dose equivalents of 18-24 Gy, studies have demonstrated a local tumor control rate of 80-96%,[9-11] and a 86% chance of long-term pain relief.[12]

A NEW PARADIGM

The success of spinal radiosurgery in terms of local control and pain relief of spinal tumors has dramatically altered treatment paradigms. It has supplanted both EBRT and surgery in the primary treatment of solitary spine tumors without significant epidural compression. In those patients with significant neural element compression, or in those patients with spinal instability due to an unstable pathologic fracture, surgery remains the gold standard. Similarly, EBRT continues to be used for the treatment of radiosensitive spinal metastases. To minimize surgical morbidity from an extensive circumferential decompression including vertebral body resection, Laufer et al have advocated 'separation surgery' which entails circumferential resection of epidural tumor, a limited resection of vertebral body tumor, followed by adjuvant radiosurgery to the remaining tumor and resection cavity.[13] In their series of patients, Laufer et al reported a 4.1 – 22.6% local recurrence rate at 1 year depending on the radiation dose/fraction regimen utilized post-operatively. Despite these impressive results, further study is needed to determine whether this is a more efficacious strategy versus a more aggressive surgical resection and spinal reconstruction.

CONCLUSION

Recent advances in the surgical and radiation management of patients with spinal metastases has led to significant improvement in patient outcome. Despite these advances, treatment remains palliative. The goals of care should be to minimize patient morbidity, and maximize patient quality of life in terms of pain, mobility, and neurologic function. A multi-disciplinary approach to management of these patients that incorporates medical oncology, radiation oncology, and neurosurgery is necessary for optimal treatment planning in this complicated group of patients.

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The Role of Radiation Therapy in the Treatment of Metastatic Brain Disease

KUNAL SINDHU, BS; SOHAIL SYED, MD; DEUS CIELO, MD

ABSTRACT

Brain metastasis is the most frequent central nervous system malignancy. Although surgery and chemotherapy have roles to play in the treatment of brain metastasis, radiation therapy remains a mainstay of therapy. We will review the role of fractionated radiotherapy and stereotactic radiosurgery in the treatment of newly diagnosed and recurrent brain metastasis.

KEYWORDS: brain metastasis, radiotherapy, stereotactic radiosurgery

INTRODUCTION

In adult patients with cancer, 20-40% of ultimately develop brain metastases.[1]patterns of intracranial disease and factors influencing survival become important considerations when examining potential treatment options. METHODS: The records of 729 patients with metastases to the brain treated during the period between 1973 to 1993 were reviewed. RESULTS: Primary tumor histologic type in order of descending frequency included nonsmall cell lung carcinoma (NSCLC Historically, the prognosis for these patients was poor, ranging from one month for untreated patients to four-to-six months in patients who received corticosteroids and whole brain radiation therapy (WBRT).[2,3] Recently, changes in management have significantly improved the prognosis of patients, especially those with high functional status at time of diagnosis.[4] While surgical resection has been increasingly employed for patients with limited disease, radiation therapy remains the mainstay of treatment for patients, either as a primary or adjuvant therapy. While the precise role of stereotactic radiosurgery (SRS) is still evolving, a considerable body of evidence has confirmed the efficacy of both SRS and WBRT. In fact, the persistence of radiation therapy over time despite the emergence of alterative therapeutic modalities suggests that SRS and WBRT are likely to continue to play critical roles in the treatment of this patient population well into the future.

Brain metastases are the most common form of intracranial tumors. With an annual incidence of at least 200,000 cases in the United States, they are nearly ten times more common than primary malignant brain tumors.[5,6] In 85% of cases, they are found in the cerebral hemispheres, but they can also involve the cerebellum and, very rarely, the brainstem.[7] While brain metastases most commonly originate from primary tumors in the lungs, breast, or skin (melanoma), they can ultimately originate from any type of cancer.[1,8]patterns of intracranial disease and factors influencing survival become important considerations when examining potential treatment options. METHODS: The records of 729 patients with metastases to the brain treated during the period between 1973 to 1993 were reviewed. RESULTS: Primary tumor histologic type in order of descending frequency included nonsmall cell lung carcinoma (NSCLC

With improved management, a significant number of patients with brain metastases are living considerably longer compared to historic figures. In 2008, Sperduto et al. published a new prognostic assessment tool for patients with brain metastases called the Graded Prognostic Assessment (GPA). The GPA takes four aspects of a patient's clinical status into account: age, Karnofsky Performance Status (KPS), the number of intracranial metastases, and the presence of extracranial metastases[11] and found that a substantial number of patients with brain metastases, especially those with the highest GPA scores, were living longer than one year.[4]

THE TREATMENT OF BRAIN METASTASES

Treatment regimens for brain metastases are frequently complex and multimodal. For symptomatic relief from brain edema, corticosteroids are used. Antiepileptics are often useful in controlling seizures in symptomatic patients. For definitive treatment, chemotherapy, radiation therapy, and surgery may be used.[5]

Historically, radiation has played a dominant role in the treatment and palliation of brain metastases and was first described as a treatment for brain metastases in 1954 by Chao et al.[12] In the 1980s, SRS was widely adopted to treat patients with a limited number of brain metastases.[5] In 1990, the role of surgery was first established by Patchell et al., who demonstrated that patients with a solitary brain metastasis who underwent surgical resection and WBRT had lower rates of local recurrence, longer periods of functional independence, and improved overall survival as compared to patients who received WBRT alone.[13]we randomly assigned patients with a single brain metastasis to either surgical

removal of the brain tumor followed by radiotherapy (surgical group Numerous clinical trials have reinforced the roles of surgery and radiation in the management of these patients.

WBRT

Tumor metastases to the brain disseminate hematogenously and may thus seed broadly within it. The role of WBRT in the treatment of patients with brain metastases is thus twofold: to target both the macrometastases seen on imaging, as well as any micrometastases undetected by current diagnostic testing.[14] By treating both visible and occult lesions, WBRT can improve neurologic symptoms in 63% of the patients treated.[12] Further studies have found that WBRT decreases local recurrence rates, improves neurologic function, and improves overall survival in patients with brain metastases.[2,3,15–17] Multiple clinical trials have established the efficacy of WBRT. Nonetheless, there is no Class I evidence that suggests that there is an advantage of a specific dose regimen with respect to overall survival, local control, or neurocognitive function.[18] In common practice, though, the two most common schedules remain 30 Gray delivered in 10 fractions or 37.5 Gray delivered in 15 fractions.

Unfortunately, WBRT can cause side effects by causing tissue damage in its intended target or the surrounding tissues. In the acute period after receiving WBRT, days to weeks after treatment, patients most commonly may experience fatigue, nausea and vomiting, radiation dermatitis, and alopecia. Within one to six months of treatment, patients may experience a transient worsening of symptoms and, rarely, somnolence syndrome. In the delayed period, six months or more after treatment, patients can develop more permanent side effects, including radiation necrosis, vascular abnormalities, and cognitive deficits.[19] Just six months after receiving WBRT, in fact, 50–90% of patients show evidence of radiation-induced cognitive impairment, including effects upon verbal and spatial memory, attention, and novel problem-solving ability.[19] As patients with brain metastases live longer, increasing attention is being paid to the neurocognitive sequelae associated with WBRT.[20] Not surprisingly, two controlled trials found worse neurocognitive outcomes in patients treated with WBRT and SRS compared to those treated with SRS alone.[21,22] 2001, to September 14, 2007. Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radioresistant histology. The randomisation sequence was masked until assignation, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline In response to these neurocognitive outcomes, hippocampal-sparing WBRT has been advocated and seems to have improved neurocognitive outcomes compared to traditional WBRT.[23] Nonetheless, it is the total burden of brain metastases that is the most important factor in predicting the cognitive outcome in patients with brain metastases.[23]

Despite its adverse effects, WBRT remains a cornerstone of management of patients with brain metastases. WBRT is especially useful in treating patients who are not candidates for SRS or surgery due to a large number of intracranial metastases, poor performance status, tumor location, or leptomeningeal spread.[24] Unfortunately, WBRT suffers from high rates of recurrence which are highly tumor histology dependent.[25,26,27]especially of tumor volume, on remission and to evaluate whether particular subgroups of metastases are controlled by low-dose radiotherapy. METHODS AND MATERIALS: Contrast-enhanced CT scans before and after radiotherapy were analyzed. INCLUSION CRITERIA: brain metastases treated with whole-brain radiotherapy (10 fractions of 3 Gy over 2 weeks Thus, providers must exercise clinical judgment in carefully selecting the candidates who are most likely to derive benefit from undergoing WBRT.

The use of WBRT has also been explored as an adjuvant to surgery or SRS. In patients with 1–3 brain metastases, the addition of adjuvant WBRT to SRS or surgery has been shown to improve local control and decrease the risk of neurologic death, but it does not appear to extend the length of functional independence or improve overall survival.[28, 29] 199 underwent radiosurgery, and 160 underwent surgery. In the radiosurgery group, 100 patients were allocated to OBS, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to OBS, and 81 were allocated to adjuvant WBRT. The median time to WHO PS more than 2 was 10.0 months (95% CI, 8.1 to 11.7 months

Stereotactic Radiation Surgery

Gamma Knife, first developed by the Swedish neurosurgeon Lars Leksell in 1951, is the most widely used SRS device.[30] 192 sources of cobalt-60 are organized around a circular frame that is secured to the patient's head by four screws to ensure immobilization. During treatment, the sources of cobalt-60 produce gamma ray beams with an average energy of 1.25 MeV. The intersection of the beams, known as the isocenter, can be manipulated to ensure adequate coverage of the targeted lesion. While treatment time is variable, and depends on factors such as the number and morphology of the lesions to be treated, therapeutic radiation is delivered in a high-dose, single fraction. As a result, patients generally may return home on the same day of treatment.

Linear accelerator-based radiosurgery may be delivered in many different forms utilizing rigid, frame-based patient immobilization or mask-based frameless immobilization systems. CyberKnife, first developed by John Adler at Stanford University, utilizes image-guidance technology and a 6-MV linear accelerator with 12 circular collimators mounted upon a robotic arm to compensate for target movement when delivering treatment.[31,32]emerging technology that is a significant departure from current stereotactic radiosurgery and external beam radiotherapy technologies.

In its clinical application and quality assurance (QA X-ray images taken by mounted cameras during treatment adjust beam trajectory to ensure accuracy.[31] Frameless SRS may enhance patient comfort and allows radiation treatment to be delivered in multiple fractions with impacting outcomes.[32–3]proximity to critical structures and variable tumor volumes. In this study, we investigate whether acceptable treatment plans with excellent conformity and homogeneity can be generated for complex skull base tumors using the Cyberknife(\u00ae [4] In light of the complexity of treating patients with brain metastases, the input and cooperation of neurosurgeons, radiation oncologists, and medical physicists is required to assess the feasibility of SRS treatment plans.

SRS is increasingly being utilized and is capable of delivering high, focal doses of radiation that rapidly drop off outside of the targeted treatment volume. Patient survival with SRS treatment of brain metastases appears to be less influenced by tumor histology than WBRT and offers high rates of local control.[35–37]the primary therapeutic aim is symptom palliation and maintenance of neurologic function, but in a subgroup, long-term survival is possible. Local control in the brain, and absent or controlled extracranial sites of disease are prerequisites for favorable survival. Stereotactic radiosurgery (SRS Patients who receive SRS in the absence of adjuvant WBRT have an increased risk of recurrence in untreated areas of the brain.[35,3]the primary therapeutic aim is symptom palliation and maintenance of neurologic function, but in a subgroup, long-term survival is possible. Local control in the brain, and absent or controlled extracranial sites of disease are prerequisites for favorable survival. Stereotactic radiosurgery (SRS[6] Despite this finding, there is no difference in overall survival between patients who received SRS alone and those who received SRS and WBRT.[21,28,38] 2001, to September 14, 2007. Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radioresistant histology. The randomisation sequence was masked until assignation, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline

Although SRS may be used as monotherapy, avoiding the negative neurocognitive effects associated with WBRT, it should be noted that SRS monotherapy increased overall survival in patients under 50, but decreased survival in patients over the age of 50 in one study.[39] Additionally, SRS is not recommended for tumors greater than 40 millimeters in diameter because of the risk of radionecrosis in neighboring tissue. RTOG 90-05 found that the risk of neurotoxicity in patients treated with SRS was related to the size of metastases and established appropriate dose limits for SRS: 24 Gray for tumors less than 20 millimeters in diameter, 18 Gray for those 21–30 millimeters in diameter, and 12 Gray in those 31–40 millimeters in diameter.[40]

The efficacy of SRS monotherapy in patients with multiple brain metastases is the subject of ongoing research. A recent multi-institutional, prospective observational study in Japan found that the use of SRS alone was non-inferior in patients with 5–10 brain metastases as compared to its use in patients with 2–4 brain metastases. While more data is required to establish the superiority of SRS monotherapy over SRS and WBRT combination therapy in patients with 5–10 brain metastases, this study suggested that SRS alone may be a feasible treatment strategy in patients with up to 10 brain metastases.[41]

Since WBRT often fails to control local disease, the use of SRS as an adjuvant to WBRT alone was explored in RTOG 9508 in patients with 1–3 brain metastases. Both local control and KPS were improved in patients receiving SRS and WBRT versus those who received WBRT alone and patients with solitary metastasis, favorable tumor histology, or Recursive Partitioning Analysis Group 1 who received adjuvant SRS had a survival benefit.[42] Similarly, a trial that analyzed patients with 2–4 brain metastases found that those who received WBRT and adjuvant SRS had lower rates of local recurrence and longer progression-free survival as compared to those who received WBRT alone; however, no statistically significant differences in overall survival were found.[43]frequently diagnosed in patients with cancer. The prognosis, even after treatment with whole brain radiation therapy (WBRT Likewise, after surgical resection, SRS has been found to increase rates of local control.[44]

SRS may also be used in the salvage setting. Untreated, recurrent brain metastases are typically fatal within 2–4 months. A retrospective review by Caballero et al. that analyzed 310 patients who received SRS for brain metastases after prior WBRT found that overall median survival was 8.4 months after receiving SRS. Patients with a solitary brain metastasis had a higher median survival at 12.0 months, while those with multiple brain metastases had a median survival of 7.9 months. In this study, every patient, regardless of the total number of brain metastases, benefited from receiving salvage SRS.[45]

CONCLUSION

While the treatment of patients with brain metastases remains challenging, the prognosis for these patients has improved significantly over the past two decades. Despite the many improvements in management that have been made, radiation therapy remains a cornerstone of treatment. For a significant number of these patients, including those with a large number of brain metastases, poor performance status, and leptomeningeal spread, WBRT remains a clearly-defined, first-line treatment option. The role of SRS, in contrast, is rapidly evolving. While SRS monotherapy is appropriate for properly selected patients with 1–4 brain metastases, its sole use in the treatment of patients with

5-10 brain metastases is the subject of ongoing investigation. Additionally, SRS has been shown to increase rates of local control as an adjuvant and salvage treatment in patients receiving WBRT or surgery. As further advances are made in the medical management of patients with brain metastases, including in the emerging field of immunotherapy, radiation therapy is likely to remain a useful tool in treating this population of patients.

