Defining and Achieving Excellence in Surgical Neuro-Oncology

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To achieve excellence in surgical neuro-oncology, the neurosurgeon must achieve 3 particular things. The first is to provide impeccable clinical care. The second is to participate in basic translational and clinical research. The third is to devote one's career to a lifelong commitment to excellence in education and training. All 3 domains interact in the 3 daily venues of the neurosurgeon: the preoperative, intraoperative, and postoperative care of patients. From a preoperative point of view, we must know everything possible about the patients, including their entire medical history. We have to be aware of the anesthetic risk assessment for each individual, and we have to have a thorough understanding of the clinical laboratory data, which include neuroendocrine evaluation for pituitary tumors. In addition, a full neuropsychological evaluation for patients should be obtained if they are undergoing cortical-based resections. The preoperative setting is an ideal time to perform population-based studies, including obtaining questionnaire data from patients and constitutive tissue samples such as blood or skin. Finally, it is imperative to move beyond the pure anatomic imaging to obtain physiological studies, including magnetic resonance spectroscopy, diffusion-weighted imaging (DWI), perfusion imaging, and functional studies from either functional magnetic resonance imaging (MRI) or magnetoencephalography. On occasion, interventional techniques are necessary to preoperatively embolize tumors to reduce blood loss.

PREOPERATIVE ASSESSMENT

An excellent example of obtaining population-based science data comes in the information provided by the San Francisco Bay Area Adult Glioma Study.[1] This study pointed out that there are a number of established risk factors for gliomagenesis, including high-dose radiation, hereditary syndromes, and increasing age. However, it has recently been demonstrated by the University of California, San Francisco (UCSF) Neuroepidemiology Group that there is an inverse relationship of allergies and serum IGE levels to the risk of glioma formation.[2] Another significant finding published recently from $>$ 700 high-grade glioma cases from the San Francisco Bay Area Adult Glioma Study, along with cases from the Cancer Genome Atlas for glioblastoma, is that there are 2 key regions of inherited variation on chromosomes 9p21 and 20q13.3. This finding was independently validated from a separate data set from the Mayo Clinic, confirming that these 2 variants of CDKN2B and RTEL1 are associated with high-grade glioma susceptibility.[3]

Anatomic imaging plays a critical role in defining the area of abnormality and its associated region of interest. However, there are numerous examples of contrast-enhancing lesions, for example, that can masquerade as lesions not associated with gliomas, ie, abscess, demyelination, and radiation necrosis. Thus, physiological imaging modalities have become very useful. Using the number of elevated lipid voxels and an increased proliferative index measured by the choline–to–n-acetyl-aspartate levels and combining this with the degree of cellularity based on the apparent diffusion coefficient of the DWIs, we can begin to predict which patients with glioblastoma are more likely to have a worse outcome. In addition to the information on cellularity that DWI provides, we can use the apparent diffusion coefficient and fractional anisotropy to differentiate between histologies such as oligodendrogliomas and astrocytoma. Another DWI paradigm is diffusion tensor imaging, and with some of the newer probabilistic algorithms, we are able to very nicely identify descending motor pathways from the entire motor homunculus.[4,5] Additional information can be gained by perfusion MRI, which can readily demonstrate permeability via dynamic contrast enhancement, as well as blood volume and blood flow. This information helps to differentiate tumor from surrounding edema on the basis of these patterns of perfusion.

Functional imaging is done most readily with magnetoencephalography, which allows us to identify the neuronal areas of activation of a given function such as the somatosensory cortex or primary motor cortex. These points of information can be inserted into the navigational workstation and incorporated with the diffusion tensor images to demonstrate the relationship of these functional pathways to the tumor.[6]

Finally, preoperative embolization can be a useful strategy, especially for very vascular meningeal-based tumors

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such as meningiomas or hemangiopericytomas. This technique is rarely useful for intrinsic glial tumors.

INTRAOPERATIVE CONSIDERATIONS

Intraoperatively, a dedicated neurosurgical team is mandatory to achieve an excellent outcome. This team includes dedicated neuroanesthesia, neurosurgery nurse, and neuropathology availability, as well as a neurocentric operating room configuration. Technical adjuncts should be used to enhance the extent of resection, including advanced instrumentation, navigation, microscopy, endoscopy, intraoperative MRI when available, and specific tumor-enhancing dyes such as aminolevulinic acid (5-ALA). Neurophysiological monitoring techniques such as cortical and subcortical mapping, somatosensory evoked potentials, brainstem auditory evoked potentials, and cranial nerve monitoring are used to minimize morbidity. Thus, the overarching goal is to achieve a maximal safe resection done in either an open fashion or a minimally invasive fashion or to obtain an accurate image-guided biopsy. During the course of surgery, tissue acquisition should be done on every case and preferably linked to imaging for correlative laboratory studies.