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Current Strategies in the Surgical Management of Ischemic Stroke

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ABSTRACT

Stroke is a major cause of death and disability in the United States and rapid evaluation and treatment of stroke patients are critical to good outcomes. Effective surgical treatments aim to restore adequate cerebral blood flow, prevent secondary brain injury, or reduce the likelihood of recurrent stroke. Patient evaluation in centers with a comprehensive stroke program and a dedicated neurovascular team is recommended.

KEYWORDS: stroke, embolectomy, cerebrovascular occlusion

INTRODUCTION

Stroke is the leading cause of long-term adult disability in North America and the fifth leading cause of death.[1,2] Although some strokes are hemorrhagic, the majority (87%) are ischemic due to insufficient cerebral blood flow secondary to occlusion or flow limiting stenosis. Brain tissue is exquisitely sensitive to ischemia, and an estimated 1.9 million neurons die every minute that blood flow is not restored. Time is brain.[3]

Surgical treatment for stroke can be classified into acute (emergent) or non-acute. Acute interventions, initiated within hours of stroke onset, are aimed at reestablishing cerebral blood flow, restoring lost neurologic function, and preventing permanent tissue damage. Non-acute surgical therapies focus on reducing secondary injuries resulting from brain swelling or preventing recurrent stroke.

The effective surgical management of stroke requires continuous and immediately available treatment by dedicated personnel specializing in complex cerebrovascular interventions. These requirements may be best accomplished in facilities with a dedicated neurovascular center and stroke program.

EMERGENT EMBOLECTOMY FOR STROKE

Intravenous tissue plasminogen activator (IV-tPA) remains an effective medical treatment in stroke patients if administered within 4.5 hours of symptom onset. However, 20–30% of acute ischemic stroke patients have evidence of large vessel occlusion (LVO) involving a major proximal intracranial artery and the efficacy of IV-tPA is significantly reduced in these cases.[4] Furthermore, many patients do not fit the strict time window and inclusion criteria for the administration of IV-tPA and therefore are ineligible to receive treatment.

The recent refinement of endovascular catheter-based surgical techniques, which use a stent-retriever device to directly remove clots from occluded vessels and restore blood flow, have proven effective in reducing morbidity and mortality in stroke patients with LVO. Several recent randomized studies have demonstrated a significant benefit of embolectomy compared to standard medical treatment alone.[5,6] Due to improved outcomes, embolectomy in combination with IV-tPA has now become the standard of care for patients with LVO stroke. **Figure 1** demonstrates pre- and post-angiographic images in a patient who underwent emergent embolectomy and shows the dramatic improvement of cerebral perfusion following recanalization.

In addition to improving outcomes, embolectomy has less restrictive enrollment criteria and a longer time treatment window (usually 6 hours from stroke onset, though 12 or more hours in suspected basilar artery occlusion). It is estimated that the likelihood of a good outcome decreases by 10% for every 30-minute delay in recanalization from embolectomy, making efficient diagnosis and management critical. Computed tomographic angiography (CTA) can rapidly and accurately demonstrate the presence of an occlusion, and should be part of the minimum imaging workup for suspected stroke patients. A national study in 2015, led by members of our neurovascular team, identified several elements that are required to achieve timely revascularization in LVO patients.[7] Expanding upon these findings, our Comprehensive Stroke Center (CSC) developed a standardized practice to decrease procedure times and initiated a protocol for LVO patients who first presented to an outside primary stroke center (PSC) to facilitate quick treatment (**Figure 2**).[8] This method was designed to minimize waiting times for suspected LVO patients, getting them closer to intervention as soon as possible. Initial results demonstrate that when fully executed, median time from PSC arrival to CSC intervention was reduced from 151 to 111 minutes ($p<0.0001$). This protocol also made patients twice as likely to have a favorable outcome (50% vs. 25%). Evidence

Figure 1. A) AP view of left ICA angiogram demonstrating MCA occlusion (arrow).
B) AP view of left ICA post-embolectomy angiogram showing recanalization of MCA (arrow)

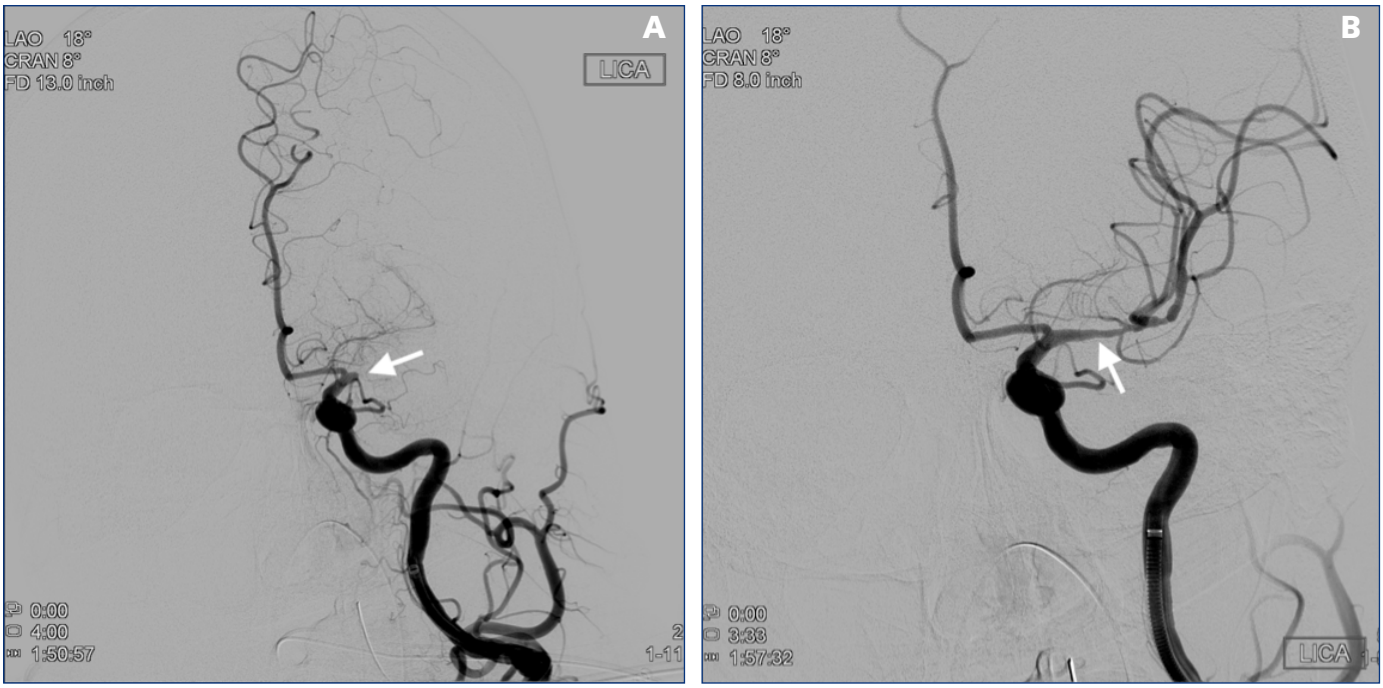


Figure 2. Protocol to expedite time to embolectomy

Outside hospitals (PSC) notify the CSC immediately upon patient arrival
Obtain a CTA in addition to non-contrast CT in all patients with suspected LVO, although this should not delay IV-tPA administration
Share imaging with CSC using a secure cloud-based platform
Activation of the neurointerventional surgical team as soon as possible based on LVO confirmation or clinical stroke severity
Additional imaging techniques, particularly those intended to physiologically select patients for embolectomy, may provide additional value but should not delay the procedure
Avoidance of routine general anesthesia during intervention

strongly supports that prompt evaluation and treatment of stroke patients with documented LVO in centers capable of performing embolectomy is crucial to obtaining optimal clinical outcomes.

DECOMPRESSIVE HEMICRANIECTOMY

Despite acute interventions such as IV-tPA and embolectomy, up to 10% of ischemic strokes result in large areas of infarction. This can lead to significant brain swelling, raised intracranial pressure (ICP), and in severe cases, life-threatening herniation syndromes. These conditions are associated with worse outcomes, as they promote further reductions in cerebral blood flow leading to additional ischemic tissue damage (secondary brain injury).

Significant edema that occurs in the supratentorial space after a stroke is referred to as malignant infarction of the middle cerebral artery (MCA).[9] This condition is associated with CT evidence of infarction involving at least 50% of the MCA territory or an infarct volume of greater than 145 cm^3 on diffusion weighted magnetic resonance imaging (MRI). Despite aggressive medical management including hyperventilation, barbiturates, hyperosmolar therapy, and corticosteroids, malignant MCA infarctions have been associated with an 80% fatality rate. However, recent multi-center trials and pooled analyses strongly support the role of surgical intervention, consisting of a decompressive hemicraniectomy (DHC), in reducing mortality and disability after malignant MCA infarction in select patients.[9,10] The surgical procedure involves removal of a large bone flap, followed by insertion of a dural patch. This results in reduced constriction of the injured brain and culminates in lower ICP and reduced risk of brain herniation.

Three European prospective, multi-center, randomized controlled trials have investigated the benefit of DHC versus medical treatment in patients with space-occupying hemispheric strokes and altered level of consciousness.[9,10,11] The DESTINY trial enrolled patients, between 18 and 60 years of age, within 36 hours of stroke onset. The trial was terminated per the study protocol when statistical significance was reached for reduction in 30-day mortality in the surgical arm (88% of patients randomized to DHC versus

47% receiving conservative therapy survived after 30 days). DECIMAL randomized 38 patients, 18–55 years old, within 24 hours of stroke onset. There was a 52.8% absolute reduction in death in the surgical cohort. Lastly, the HAMLET trial included 64 patients between 18 and 60 years of age treated within 96 hours of symptom onset and found that DHC reduced case fatality by 38%. A pooled analysis of 94 patients from all three trials demonstrated a significant increase in favorable outcome in the DHC cohort.[11] However, there was no statistically significant evidence in any individual trial regarding improved functional outcomes for patients undergoing DHC.

Current evidence suggests a role for DHC in patients younger than 60 with malignant infarction of the MCA associated with altered consciousness who are treated within 48 hours of stroke onset. For patients older than 60, surgical decompression is controversial. There are notable improvements in mortality, but many of the surviving patients have severe disability.[12]

CAROTID ENDARTERECTOMY AND CAROTID STENTING

Carotid artery stenosis causes up to 10% of all ischemic strokes. The risk of recurrent stroke is significantly higher in patients who have previously suffered an initial stroke or transient ischemic attack (TIA). It is estimated that 25% of patients presenting with a stroke are suffering from a recurrent ischemic episode. The risk of stroke is particularly high in symptomatic patients who have severe narrowing of the extracranial internal carotid artery, and several large randomized studies have demonstrated the effectiveness of carotid endarterectomy (CEA) in reducing future stroke risk in these patients. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported that in symptomatic patients with greater than 70% carotid stenosis who undergo CEA, the absolute risk of future stroke is reduced by 17% compared to medical therapy alone[13], which has been confirmed by other large studies.[14] Pooled analysis of three large trials of CEA versus medical therapy has shown a 16% absolute risk reduction when CEA was performed in patients with symptomatic stenosis of 70% or more.[15] For patients with 50–69% stenosis, there was still a benefit but to a lesser degree. Patients with less than 50% narrowing of the carotid artery do not appear to benefit from surgical intervention.

Despite the proven effectiveness of CEA, carotid artery stenting (CAS) has been promoted as an attractive, less invasive option for revascularization. Potential advantages of CAS include decreased patient discomfort and a shorter recuperation period. Early studies indicated a higher procedural risk during CAS compared to CEA, but these studies have been criticized for inadequate and non-uniform operator experience.[16] Furthermore, advances in endovascular techniques and devices used for CAS have made the procedure safer.

The largest trial to date, the Carotid Revascularization Endarterectomy versus Stent Trial (CREST) was a prospective, randomized trial of 2,502 patients comparing the efficacy of CAS with CEA.[17] The primary endpoint was the composite of any stroke, myocardial infarction, or death during the periprocedural period and ipsilateral stroke within 4 years thereafter. The study found that CAS and CEA had similar outcomes, although there were varying complications with each intervention. The rate of any periprocedural stroke or post-procedural ipsilateral stroke within 30 days was significantly higher in the CAS group than in the CEA group (5.5% versus 3.2%). However, the rate of myocardial infarction was higher in the CEA group (2.3% versus 1.0%). Overall, the CREST study demonstrated that CAS and CEA had similar short- and long-term outcomes. Carotid artery stenting may prove especially useful in cases of surgically inaccessible lesions, radiation-induced stenosis, or and in patients with severe cardiac or pulmonary disease.

To date, studies have shown that surgical interventions aimed at preventing stroke in patients who have already suffered a stroke or TIA from extracranial carotid stenosis have proven more effective than medical treatment alone. However, previous studies did not include optimal medical therapies such as statins. As advances in the medical treatment of stroke continue, it is imperative to compare these with both CEA and CAS. The CREST 2 trial currently underway attempts to compare current best medical therapy versus CEA and CAS.

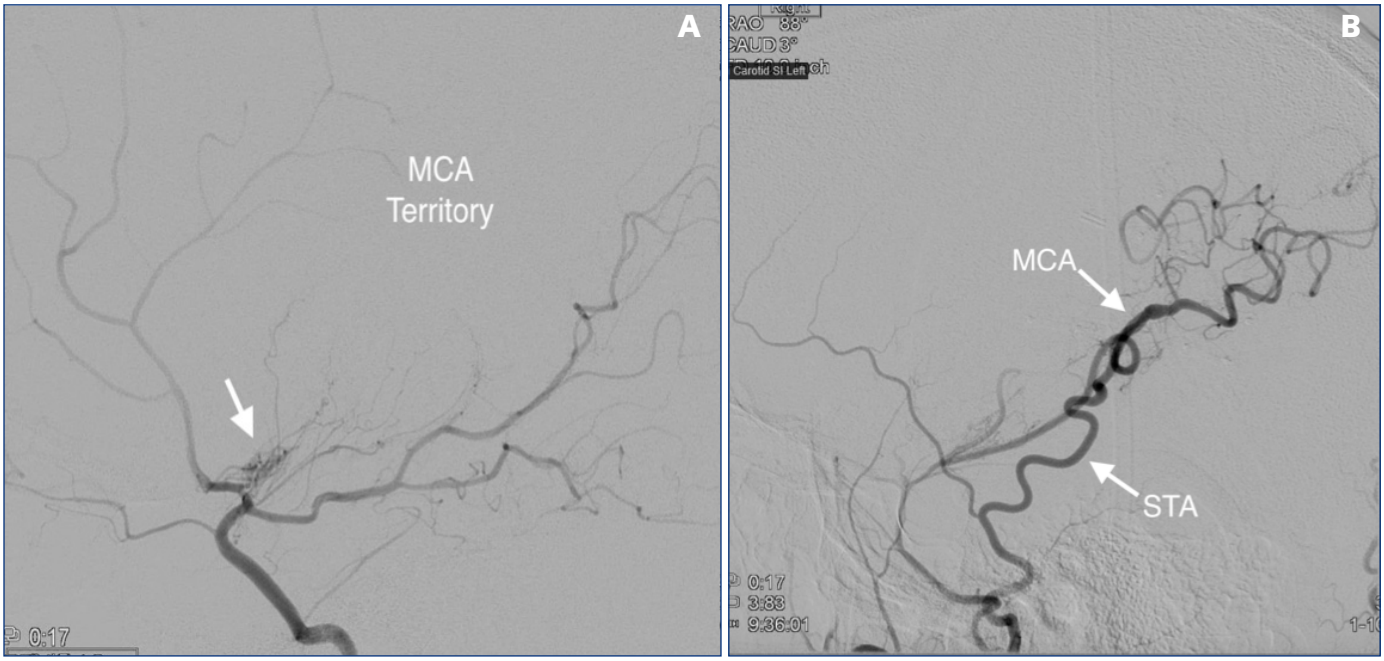
EXTRACRANIAL TO INTRACRANIAL ARTERIAL BYPASS

Extracranial-intracranial (ECIC) bypass surgery has not been shown to provide any benefit for patients with atherosclerotic carotid occlusion or carotid artery narrowing distal to the carotid bifurcation. However, in patients with moyamoya disease or syndrome, ECIC bypass has been shown to be effective at reducing stroke risk.

Moyamoya can occur in children and adults and is a cerebrovascular condition that predisposes affected patients to stroke due to progressive stenosis of the intracranial internal carotid arteries and their branches (**Figure 3a**). Genetic factors play a role, and moyamoya can be associated with other conditions such as Down's syndrome, sickle cell disease, neurofibromatosis, or previous cranial irradiation. If the disease is unilateral, or is associated with one of these conditions, it is called moyamoya syndrome. Moyamoya disease is bilateral and is not associated with other risk factors. Most patients present with stroke or ischemic symptoms with 50–75% of known moyamoya patients experiencing ischemic stroke.[18]

It has been estimated that up to two-thirds of patients

Figure 3. A) Lateral left ICA angiogram in a patient with moyamoya disease. The MCA is occluded and there is poor angiographic filling in the MCA territory. Small collateral vessels develop at the ICA terminus (arrow).
B) Lateral left ICA angiogram in a patient who underwent a STA-MCA bypass for the treatment of moyamoya disease.



with moyamoya have symptomatic progression over a 5-year period with poor outcomes without treatment. Medical therapies have not been shown to be beneficial in reducing stroke risk and surgical revascularization (ECIC bypass) is the primary treatment for moyamoya. This procedure utilizes extracranial arterial supply (usually the superficial temporal artery) which is either directly or indirectly anastomosed to an intracranial cortical artery (**Figure 3b**). Following ECIC bypass, there is a 96% probability of remaining stroke-free over the subsequent 5 years, and a meta-analysis concluded that 1003 of 1156 patients (87%) derived symptomatic benefit from surgical revascularization.[19]

FUTURE DIRECTIONS

Time to treatment is a critical factor in improving outcomes in acute stroke, and the development of additional strategies to decrease time to intervention are warranted. Field triage based on clinical severity to a Comprehensive Stroke Center can help decrease time to treatment. Perhaps the ultimate solution, Mobile stroke ambulances (composed of trained medical personnel, a CT scanner, and telecommunications) can allow ultra-rapid patient assessment, in-field administration of IV-tPA, and rapid transport to a dedicated neurovascular center. Only a few units currently exist, but preliminary reports show improvement in treatment times and clinical outcomes.

The precise time window for acute embolectomy has not been fully evaluated. A select group of patients, with defined areas of reversible ischemia, may benefit from recanalization outside of the current time recommendations. Further refinement of patient selection using advanced CT or MR based imaging will likely allow us to offer treatment to a greater group of patients. In addition, as endovascular technologies continue to improve, treatment of non-LVO stroke patients with occlusion in smaller, more distal vessels may benefit from embolectomy.

Despite treatment, many stroke patients have permanent neurologic deficits such as hemiplegia, aphasia, or visual loss. Surgical techniques to restore function are needed. Stem cell transplantation, neuromodulation and cortical stimulation techniques, and brain-computer interface technologies have potential to improve neurorestoration and warrant future investigation.

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A Comprehensive Approach to Deep Brain Stimulation for Movement Disorders

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ABSTRACT

Deep brain stimulation (DBS) is a well-established form of neuromodulation, used primarily for movement disorders such as Parkinson's disease (PD) and Essential Tremor (ET). The selection of patients who will benefit most from DBS depends on a team of clinicians from various disciplines, including neurology, neurosurgery, psychiatry, neuropsychology and rehabilitation specialists. The actual surgical procedure can take many forms. We apply a combination of multidisciplinary, team-based evaluations and intra-operative neurophysiology, test stimulation and imaging to optimize DBS therapy for individual patients.

KEYWORDS: movement disorders, Parkinson's disease, Essential Tremor, Deep Brain Stimulation, neurosurgery

INTRODUCTION

Neurosurgery for movement disorders has evolved dramatically over the past century culminating in the widespread acceptance and use of deep brain stimulation (DBS). While DBS has been and is being tested for a wide variety of neurological and psychiatric conditions (**Figure 1**), DBS is most widely used to treat the motor symptoms of two common movement disorders, Parkinson's disease (PD) and Essential Tremor (ET). DBS surgery entails the insertion of electrodes ("wires") into the brain through a small burr-hole and connected subcutaneously to a pacemaker-like battery powered device implanted in the chest wall. The implanted pulse generator battery is then programmed to deliver electrical stimulation to the brain to regularize, or at least limit, abnormal brain activity.

Figure 1. Approved and Experimental Applications of DBS.

Approved	Experimental
Parkinson's Disease	Depression
Essential Tremor	Alzheimer's Disease
Dystonia*	Tourette's Syndrome
Obsessive Compulsive Disorder*	Minimally Conscious State
Epilepsy**	Obesity
	Anorexia
	Autonomic instability due to spinal cord injury
	Neuropathic Pain
	Addiction
	Tinnitus
	Schizophrenia
	Traumatic Brain Injury
	Huntington's Disease

* Approved under FDA Humanitarian Device Exemption (HDE)
** Approved in Europe; USA FDA approval anticipated

PD affects over 1 million people in the United States (US) and the prevalence is expected to double over the next two decades. The cardinal motor symptoms of PD – bradykinesia, tremor and rigidity – are often adequately treated with medications early in the course of the disease. As the disease progresses, patients develop medication-refractory tremor, motor fluctuations (early "wearing-off" of medication benefit) and dyskinesias, in addition to non-motor symptoms such as mood, cognitive, sleep and autonomic symptoms. The efficacy of DBS for these medication-refractory motor symptoms has been well established through several high-quality, randomized controlled trials.[1-3] A meta-analysis of 22 studies demonstrated that subthalamic nucleus (STN) DBS improved motor symptoms (Unified PD rating scale, part 3) by 52%, dyskinesias 69%, off-periods 68%, and activities of daily living by 50%.[4] GPi DBS is also effective and is often favored for more severe dyskinesias or dystonias, and may have a slightly lower risk of cognitive- and mood-related adverse effects.[5-7] Non-motor symptoms of PD do not directly respond to DBS but can improve indirectly. For example, a patient with difficulty sleeping or depressed mood due to excessive slowness and stiffness may feel improvement in these symptoms after DBS because of improved overall mobility and physical comfort.

In contrast to the resting tremor of PD, ET tremor is typically postural and worsens with movement. Early in the disease, patients with ET often manage their symptoms with behavioral modifications, without medications. Over time, increasing tremor amplitude may lead to difficulty with fine motor tasks, such as handwriting, eating, drinking and dressing. Medications can reduce tremor by about 50%, but benefit wanes over time as the tremor worsens. In these patients, DBS of the ventral-intermediate nucleus of the thalamus can reduce tremor by ~80% (range ~50–100%).[8,9]

DBS for movement disorders should be considered when the quality of life becomes impaired by motor symptoms that are refractory to medical therapy. Patients should generally have preservation of mood and cognitive functions, and should be medically able to undergo surgery.

THE COMPREHENSIVE FAST-TRACK PRE-OPERATIVE EVALUATION

Even though quality of life in many domains improves with DBS, some areas may worsen. A 4-year follow up study of STN vs. globus pallidus interna (GPi) DBS showed increased risk of speech, gait, cognitive and mood adverse effects, and up to 30% of patients undergoing DBS may have negative outcomes due to inappropriate screening.[10] However, comprehensive and thorough pre-operative screening can detect problems and stratify the risk of post-operative worsening based on baseline functioning. To achieve this, our institution utilizes a unique, multi-disciplinary, pre-operative DBS clinic in which patients are evaluated by neurology, neurosurgery, psychiatry, neuropsychology and rehabilitation services (physical therapy, speech therapy and swallowing assessment); these are typically conducted at a single, convenient location in a one-day visit.

- Neurology – confirm diagnosis; ensure medical optimization; assess severity of disease and appropriateness for surgical intervention; identify motor symptom(s) to be treated by surgery; discuss unilateral vs. bilateral; discuss target selection; discuss risks/benefits;
- Neurosurgery – discuss surgical options; discuss surgery-related risks; assess overall medical condition to undergo surgery; discuss contraindications for surgery;
- Psychiatry – screen for mood and behavioral problems; ensure chronic, underlying mood issues are adequately treated; discuss risk of mood and behavioral problems with DBS;
- Neuropsychology – conduct a thorough assessment of cognitive functions; compare baseline performance to peers; discuss risk of cognitive decline after DBS;
- Physical therapy – assess baseline gait and balance; make recommendations to optimize gait before DBS; discuss risk of worsening after DBS;
- Speech therapy – assess baseline speech function; make recommendations to optimize speech before DBS; discuss risk of worsening after DBS;
- Swallowing assessment – assess baseline swallowing function; make recommendations to optimize swallowing function before DBS; discuss risk of worsening after DBS.