Neurosurgeons have no shortage of advanced neurosurgical techniques. But what evidence exists that these new surgical techniques improve outcome? New techniques for surgical treatment are often first piloted by a select group of surgeons at limited institutions. Reports of the results of the outcome of these techniques are often limited to retrospective, single-institution series that compare with historical controls. However, evaluation for generalization and incorporation into the standard of care should be prospectively assessed, preferably in a clinical trial setting that captures toxicity and outcomes. For example, endoscopic nasal approaches for pituitary tumors have reached widespread use throughout neurosurgical operating rooms around the world. However, there have been no randomized trials comparing endoscopic techniques and standard microsurgical methods. Retrospective studies have shown that this approach is safe and effective but not necessarily superior to microsurgical methods.[7-9] In addition, the hospital stay and complication rates are not lowered by endoscopic approaches, and long-term follow-up for this technique is not available. Compare this with the only randomized phase III study for a surgical technique to remove malignant gliomas, namely the use of 5-ALA. A phase III randomized study was published using fluorescence-guided surgery with 5-ALA for the resection of malignant gliomas in 322 patients. Patients were selected for gross total resection and randomized to enter the study. The end points were the percent of patients achieving a gross total resection of the enhancing component of the tumor and 6-month progression-free survival. This study demonstrated that a gross total resection was achieved in 65% of patients who received 5-ALA vs 36% of patients who did not ($P < .001$). In addition, the 6-month progression-free survival was 41% vs 21%.[10] Thus, if a gross total resection is the goal of a procedure for a high-grade glioma and we wish to obtain a greater 6-month progression-free survival, then the use of 5-ALA to guide the resection is clearly indicated.

At UCSF, we have looked at the role of eloquence as a prognostic factor for overall survival in patients with low-grade glioma and how this particular factor affects survival when functional mapping is used to aid in the resection of eloquent region tumors.[11] In this study, nearly 300 patients underwent a blinded MRI review to determine whether the tumor was located in eloquent regions, ie, the left perisylvian area and dominant insula. Patients who were presumed to have eloquent tumors either received no mapping or had intraoperative functional mapping and were found to have eloquent region tumors vs noneloquent region tumors. This was a retrospective analysis from 1993 to 2008 with long-term follow-up. The study demonstrated that for those patients presumed to have an eloquent location of a low-grade glioma in which mapping was not offered, the 5-year overall survival was between 70% and 75% for a low-grade glioma. However, for those patients who were offered mapping and were found not to have eloquent region tumors, the resection was enhanced similar to the degree of resection for patients who had noneloquent region tumors, and thus their overall 5-year survival was 96% to 98%. The difference between the 2 groups was significant, demonstrating that if an individual has a tumor located in an eloquent area, then the best option for prolonged survival is to have functional mapping to remove as much tumor as possible, avoiding these eloquent regions. Not mapping patients with presumed eloquent location tumors denies them additional survival time.

There is a growing body of evidence that lower inpatient mortality and morbidity in those patients undergoing brain tumor surgery in general are related to their surgical procedures being done at high-volume centers and by high-volume physician/surgeon providers. This has been documented for several neurosurgical oncology procedures, including craniotomy for primary brain tumors[12] and craniotomy for meningioma.[13] Thus, it is becoming quite apparent that patients offered surgery by dedicated neurosurgeons who perform significant numbers of tumor operations in high-volume surgical centers have the best chance of a prolonged survival. From those centers and surgeons of excellence comes mounting evidence that the extent of resection improves tumor progression and overall survival for low-grade glioma and high-grade malignant gliomas.[14]

Experience from the UCSF group conducting resections of adult patients with low-grade glioma demonstrates a nearly 100% 10-year survival for patients undergoing a resection that is radiographically complete.[15] That study also demonstrated a graded degree of benefit for patients undergoing radical resections down to the 40% level of extent of resection. In addition, that study clearly showed in a multivariate analysis that malignant progression-free survival was affected when the extent of resection was considered in a statistically significant fashion. The relative hazard ratio for overall survival for

100% vs 50% radiographic resection was 0.24, indicating that a radical resection of low-grade glioma can influence the natural history of the disease in terms of significantly delaying malignant transformation. In addition, experience with high-grade gliomas at UCSF in $>$ 400 cases demonstrates that the extent of resection for newly diagnosed glioblastoma is of benefit beyond the traditionally accepted 97% extent of resection.[16] The benefit of an aggressive resection goes all the way down to the 75th percentile, demonstrating for newly diagnosed glioblastoma that even if a $\geq$ 97% resection cannot be achieved, there is benefit to the patient in terms of overall survival if at least 65% of the tumor can be removed.[17]

Finally, it is absolutely imperative that surgeons take the time to acquire tissue during the course of surgery and correlate it with the location from the preoperative imaging studies using the navigational workstations. This will help the field of neuro-oncology develop a set of surrogate imaging markers for biological processes in gliomas.