The multidisciplinary team discusses the candidacy of each patient in a meeting at the conclusion of the clinic. The patient is rated on a scale of low, medium or high risk by each specialist based on their evaluations, and the final recommendation is communicated to the patient.

DBS SURGERY: BENEFITS, RISKS AND OPTIONS

The primary goals of DBS surgery are safety and accuracy. The risk profile of DBS surgery has been extensively studied.[11-13] Some risks, such as hemorrhage, are significant and potentially life threatening, but are fortunately rare. Other risks include seizure, hardware infection, discomfort, hardware failure and suboptimal electrode placement (**Figure 2**). This last risk is minimized by careful design and meticulous execution of the surgical procedure. There are many different ways to "do" DBS surgery. Individual surgeons often develop customized, stereotyped workflow preferences to promote reproducibly good results.

DBS is currently approved by the FDA to be implanted while the patient is awake in order to confirm neurologic benefit without intolerable side effects. Nonetheless, there is a growing utilization of asleep procedures for the implantation of DBS as an off-label approach. But even within these categories of "awake" vs. "asleep" there are many different ways in which surgeons can perform the procedure.

The main technical goal is accurate placement of electrodes within a target, typically with about 1mm precision. Classically, this is achieved with the use of a stereotactic frame affixed to the head while a scan (MRI or CT) is obtained. The target location is then computed with respect to the frame coordinates, and these x, y and z values are manually dialed into an arc attached to the frame. More recently, some centers including ours, have switched to using a different system consisting of a patient-customized 3D-printed stereotactic platform (FHC Inc, Bowdoin, ME). Here, temporary skull screw fiducial markers are implanted a week prior to electrode implantation. These then serve as the reference coordinate system for selecting targets and trajectories by co-registering a CT scan showing these fiducials with a "clean" pre-operative MRI. Computer assisted design (CAD) software then designs a frame specifically for that patient and the planned trajectories. While adding an extra step, this approach reduces the potential for human or mechanical error (because the targets and trajectories need not be manually transferred to a mechanical frame, which itself would have moving parts and mechanical backlash). It also may increase patient comfort during awake procedures,

Figure 2. Major Surgical Complications of DBS.
These data are summarized from Zrinzo et al., and Boviatsis et al.[12,13]

Complication	Incidence: Mean (range)
Radiographic Hemorrhage	6.5% (0-34.4%)
Symptomatic Hemorrhage	2.6% (0-8.9%)
Infection	5.4% (0 - 15.2%)
Electrode Breakage	4.2% (0 - 15.2%)
Electrode Misplacement	5.4% (0 - 18.8%)

because it does not apply intense pressure to the skull as does a classical stereotactic frame.

In an awake procedure, microelectrode recordings are typically used to map the target region using a combination of neurophysiological patterns and neuronal responses to interactive patient testing. Once the target has been characterized, the permanent DBS electrode lead is placed according to those findings and test stimulation is delivered. Because the patient is awake, neurologic benefit with no or minimal side effects can be assessed. If these results are satisfactory, the lead is locked in-place. If results are suboptimal, a different location can be assessed for lead implantation.

Awake procedures are feasible because only the skin perceives pain (although some patients will report brief discomfort upon passing through the dura); generous infusion of local anesthetic typically eliminates most discomfort. PD patients, because they are off medications for neurologic assessment during the procedure, typically experience discomfort mostly due to the primary disease symptoms, such as rigidity and dystonia.

The need for empirical assessment of lead placement derives from two main factors: first, once the skull is opened for insertion of electrodes, there may be an egress of cerebrospinal fluid (CSF) and an ingress of air. Good surgical technique aims to minimize these factors but even a slight change in skull contents can cause brain shift of a magnitude which, although small in absolute terms, may diminish surgical accuracy in a clinically meaningful way.[14,15] Second, there is debate in the field over the question of whether the visually identified "optimal" target on imaging is truly the best target for that individual patient, both in terms of maximizing benefit and minimizing side effects. Therefore, empirical assessment of potential targets adds a level of certainty that is otherwise unavailable.

The first factor, brain shift, can be addressed by the use of intra-operative imaging. Indeed, asleep procedures typically use this as the primary method of achieving accurate electrode placement. Many major academic centers now have intra-operative MRI suites which allow visual confirmation of targeting during the electrode implantation procedure. However, many centers use intra-operative CT imaging; the brain tissue resolution of CT, especially intra-operative CT, is less than that of MRI, and so these CT scans are often co-registered with pre-operative MRI. Because most co-registration algorithms are "rigid" (in the sense that they cannot account for brain movement with respect to the skull), brain shift is potentially a limitation with this approach. Yet even procedures performed with intra-operative MRI cannot address the second factor, that is, whether the visually identified target truly represents the optimal brain circuit for patient-specific neuromodulation. So far, several studies have compared results of awake vs. asleep DBS and, according to the fairly course measures used, there do not seem to be major differences.[16-18] However, one study has observed that thresholds to motor side effects may not be predictable based upon the imaging alone,[19] and so clinical assessment of these side effects in an awake patient may in some cases yield a larger available dynamic range of stimulation and thus potentially more optimal results.

Most centers implant the battery in a delayed fashion, typically one week later. In the case of awake DBS surgery, this allows continuous neurological monitoring of the patient without a period of general anesthesia for battery implantation.

DBS SURGERY AT RHODE ISLAND HOSPITAL

Our preference is to perform DBS as an awake procedure in order to maximize the possibility of obtaining optimal results for each individual patient. We typically perform microelectrode recordings along three tracks on each side, aligned according to the dimension of highest anatomical-radiographic uncertainty about the target. The best track in terms of neurophysiological patterns and responses is selected first for test stimulation using the permanent DBS electrode. If results are good, the electrode is locked in-place at that location; otherwise additional locations are tested in order of the quality of their neurophysiological signals. In addition, we perform most of our procedures with the aid of an intra-operative CT scanner. This adds an extra level of safety and certainty regarding our targeting, should there be any question about the signals we are observing or about the patient's condition.

Many of our procedures are performed as a collaboration between our lead movement disorders neurologist and functional neurosurgeon. Both have extensive experience interpreting neurophysiological signals and assessing clinical responses. This team-based approach affords an added level of confidence about the quality of these procedures and the ultimate clinical benefit.

CONCLUSION

DBS is potentially a valuable therapy for patients whose movement disorders are poorly managed on medications alone. Comprehensive, multidisciplinary evaluation of patients pre-operatively maximizes good outcomes by screening out those who are more likely to decline after surgery. The surgery itself can be performed using a variety of approaches, but ultimately, surgical safety and precision are the main goals. Throughout this process, a team-based approach works to ensure the best course of treatment for each patient.

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Rhode Island Hospital's Contribution to the Field of Endoscopic Spine Surgery

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ABSTRACT

The first academic program in endoscopic spine surgery in the United States opened its doors at Rhode Island Hospital in 2012. Published advances in the field since its inception have included treatments for a myriad of pathologies including lumbar and thoracic disc herniations, spondylolisthesis, spine tumors as well as treatments for complications of other spinal procedures including spinal fusion, kyphoplasty, and total disc replacement. In this issue of the *Rhode Island Medical Journal* we summarize the history of the procedure as well as some of the interesting progress going on in this field in Rhode Island.

KEYWORDS: endoscopic discectomy, minimally-invasive, transforaminal

INTRODUCTION

"Necessity is the mother of invention," is a proverb that dates back to 16th century England and describes well the challenge that faces those practicing medicine today and the generation who follow us. With health care costs rising, how will we face the upcoming challenge of providing care to our patient population?

Patients who would have had open-heart surgery in the past, are now candidates for outpatient interventional cardiology procedures. Complex intracranial vascular pathologies and skull base tumors that would have been treated with lengthy intracranial surgeries in the past are now treated with interventional radiology procedures and stereotactic radiosurgery. But what is being done in the field of spine surgery? For the answer to that question, much of the world looks to the research coming out of the institution that is at the center for publishing the latest advances in endoscopic spine surgery: The Department of Neurosurgery at Rhode Island Hospital and Warren Alpert Medical School of Brown University.

PERCUTANEOUS LUMBAR ENDOSCOPIC DISCECTOMY — THE HISTORY

The natural history of surgical techniques seem to be an evolution of "big to small." But the history of endoscopic spine surgery is really an evolution of "small to big." Early practitioners developed needle-based procedures to try to decompress the disc nuclear material to relieve back and radicular symptoms. Needles got bigger and the first endoscopic views of a herniated disc were published by Kambin in 1988,[1] and the first reported introduction of a modified arthroscope into the intervertebral disc space was reported by Forst and Hausman in 1983.[2]

In 1990, Parvis Kambin described a triangular safe zone bordered by the exiting root anteriorly, the traversing root medially, and the superior endplate of the lower lumbar vertebra inferiorly.[3] The anatomic description of this safe zone allowed the advancement of the field of endoscopic spine surgery to outgrow the technique of percutaneous nucleotomy which was limited by the use small needle-like instruments. Kambin's triangle was a working corridor that allowed the introduction of larger instruments and working channels to be introduced even closer to foraminal pathology without injuring the exiting nerve.

With the idea of a safe working triangle between the exiting and traversing roots in the foramen, the field of endoscopic spine surgery started to leave the safety of the indigo carmine blue stained nucleus and explore the foramen. An angled lens scope was used by Mayer and Brock in 1993 that allowed more dorsal visualization of annular pathology.[4] Foraminoscopy was described by Mathews in 1996[5] and Ditsworth in 1998.[6] Kambin and Zhou in 1996 described lumbar nerve root decompression by annulectomy and decompression of lateral recess stenosis with the use of forceps and trephines.[7] Schubert and Hoogland in 2005 described their technique for transforaminal endoscopic removal of a sequestered disc fragment using reemers to expand the foraminal window by removing the ventral portion of the superior articular process.[8] Multichannel endoscopes with larger working channels were introduced by Tsou and Yeung in 1997[9] and Reuten et al in 2007.[10] What would follow would be multiple reports of the clinical success of direct endoscopic decompression of foraminal pathology: Yeung and Tsou in 2002,[11] Reutten el al 2007,[10] Reutten et al 2008,[12] Jasper et al 2013.[13]

THE CLINICAL SUCCESS OF ENDOSCOPIC SURGERY

Seven papers published between 2013 and 2014 on awake endoscopic spine surgery indicated the possible efficacy of this procedure performed through a 5 mm incision for the

treatment of Lumbar radiculopathy.[13-19] For patients with single level disc disease, the success rate reported was an 84% reduction in pain, and for patients with multi-level pathology, the average pain relief was 70%.[13] In a series of 50 consecutive patients over the age of 75, over 80% of patients described either a "good" or "excellent" outcome: many of these patients were offered fusion surgeries at other centers before being considered for endoscopic surgery.[15] Patients who underwent endoscopic treatment for radicular symptoms due to spondylolisthesis reported a 72% reduction in pain – up front instrumented fusion is currently a mainstay treatment for this pathology.[18] **Figure 1** displays in a step-by-step manner how the endoscopic technique is used to treat a patient (former NFL player) with lumbar radiculopathy in the setting of spondylolisthesis.

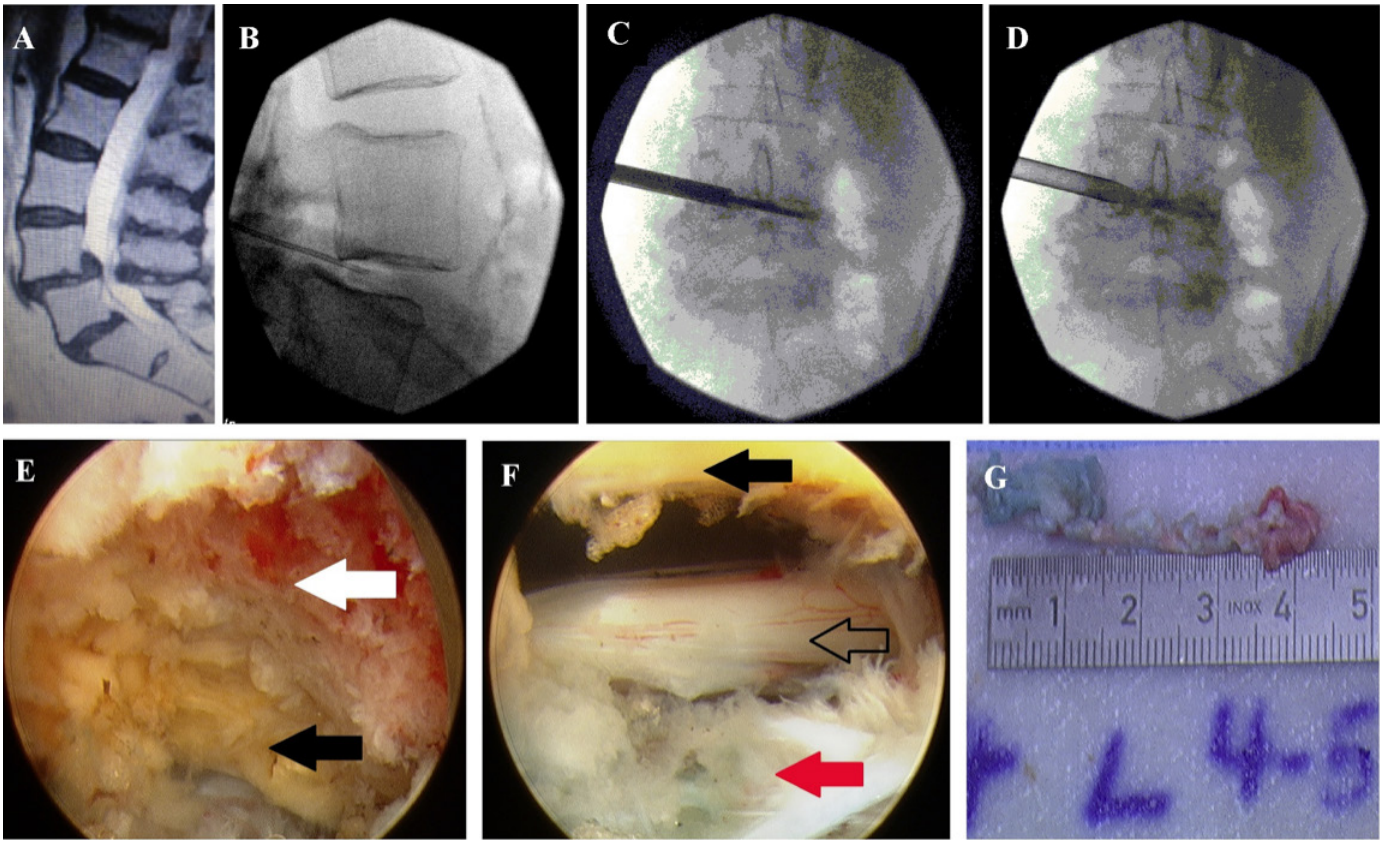
The mainstay for the treatment of lumbar degenerative pathology is conservative treatment with weight loss uniformly recommended for lumbar radicular symptomatology in the setting of morbid obesity. But the success of conservative management in reducing obesity is difficult. 82 patients in one study published showed pain reduction close to 70% for patients with BMIs between 30 and 40 but closer to 45% for patients with BMIs over 40.[19]

The first paper in the world describing the feasibility and technical steps that enable a surgeon to circumnavigate and reach into the epidural space for intracanal pathology was also published in these period, opening the possibility for treating more than routine herniated lumbar discs.[14]

FAILED BACK SURGERY

There has been a 15-fold increase in complex spinal fusion procedures in the past decade. But innovative treatment strategies for treating the complications from these procedures has lagged. In 2015 a series of 3 papers have described innovative minimally invasive treatments for herniated

Figure 1.



A. Preoperative sagittal T2 MRI showing pathology of L4-5 spondylolisthesis.

B. Spinal needle entry into L4-5 disc on lateral fluoroscopic view.

C. Small dilator and large crown reamer in L4-5 foramen during foraminoplasty on AP fluoroscopic view.

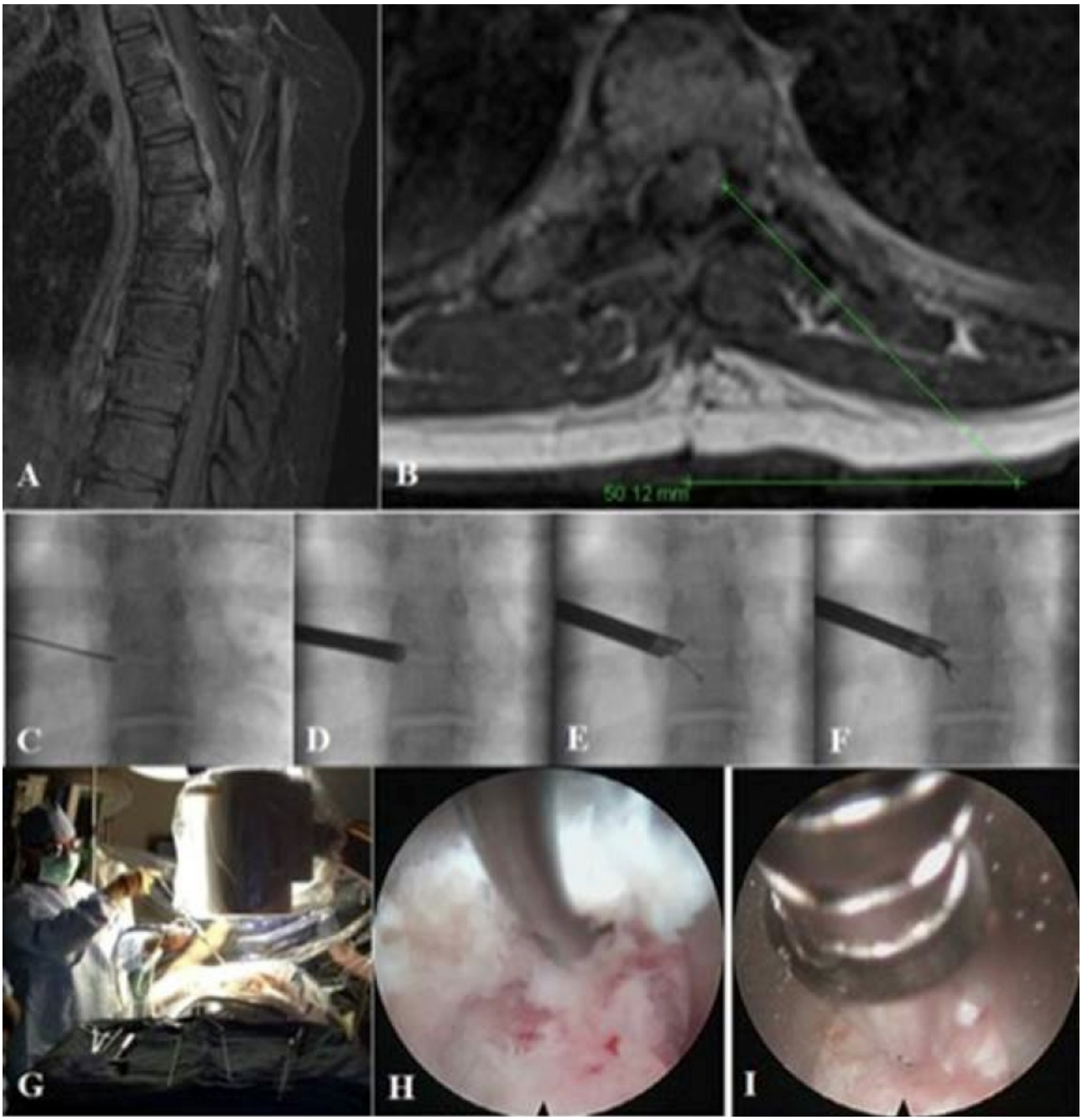
D. Bevelled working canulla in L4-5 foramen on AP fluoroscopic view.

E. Endoscopic view of the residual reamed ventral border of the SAP (white arrow) and ligamentum flavum (black arrow).

F. Endoscopic view of the ligamentum flavum (black arrow), traversing nerve root (black border arrow), and herniated disc (red arrow).

G. Intraoperative photograph of the L4-5 herniated disc fragment removed with an endoscopic forceps during the procedure.

Figure 2.



A. Sagittal T1 MRI with gadolinium of the thoracic spine demonstrating recurrence of the ventral extradural tumor.

B. Axial T2 MRI with gadolinium showing preoperative planning for spinal needle trajectory for transforaminal approach.

C. Intraoperative AP fluoroscopic image demonstrating passage of spinal needle into the left T5-6 neural foramen.

D. Intraoperative AP fluoroscopy showing reaming of the superior articular process.

E. Intraoperative AP fluoroscopic image showing working channel within the left T5-6 neural foramen, along with ball probe passed to confirm position of T6 pedicle.

F. Intraoperative AP fluoroscopy confirms position of malleable curved grasping forcep.

G. Patient positioned prone with working channel 5cm lateral to midline and communicating author shown manipulating bendable grasper in working channel.

H. Intraoperative endoscopic view with ball probe pushing on the dorsal aspect of the tumor capsule.

I. Intraoperative endoscopic view demonstrating the bendable grasper reaching inside the tumor capsule.

discs after fusion,[20] lumbar radiculopathy after instrumented fusion,[21] and lumbar radiculopathy after interbody fusion.[22] All of these "rescue" or "salvage" procedures were performed without general anesthesia on outpatients.

SPINAL TUMORS

In the international journal Clinical Neurology and Neurosurgery in July 2015, the first report in the world of performing a resection of a spinal canal tumor endoscopically in an awake patient was reported.[23] The case was performed on a 15-year-old patient who underwent the procedure in order to avoid a complex instrumented fusion procedure. **Figure 2** shows the patient's MRI, intraoperative x-rays, a photograph from the operating room, and endoscopic images from the surgery. The NBC news story of this historic surgery was shared around the world.

THORACIC DISC SURGERY

Surgery for the treatment of thoracic disc herniations has for years meant operating through a thoracotomy to remove disc pathology and fuse the spine. In 2016 the first 2 descriptions of technical nuances for performing awake endoscopic surgery for thoracic and thoracolumbar disc herniations were published in the Journal of Neurosurgery[24] and World Neurosurgery.[25] The advances in this area were the result of a collaboration between physicians at Rhode Island Hospital and surgeons in Germany and the Netherlands.

ENDOSCOPIC SURGERY TO TREAT OTHER SPINE SURGERY COMPLICATIONS

Kyphoplasty is a treatment for painful compression fractures of the osteoporotic spine. Cement leakage can be a disastrous complication that results from the procedure because an open laminectomy and instrumented fusion can be necessary to remove the extravasated cement. This surgery is made even more complicated by the fact that these osteoporotic patients are not favorable candidates for instrumented fusion procedures. In 2016 the first paper in the world describing an endoscopic solution for this problem in an awake patient was published.[26]

Artificial lumbar discs or total disc replacement surgery is performed more popularly in Europe than in the United States because of difficulty getting this non-fusion technology approved by insurance carriers. Patients interested in this surgery in the U.S. will sometimes travel to Europe for the procedure. Approximately 10% of these surgeries ultimately go on to need instrumented fusion due to complications from the original implant. In 2016 the first endoscopic treatment for a total disc replacement surgery was published in the Journal of Neurosurgery.[27] The surgery in Germany to place the artificial disc dislodged a fragment of bone that caused nerve compression. With the patient awake, an endoscope was used to drill out the fragment to free it and then remove it. The patient was able to avoid a laminectomy and fusion and ultimately benefited from a successful total disc replacement. The future of total disc replacement surgery in the U.S. remains to be seen but certainly endoscopic surgery may have a role in treating the complications seen in this procedure.

CONCLUSION: THE FUTURE OF SPINE SURGERY

Laser spine surgery that is advertised ubiquitously is not, in fact, performed with a laser. It is, in fact, an aggressive marketing program for a minimally invasive open surgical procedure that is performed with the patient under general anesthesia. Endoscopic spine surgery is performed with a working channel rigid endoscope, high definition camera, drills, trephines, articulated graspers, and sometimes, yes, a laser. But it has at its endpoint, the same surgical goal as many more open surgical spine procedures. The essence of what makes it different and the heart of what may be at the future of spine surgery is moving the point of visualization from the surgeon's eye to the endoscopic camera, which allow us to move the "eye's" lens remotely to the site of the surgical pathology. Innovation that brings the surgeon's "eye" to within millimeters from the patient's pathology allows complex spine surgery to be performed in awake patients through a tube the size of a pencil.

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Updates On Chimeric Antigen Receptor-Mediated Glioblastoma Immunotherapy

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ABSTRACT

Glioblastoma multiforme (GBM) is the most malignant of the primary central nervous system (CNS) neoplasms, accounting for nearly 80% of all primary brain tumors and is associated with high morbidity and mortality. Immunotherapy is proving to be a fertile ground for next-generation GBM therapy, with large translational research projects and clinical trials currently underway. One particularly promising area is the chimeric antigen receptors (CARs) in the context of lymphocyte adoptive cell therapy (ACT), which has achieved success in the treatment of hematological malignancies. In this review, we will discuss CARs and review current challenges facing their use in GBM therapy.

KEYWORDS: glioblastoma, immunotherapy, CAR

INTRODUCTION

Glioblastoma (GBM) is the most common and most malignant of all the primary cancers of the central nervous system. It is an aggressive and heterogeneous cancer characterized by densely packed pleomorphic cells with high mitotic activity, necrosis, and high degree of vascularization. GBM most commonly strikes older individuals, with a slight predilection for males over females. The current standard of care therapy for GBM, which consists of maximum allowable surgical resection, focal beam radiation, and chemotherapy with Temozolomide, is not curative. Survival remains abysmal, as fewer than 10% of patients survive after 5 years. The difficulty in treating GBM arises from the cancer's cellular heterogeneity, their diffuse infiltration into the brain, protection provided by the blood brain barrier, the chemo- and radiotherapeutic resistance and regenerative capacity of glioma stem cells [1-3].

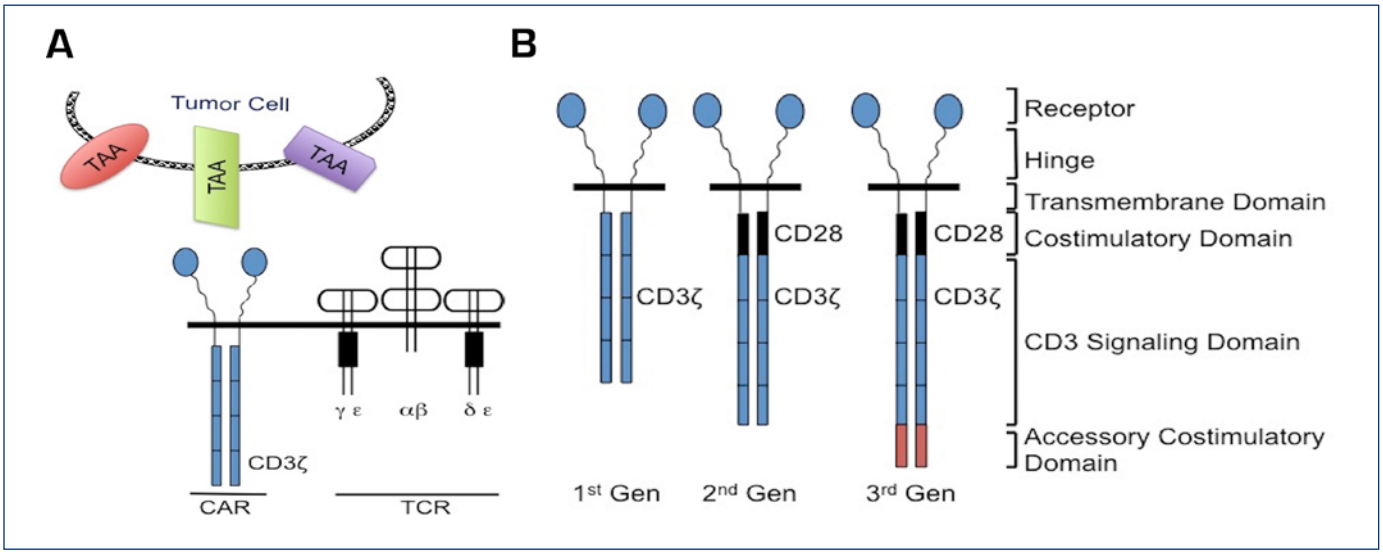
With these barriers in mind, immunotherapy may offer an avenue of treatment for GBM that may be both safer and more effective. Immunotherapy offers a targeted approach to treatment, via utilization of unique molecular and genetic signature of tumor cells. It has been noted in several malignancies that cancer patients who had more activated immune systems seem to have better outcomes. Thus, techniques have been developed to enhance a patient's immune response against GBM. Immunotherapy encompasses a wide variety of techniques, which are beyond the scope of this review. The most developed of these immunotherapeutic methods is the use of monoclonal antibodies (mAbs). While mAbs have been developed against multiple GBM-specific antigens, they have not yet enjoyed wide success due to a combination of tumor and host factors. Other areas of immunotherapy for GBM under current active investigation include dendritic cell vaccines derived from lysed tumor cells, immunomodulatory checkpoint inhibitors, and engineered T-cell based therapies, which will be the focus of this paper.

CARs

Recently reported success of clinical CAR-T cell therapy of GBM [4] has generated hope in the use of this technology for GBM immunotherapy. CAR-T cell offers an attractive alternative to a limitation inherent in the other T-cell receptor (TCR) dependent cellular immunotherapeutic approaches, namely, that of MHC *independent* antigen presentation. Precluding the need for TCRs, CAR-T cell strategies greatly improve the diversity of antigen targets, and bypasses a mechanism of GBM immune evasion through MHC down-regulation [5]. Engineered CAR-Ts have much higher affinity to their targeted antigens than T cells. The antigen binding can be further modulated in subsequent development of the CAR-T cells to prevent overly strong immune responses that can result in the potentially fatal cytokine release. Since CAR-Ts are artificially constructed from functional polypeptide domains, the receptors can be configured by the addition of new effector domains, adding novel features to the CAR-T cell. Thus, CAR-T cells can be precisely tailored to the goals of therapy, and be individualized to the particular patient and clinical scenario.

CAR-Ts are very similar to TCR in structure and function, as they both combine an antigen-binding domain with downstream signal transduction domains. The antigen-binding domain of CAR can be a heavy chain and the light chain fusion protein (scFv) of a prototypical antibody, and the most common design is an scFv domain joined to a transmembrane CD3 domain. This section of the protein is physically linked to an intracellular CD3- ζ signaling domain and costimulatory domains that couple extracellular antigen recognition to intracellular signal transduction, which subsequently affect T-cell immune response (**Figure 1**). One can also look beyond the traditional antigen-antibody paradigm

Figure 1. Chimeric Antigen Receptors (CARs): Design of CARs versus TCRs (A), and evolution of CARs (B).



for ligand-binding motifs. For example, the natural receptor of a particular tumor specific antigen may be utilized as the ligand-binding domain, thus permitting CARs to bind to non-immunogenic peptides as well as carbohydrate and even lipid-based antigens.

The MHC independent nature of CAR-mediated antigen presentation and their inherent modular properties engineered into these cells make the receptors far more versatile than TCRs. After the CAR design is decided upon, the underlying genetic sequence that encodes for the CAR is encoded and transfected into the T-cell usually via a viral vector. The modified T-cells are then expanded *in vitro* and subsequently re-introduced back to the patient [6, 7].

CARS FOR GBM IMMUNOTHERAPY

Initially achieving success for the treatment of hematologic malignancies, adoptive CAR-T cell therapy is now under active investigation for a variety of solid tumors, including GBM. Presently, CARs have been developed against six GBM-associated antigens, with four having passed animal trials and currently in clinical trials. These include: EGFRvIII [8-13], IL13Rα2 [4, 14-16], HER2 [17, 18], and EphA2 [19]. Epidermal growth factor receptor, or EGFR, is directly implicated in GBM through either over-amplification of the gene (HER2/neu) or through constitutively active mutant variants, both of which result in increased growth and survival of the GBM tumor cell [10]. EphA2 is a cell-surface receptor that regulates proliferation, migration and angiogenesis, which ultimately affects the invasive and metastatic potential of GBM [20, 21]. IL13Rα2 is a unique decoy receptor for IL13, and binding of the cytokine to the decoy receptor terminates the chain immuno-stimulatory signals that lead to the generation of an appropriate immune response [22].

Currently, there are three major clinical trials involving CAR-T cells against EGFRvIII on GBM. All three are in preliminary stages, only one is currently recruiting participants, whereas the two others have not yet started or have suspended patient recruitment [23-25]. There have been two CAR-T-cell clinical trials involving the use of IL13Rα2 as the target and two clinical trials involving anti-HER2 CAR-T cells. Lastly, there is currently one clinical trial with the goal of establishing EphA2 as a safe and feasible CAR-Target, which is presently in recruitment [30] (**Table 1**).

Table 1. List of CAR-T cells currently undergoing clinical trials.

Clinical Trials	CAR Target(s)	Current Status	Special Notes
NCT01454596	EGFRvIII	Suspended recruitment	Status unclear
NCT02664363	EGFRvIII	Not yet started recruitment	Neoadjuvant ACT
NCT02209376	EGFRvIII	In recruitment	Safety/feasibility study
NCT02575261	EphA2	In recruitment	Safety/feasibility study
NCT02442297	HER2	Not yet started recruitment	Inhibitory CAR model
NCT01109095	HER2	Ongoing, not accepting new patients	Modification of preselected CMV specific T cells
NCT01082926	IL-13Rα2	Completed	T cells also engineered with HyTK suicide switch and resistance to steroids
NCT02208362	IL-13Rα2	In recruitment	Safety/feasibility study

LIMITATIONS OF CARS FOR GBM IMMUNOTHERAPY

So far, the use of adoptive CAR-T cell therapy for GBM has not yet enjoyed the level of success seen in the treatment of lymphoproliferative disorders such as in ALL and CLL. This is due to a combination of tumor and host factors, the most relevant of which is GBM's ability to evade immune surveillance and even achieve active suppression of the local immune response. GBM can actively shield itself from immune assault by concealment of targeted cell-surface antigens (including MHC proteins) and active secretion of various ligands that induce T-cell apoptosis and further inhibit the immune response [31-33]. Furthermore the intrinsic cellular heterogeneity of GBM provides further passive immunoresistance and immune escape mechanisms.

OVERCOMING THE LIMITATIONS

One of the most obvious ways to counteract the problem of tumor heterogeneity is the use of CAR T cells that recognize multiple tumor antigens. By designing CARs with multiple distinct antigen-binding domains and through the introduction of multiple different CARs onto the surface of a single T cell, there is more opportunity to overcome intratumor antigen heterogeneity [34]. CAR-T cells can be further modified to render them unresponsive to the various immunosuppressive and apoptotic-inducing signals secreted by GBM [35, 36]. In addition, checkpoint inhibitors such as nivolumab, which suppress such interaction between the inhibitory ligand and its associated receptor on the T cell, can be given in conjunction with CAR-T cell administration to impair GBM's immunosuppressive capabilities [37-39].

Further engineering of the CAR-T cells allows for potential improvement in their immune response. Examples include the addition of co-stimulatory domains to the intracellular portion of the CAR construct to amplify the immune response generated by the CAR-T cell (**Figure 1B**). Further amplification may include designing CARs that can independently secrete critical pro-inflammatory cytokines [40], priming CAR-T cells with viral particles, and/or the appropriate pre-selection of T cells for CAR engraftment, such as the use of particular T cell subsets that have greater capacity to replicate *in vivo* after exposure to GBM antigens. In addition, CAR-T cells can also be rendered resistant to various chemotherapeutic agents, so that chemotherapy may be given in conjunction with adoptive T cell therapy [41-43].

One of the major issues confronting CAR-T cells is stimulating the appropriate level of immune response that kills the tumor, while causing minimal damage to normal tissues. While *in vitro* CAR-T cells demonstrate specificity for target antigen, *in vivo* studies have shown that CAR-T cells have resulted in systemic toxicity. Three classes of toxicities are seen with CAR-T cell therapy. Off-target-off-tumor toxicity is cross-reactive due to qualitative defects in scFv design and/or production. Since these antibody fragments are often derived from murine immune systems, human toxicity resulting from murine derived antigen cross-reactivity will likely become less of an issue. A more serious problem is the on-target, but off-tumor toxicity observed with CAR-T cell therapy, as the tumor antigens are sometimes expressed in or cross react with non-neoplastic cells [44]. One way to offset this type of toxicity is designing a CAR-T cell that becomes activated only when it interacts with multiple different GBM antigens on the surface of the glioma cell [45, 46]. Because there is a dearth of antigens that are only expressed in GBM and nowhere else, investigators have turned to utilizing antigens that are highly expressed in glioma cells, but are also expressed at lower levels elsewhere in the body. By modulating the affinity of the CAR so that T cell activation occurs only after a defined threshold of binding is reached between the T-cell and its target, this type of toxicity may be abrogated [47]. The last category of toxicity due to a dysregulated immune response can range from a mild systemic flu-like illness to a massive overwhelming cytokine release that can result in multiorgan failure, and ultimately death. This may be addressed through the introduction of safety suicide switches into the adoptive T cell, which, when turned on by an exogenous signal (usually introduced by a clinician), results in the death of the T cell.

CONCLUSION

The unique modular nature of CARs allows them to be tailor-made to match the need of any particular clinical scenario and nature makes CAR-T cell therapy a good potential complement to existing conventional therapies. Protocols are in place to determine their efficacy when used in conjunction with Temozolomide. However, the full potential of CAR-T therapy will not be realized until they are designed for the individual patient. Because technology now exists to allow for rapid genome-wide sequencing of individual cells, CAR-T cell therapy allows for targeting of targets unique to the individual cancer patient. And as the patient's GBM evolves over time, due to selection pressure during therapy, new CAR-T cells may be prepared and reintroduced to the patient in response to the antigenic shift. Of course, to identify these shifts, fresh tumor samples and genetic sequencing will be required to identify antigenic changes over time in the tumor organ.

Currently, there are still major challenges facing CARs that prevent their widespread use; however, solutions are in development that address most of these hurdles. With the cost of genomic sequencing rapidly decreasing due to technical innovations and economy of scale, a personalized approach to glioblastoma therapy is nearing. CAR-T cells represent a novel therapeutic option that may soon be ready for widespread use in this and other diseases.

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Recent Advances in the Treatment of Gliomas – Comprehensive Brain Tumor Center

STEVEN A. TOMS, MD, MPH; NIKOLAOS TAPINOS, MD, PhD

ABSTRACT

Gliomas are a class of primary brain tumors arising from the supporting structures of the brain, the astrocytes and oligodendrocytes, which range from benign lesions to its most malignant form, the glioblastoma. Treatment for these lesions includes maximal surgical resection, radiotherapy, and chemotherapy. Recently, novel therapies such as immune modulatory therapies and electrical field treatment of the most malignant form, the glioblastoma, have shown promise in improving survival. We will review recent advances in clinical trials, explore the role of multimodal care in brain tumor therapy, as well as explore advances in molecular biology and nanotechnology which offer new hope for treatment of this class of disease.

KEYWORDS: glioblastoma, immunotherapy, tumor treating fields, nanotechnology, drug delivery

INTRODUCTION

Gliomas are a class of tumors which arise from the supporting structures of the brain, astrocytes and oligodendrocytes. They range in behavior from benign lesions with distinct borders such as juvenile pilocytic astrocytomas, curable with surgical resection alone, to more diffusely infiltrative cancerous lesions, astrocytomas, oligodendrogliomas, and glioblastoma, all uniformly lethal in a matter of several to many years. In this brief review, we will focus on the most lethal of these, the glioblastoma (GBM).

GBM is the most devastating primary malignancy of the central nervous system in adults. Currently, standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gray) with concomitant daily temozolomide chemotherapy, followed by maintenance treatment with temozolomide for 6- to12 months[1]. However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials[1-4]. The reported 2- and 5-year survival rates are 27% and 10%, respectively. During the last decade, all attempts to improve outcomes for patients with glioblastoma have failed when evaluated in large randomized trials[2-6]. Most recently, the development of electric current loco-regional antimitotic therapy ("tumor-treating fields") led to the first reported survivals exceeding 20 months[7].

In the United States alone, 12,000 new cases of GBM are diagnosed each year[8]. One reason cited for the failure to improve survival has been the presence of a robust blood-brain barrier within the tumor, which impedes delivery of traditional cytotoxic and novel molecular therapies[9]. Most chemotherapeutic agents are hydrophilic, and do not penetrate the blood brain barrier well. Attempts to deliver chemotherapeutic molecules into the brain have included both osmotic, chemical, and ultrasound mediated opening of the blood brain barrier to improve drug delivery, but none have improved clinical outcomes[10]. A novel method to bypass this barrier, (i.e., convection enhanced delivery), met with success in delivering high drug concentrations of hydrophilic drugs to brain tumors and led to several clinical trials. However, convection-enhanced delivery has not yet been associated with improved clinical response. This failure has been ascribed to inhomogeneous delivery of the drug to the entire tumor, as well as difficulty in modeling the bulk flow of infusate :drug to the tumor volume[11,12].

CARING FOR THE GLIOMA PATIENT – THE ROLE OF THE MULTIDISCIPLINARY CLINIC (MDC)

The care of the patient with glioma is nuanced and complex. Patients with a new diagnosis of glioma are often confused and required to make complex decisions about their care in a relatively short period. Unfortunately, the knowledge required to guide a patient through that decision making process is usually beyond the ability of the primary care provider or even the general medical or radiation oncologist. This is where a modern MDC staffed with neuro-oncologists, neuro-oncological surgeons, radiation therapists, and their support teams are crucial.

At an initial visit, the patient meets the MDC staff including nurses, social workers, and the intake team. All data are reviewed and the MDC team establishes a coordinated care plan. If necessary, advanced imaging such as functional magnetic resonance imaging (MRI) or diffusion tensor imaging is performed to aid in preparations for surgery (**See Figure 1**). Further neuropsychological evaluation may be necessary for some low-grade gliomas or those in or near speech and language areas. Intraoperatively, neurophysiological monitoring

Figure 1. (A) The red arrow points to a small low-grade glioma in the medulla of the brainstem.
(B) DTi was used to show that the descending fibers do not traverse the lesion, but rather are displaced (yellow arrow) by the lesion.

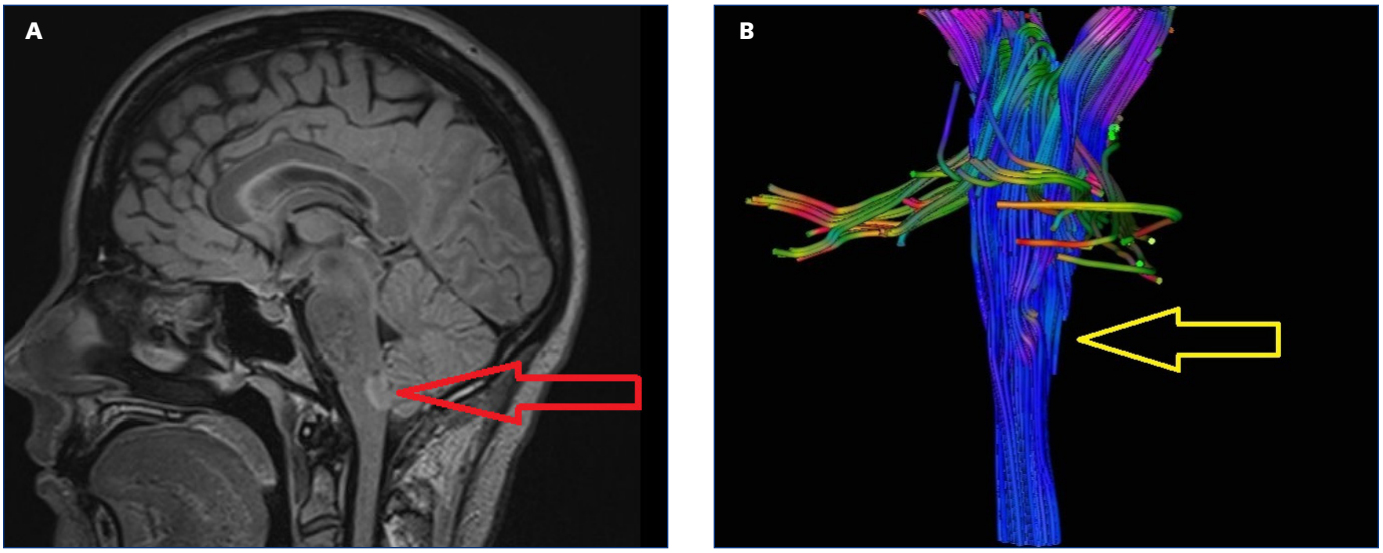
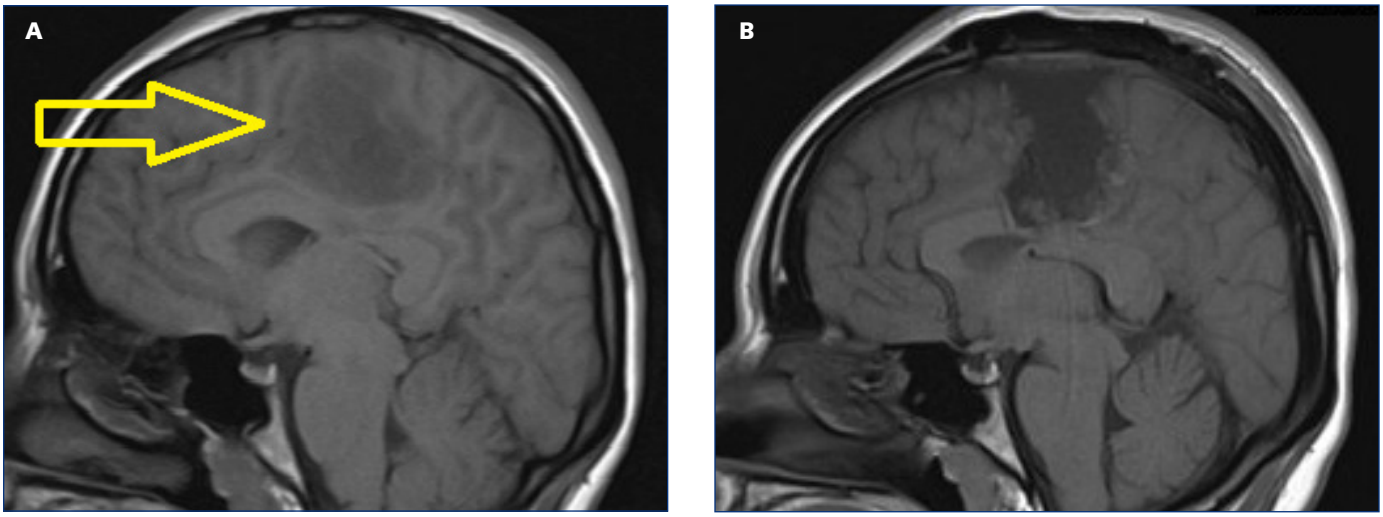


Figure 2. (A) The yellow arrow illustrates a low-grade glioma in the cingulum underlying the motor cortex.
(B) Using neurophysiological techniques including motor evoked potential and subcortical fiber tract stimulation, the lesion was successfully removed.



is undertaken to map out motor and sensory areas (**See Figure 2**) or nearby cranial nerve nuclei. If the lesion is near language areas, an awake craniotomy with speech mapping may be required to achieve maximal safe resection while minimizing the risk of language deficits.

After biopsy or resection, the tissue is studied by a dedicated neuropathologist for both histopathology and molecular markers. A detailed description of the molecular pathology of glioma is beyond the scope of this manuscript. Postoperative MRI is reviewed for completeness of resection and a care plan is formulated by the team. This care plan may include radiation therapy, chemotherapy, tumor treating fields, or clinical trials. Further discussion with the family is begun to deliver the diagnosis and care plan, as well as to engage the patient and family with resources such as local and virtual brain tumor support groups to aid in the social support network for these patients.

Follow-up routinely is weekly during radiation therapy, monthly during active chemotherapy and every three months for high-grade gliomas. Routine surveillance scanning is often used to identify progression of the disease and allow for more timely intervention upon therapeutic failure.

LANDMARKS IN THE CARE OF GLIOMA

For both low-grade glioma as well as glioblastoma, survival is dependent upon age, the patient Karnofsky Performance Score, as well as a host of histopathological and molecular pathological factors. The most important factor in the control of clinicians, is, of course, the percentage of tumor

which can be surgically resected[13,14]. It has been clearly demonstrated that for all types of glioma, the improvement in patient outcomes achieved by the cytoreduction of tumor cells gained is nonlinear and that maximum benefit to the patient is achieved when all tumor which can be removed up to the point of causing a postoperative neurological deficit is beneficial for the patient.

The most important clinical advances in glioma therapy have occurred within the past 15 years. The molecular biology of gliomas involves a host of genetic and epigenetic alterations which are of prognostic importance to tumor classification as well as patient survival. For low-grade gliomas, the most important of the diagnostic and prognostic markers are those of gene rearrangement studies, which suggest the classical oligodendroglioma phenotype and predict responsiveness to chemotherapy, that of chromosome 1p and 19q allelic loss[15]. Loss of 1p/19q alleles predict both sensitivity to chemotherapeutic agents as well as a prognosis which is nearly double that of low-grade gliomas without this genomic loss.

In GBM, attempts have been made to characterize multiple molecular phenotypes, but the single gene with the most prognostic value is IDH1[16]. Mutations in IDH1 are classically identified in GBMs arising from lower-grade gliomas (previously commonly called secondary GBMs to distinguish them from those presenting as *de novo* GBM and often having mutations in the epidermal growth factor receptor) and are associated with improved prognosis. The other commonly cited prognostic factor in GBM is the epigenetic alteration of methylation of the methyl guanine methyl transferase (MGMT) gene promoter[17]. The MGMT methylation at the promoter reduces the expression of the MGMT gene, needed to repair the damage caused by the chemotherapy temozolomide. Thus, patients with methylated MGMT promoter are more susceptible to the effects of the chemotherapeutic temozolomide and are in a better prognostic category.

Prognosis for GBM patients has been among the worst of all malignancies until recently. Survival was less than 12 months as recently as 20 years ago, and progress has been slow. The work of Roger Stupp, who showed that concurrent temozolomide along with radiation therapy improved prognosis over sequential radiotherapy followed by temozolomide marked the first major advance in glioblastoma survival (to 14.6 months) since the advent of radiotherapy and the introduction of nitrosoureas in the 1970s and 1980s[7]. More recently, a series of novel devices, drug therapies and immune strategies have begun to improve survival beyond this mark.

NOVEL THERAPEUTIC ADVANCES

The most recent therapeutic advance to be approved for clinical use in glioma is that of a novel antimitotic therapy called tumor treating fields (TTFs). TTFs are an antimitotic therapy consisting of an alternating electrical current of 100 – 300 kHz delivered via transducer arrays placed on the scalp. In both recurrent and newly diagnosed GBM, TTFs delivered for at least 18 hours per day have been shown to improve survival[7]. In newly diagnosed GBM, the addition of TTFs to radiation and temozolomide improved survival to 24.3 months in treated patients versus 20.4 in the control group. One might note that even the control group with radiation and temozolomide were surviving longer than those from a decade ago.

A host of other small molecule inhibitors and novel drug delivery systems such as convection enhanced delivery have been tried in the past several decades but have failed to show meaningful improvements in survival of GBM. More recently, techniques such as immunomodulatory molecules, such as the PD-1 and CTLA-4 inhibitors have shown improvements in survival of melanoma, lung and renal cell carcinoma and are in trials for GBMs[18].

In addition to immune checkpoint inhibitors, other immune strategies such as peptide vaccines, dendritic cell vaccines[19], and Chimeric Antigen Receptor T-cell (CAR T-Cell) strategies[20] have shown early promise in improving survival for patients with glioma. These topics will be reviewed in another manuscript in this issue.

THE ROLE OF RESEARCH IN GLIOMA – INSIGHTS FROM OUR LABORATORY

Despite many decades of work and recent advances, glioma remains a fatal disease. Thus, no development of a comprehensive brain tumor program would be complete without a research effort. This includes clinical trials with industry and large cooperative groups, but some of the most exciting prospects for improvements in glioma therapy lie within the laboratory. It is the goal of our group to bring several of these to clinical trial within the next several years. With this in mind, we will preview two fields of investigation, glioma migration and micro ribonucleic acid (miRNA) of glioblastoma stem cells.

One of the most vexing aspects of gliomas is that they migrate away from the solid tumor and diffusely infiltrate well beyond apparent margins on MRI. Thus, for anything other than compact, Grade I (benign) gliomas, surgery alone will never be curative. Therefore, we have studied within our laboratory how glioblastoma cells interact with the brain environment to migrate as well as how we might manipulate these pathways to aid in therapy. We are manipulating these pathways to promote the return of remaining cancer cells to the resection site by placing a pro-migratory protein (LCN2) in a slow release hydrogel placed within the resection cavity to hopefully improve the results of radiation therapy. In addition, we have found a small molecule inhibitor of a tyrosine kinase (Lck), which enables pseudopodia extension and migration in GBM stem cells. We feel that manipulation of the "On" and "Off" pathways for migration can be used to

improve patient outcomes and expect to begin clinical trials after we complete our small animal model data.

In addition, our laboratory is investigating the role of miRNA – the regulators of RNA transcription – to identify how regulation of these small switches controls the ability of cancer cells to self renew and replicate in GBM stem cells. Thus far, we have narrowed the control of this crucial feature of cancer – the ability of cells to remain stem-like and resist therapy – to 9 likely miRNA candidates. Our preliminary work suggests that miRNA-mediated control of RNA methylation may be the molecular switch that changes GBM stem cells to the cancer cells we typically associate with GBM. We hope that this signature may yield prognostic data and reveal pathways for therapeutic intervention.

Of course, none of this has much meaning without educating the future generation of oncologists and neurosurgeons to care for patients with glioma. We anticipate beginning advanced training of neurosurgical oncology fellows within the year. Once this is complete, the comprehensive brain tumor center will close the circle from the patient, to the student, to the laboratory, and back, to be able to provide the best care for patients afflicted with glioma.

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Current Concepts in the Pathogenesis, Diagnosis, and Management of Type I Chiari Malformations

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ABSTRACT

Type 1 Chiari malformations (CMs) are a group of congenital or acquired disorders which include the abnormal presence of the cerebellar tonsils in the upper spinal canal, rather than the posterior fossa. The resulting anatomic abnormality causes crowding of the structures at the craniocervical junction and can impair the normal flow of cerebral spinal fluid (CSF) in this region. This impairment in CSF flow dynamics can led to the development of syringomyelia or hydrocephalus. Type 1 CMs have been associated with a wide array of symptoms resulting from either cerebellar and brainstem compression and distortion or disturbances in CSF dynamics, and can affect both children and adults. The clinical diagnosis may be difficult. Age usually matters in the clinical presentation, and in symptomatic patients, surgical intervention is usually required.

KEYWORDS: Chiari I Malformation, cerebrospinal fluid, hydrocephalus, syringomyelia

INTRODUCTION

Chiari malformations are a group of disorders defined by structural defects of the cerebellum, pons, fourth ventricle, and upper spinal cord in relation to the foramen magnum and the skull base. In 1891, Chiari was the first to describe and define hindbrain herniation, representing downward displacement of the cerebellum, fourth ventricle, and brainstem.[1] Type 1 CMs are characterized by herniation of the cerebellar tonsils through the foramen magnum into the upper spinal canal. The resulting compaction and crowding at the craniocervical junction can disrupt normal cerebrospinal fluid flow, produce the so-called "Valsalva-induced" headaches, and may lead to the formation of a spinal cord syrinx or hydrocephalus.[2]

Chiari malformations are still listed as a rare disease by the Office of Rare Diseases of the National Institutes of Health. The estimated prevalence in the United States of type 1 CMs is less than one percent with a slight female predominance.[2] Speer et al. have estimated that 215,000 Americans may harbor a type 1 CM.[3] However, the routine use of magnetic resonance imaging (MRI) has led to more frequent identification of this disorder and type 1 CMs can be seen incidentally in approximately 1% to 4% of patients undergoing brain or cervical spine magnetic MRI studies.[4]

Most cases of type 1 CM are sporadic. Type 1 CMs can be found in association with other conditions such as neurofibromatosis, idiopathic intracranial hypertension (IIH), tethered spinal cord, connective tissue disorders, craniosynostosis and skull base abnormalities, intracranial hypotension and cerebellar hypertrophy in polymicrogyria.[5] It is still not fully understood whether these co-existing conditions are mere coincidences or true co-morbidities. The precise natural history of this disorder remains unclear although patients generally have symptomatic progression. There have been a few published reports of spontaneous resolution of type 1 CMs but most symptomatic cases require surgical intervention.[5,6]

PATHOGENESIS

Most cases of type 1 CM are congenital. Skull base abnormalities are seen in approximately 50% of type 1 CM cases, (i.e., basilar invagination, retroflect odontoid, platybasia etc.).[7] Although the exact etiology is unknown, this condition is thought to be secondary to insufficiency of the paraxial mesoderm after neural tube closure with underdevelopment of the occipital somites.[7,8] Milorat and coworkers examined reconstructed CT and MRI images in 388 patients with classic type 1 CMs, and morphometric analysis revealed reductions in the posterior cranial size and volume.[9] In severe cases, downward herniation of the brainstem may occur and is sometimes referred to as a type 1.5 CM.[7] Despite evidence supporting a genetic contribution to type 1 CMs (i.e., twins, familial clusters, and co-segregation with known genetic syndromes), limited research has been conducted to identify the specific genetic factors involved.[8]

Acquired type 1 CMs can occur when there is a significant cerebral spinal fluid (CSF) pressure gradient across the craniocervical junction, i.e., CSF leakage or lumboperitoneal shunts can produce negative downward pressure gradients leading to the development of a type 1 CM. In addition, conditions associated with raised intracranial pressure, such as hydrocephalus and IIH, can promote downward pressure gradient. The association of CM1 with tethered cord has led to the "caudal traction theory."[6]

Syringomyelia is identified in 30-85% of patients.[5,10,11] There are many hydrodynamic theories to explain the formation of syringomyelia[11]. Abnormal and increased pulsatile

motion of the cerebellar tonsils ("tonsillar pistoning") can produce selective obstruction of CSF flow during systole. The increased systolic CSF waves are then transmitted to the spinal subarachnoid space and drive the CSF into the central canal of the spinal cord through engorged perivascular and interstitial spaces and lead to syrinx formation.[12,13]

DIAGNOSIS

The clinical findings vary dependent on the age at presentation. Occipital headache and neck pain are the most common symptoms in adults.[10] In infants, oropharyngeal dysfunction or sleep apnea and other cranial nerve findings, i.e., strabismus, are the most common presenting symptoms, while older children often present with headaches aggravated by " Valsalva maneuvers" during coughing and sneezing or strain, and scoliosis.[14,15] Symptoms are based on the structural and functional (impaired "CSF-dynamics") pathology associated with CM, which often leads to a wide spectrum of focal and non-focal findings in the clinical and neurological presentation, making it difficult to diagnose. Even more challenging is the often reported "brain fog" that has been largely attributed to chronic pain, depression and anxiety associated with the unknowns and physical challenges of this disorder. In traditional thinking, a disorder like Chiari affecting the craniocervical junction and the cerebellum, has not been thought to affect cognitive function: Altered MRI diffusion tensor imaging (DTI) metrics in the genu of the corpus callosum, splenium, fornix have been correlated with cognitive neurocognitive function in Chiari.[16]

Magnetic resonance imaging is the widely accepted diagnostic tool for type 1 CMs. The McRae line is a radiographic line drawn on a lateral midsagittal section of CT or MRI, joining the basion and opisthion representing the level of the foramen magnum. The traditional definition of type 1 CM as greater than 5 mm displacement of the cerebellar tonsils below the foramen magnum is challenged.[15] Even a "mild" displacement of 3-5 mm may be considered significant in the presence of neurological signs or symptoms or in the presence of syringomyelia. Also, the level of tonsillar ectopia evidenced in the sagittal MRI varies based on head position, and whether the measurement of the tonsillar position is based on a brain or spinal MRI. Recently, upright MRIs have challenged this view also, as gravity might reveal tonsillar displacement that was not seen in the traditional supine MRI versions.

The future lies in computation of the CSF space at the craniocervical junction and the resulting altered compliance and failure to synchronize transmission of systolic CSF pressures between the cranial and cervical subarachnoid space.[12]

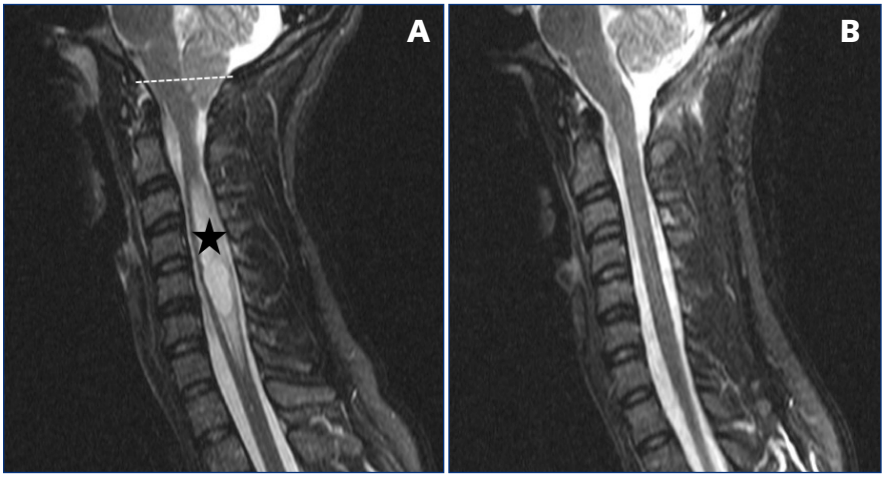
SURGICAL MANAGEMENT

The management of acquired forms of type 1 CM is directed at correcting the primary causative condition. For example, ventricular shunting for the treatment of hydrocephalus, repairing spinal CSF leakage, or correcting a tethered spinal cord usually results in anatomic and physiologic correction of the acquired CM. Intervention to directly treat the acquired CM is typically not necessary.

Asymptomatic patients who have an incidental finding on imaging are usually observed and monitored with follow-up MRI studies. Most patients with symptoms, or those who harbor a large associated spinal cord syrinx, should be recommended surgical intervention. Close follow-up and serial MRI imaging is required in patients who undergo observation alone in the presence of a syrinx. Appropriate management of an asymptomatic patient with a small syrinx is controversial.[17,18]

Many different surgical techniques are utilized to treat type 1 CMs, and there is no consensus. Surgical correction of type 1 CMs may include bony decompression of the posterior fossa with or without duraplasty, arachnoid dissection, or shrinking of the cerebellar tonsils. The goal of any of these operations is to restore adequate CSF flow at the level of the foramen magnum and establishment, basically an "anatomical reconstruction," of the Cisterna magna (**Figure 1A, B**). Bony decompression alone has been associated with a decreased risk of CSF related complications such as pseudomeningocele, meningitis, and hydrocephalus.

Figure 1. (**A**) Sagittal T2 STIR magnetic resonance imaging showing Chiari I with significant cervical syringomyelia (black asterisk) and the classical "crowding" of the cerebellum and the brain stem at the level of the foramen magnum (dashed white line equals the McRae line, which indicates the level of the foramen magnum on a midsagittal section of CT or MRI joining the basion and opisthion). (**B**) At 3 months follow-up, there is evidence of restored CSF signal anterior to the brain stem, decompression of the obex and restoration of the cisterna magna associated with an almost complete resolution of the syrinx.



However, multiple studies have shown that reoperation rates are higher for patients who have undergone bony decompression alone.[19,20,21] Duraplasty involves the use of autologous pericranium or allografts, none of which have been found superior to the other. More involved arachnoid dissection to ensure flow through native CSF channels may be required, particularly if scarring or webbing is restricting CSF flow. Shrinking of the cerebellar tonsils using meticulous bipolar cautery is also controversial, although we do advocate this approach in select cases. A recent meta-analysis suggested shrinking the cerebellar tonsils during the procedure showed better clinical results in patients with syringomyelia.[20] Shunting of an associated spinal cord syrinx has been largely abandoned. CM1.5 and associated skull base anomalies may require occipital-cervical fusion and instrumentation due to associated craniocervical instability.

FUTURE DIRECTIONS

All efforts need to be directed to identify potential subgroups of type 1 CMs. This will result in better diagnostic methods and treatment that will eventually be tailored to the individual anatomic and physiologic characteristics. This includes experimental and molecular studies to further our understanding of the genetics and pathophysiology of type 1 CMs. Also, MRI studies need to advance imaging to allow computation of cerebrospinal fluid space before and after surgery and provide a reliable "disease biomarkers." A large randomized, prospective study evaluating available surgical techniques is required to definitively determine the most successful and safest treatment options for type 1 CMs.

The Center for CSF Disorders of the Brain and Spine at the Warren Alpert Medical School of Brown University supports these endeavors, and has recently started exploring cognitive mechanisms in conditions such as hydrocephalus, CM and syringomyelia and optogenetic manipulation of choroid plexus cells to gain new insights into CSF physiology in collaboration with the Brown Institute for Brain Sciences and the Neuroscience Department. The annual CSF disorder symposium at the Brown medical school supports the interdisciplinary management of Chiari and related CSF disorders in collaboration with the Chiari and Syringomyelia Foundation (http://csfinfo.org/).

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