POSTOPERATIVE MANAGEMENT

Postoperatively, it is critical to assemble a multidisciplinary care team that works within the intensive care unit and on the neurosurgical wards that is composed of neurointensivists, neurointensive nurses, and hospitalists. In addition, it is critical to have a dedicated social worker and rehabilitation services available for patients with postoperative deficits. Once again, a full range of imaging modalities is useful in assessing extent of resection, postoperative morbidity, and response to therapy. It is also critical to have a portable computed tomography scanner in the intensive care unit for imaging capability without having to transport the patient. Neuropathology services revolve around standard options and provide a full range of molecular-based markers. This is done in conjunction with a large tumor bank and repository for all the specimens obtained during the course of surgery. Finally, it is critical to have a diverse laboratory-based research portfolio dedicated to neuro-oncology.

The clinical services revolve around neuro-oncology as a multidisciplinary team of adult and pediatric specialists devoted to the field of neuro-oncology. This also includes radiation oncologists who specialize in neuro-oncology, along with nursing and data managers. A neuropsychologist is also a very useful member of the team for assessing patients after surgery, performing quality-of-life studies, and helping with patient support groups. The neuro-oncology service typically provides postoperative inpatient consultations, daily neuro-oncology clinics, and a weekly neuro-oncology tumor board. They are the centerpiece of outcome assessment studies and comparative effectiveness research as it relates to clinical trials and new surgical techniques. In addition, a full range of education and training formats for residents and fellows should be available, and these individuals must be encouraged to pursue a lifelong learning program. Finally, it is critical to achieve excellence in patient satisfaction.

Postoperatively, we obtain various physiological imaging tests to attempt to define the true extent of residual disease. Despite often achieving a gross total or radical resection of tumor using MR spectroscopy, we can often identify a residual lesion using the parameters of choline as a marker of increased proliferation, as well as lactate, which is a surrogate marker of hypoxia. In addition, it is critical to use perfusion-weighted imaging to determine the cerebral blood volume of the tissue around the resection cavity, and putting all this information together allows us to predict the actual time to tumor recurrence. In addition, when patients have postoperative deficits, it is important to use these physiological imaging studies to determine the origin of that deficit. For example, DWI can demonstrate postoperative ischemic injuries that are seen immediately postoperatively and would be expected to enhance soon thereafter. Unless this imaging is done, the early enhancement would indicate failure of the current treatment regimen, which could be misinterpreted. Thus, if there is a DWI-positive lesion showing restricted diffusion indicating ischemia, then it is critical to get a subsequent follow-up scan 3 to 4 months after the first month postoperative scan to determine whether the enhancement has resolved, which is expected to be the case. In addition, spectroscopy can be used in the setting in which anatomically the lesion looks to be progressing during the course of postoperative treatment, but indeed the spectroscopic pattern is becoming less prominent. This would be a good indication of radiation-induced inflammation, which should have decreasing evidence of increased proliferation based on the choline–to–n-acetyl-aspartate index, which should improve over time.

Although our neuropathologists typically provide histological classification, we need to move beyond the usual standard hematoxylin and eosin on H and E stains to further define the biology of the tumor. This can be seen with the use of immunohistochemistry, fluorescent in situ hybridization analysis, etc, which can show a full range of protein expression and gene amplification for critical markers such as endothelial growth factor receptor, platelet-derived growth factor, and PTEN. This has been essential to our ability to better define how patients will respond to therapy. For example, Phillips et al[18] were able to demonstrate that in histologically similar cases of high-grade gliomas, one could actually define a molecular subclassification based on whether the tumor cells had a proneural vs mesenchymal vs proliferative genotype. This study was able to very nicely differentiate tumors that were anaplastic from glioblastoma, despite having difficulty achieving this differentiation with histology alone. Perhaps the most impressive piece of work to demonstrate the utility of the molecular subclassification strategy was recently published by the Cancer Genome Atlas Research Network.[19] In this study, a comprehensive genomic characterization was undertaken to define various glioblastoma genes and pathways associated with the biology of this tumor. In essence, this work showed 3 major genomic alterations seen in glioblastoma: alterations of the

RTK/RAS/PI3 kinase signaling pathway, p53 signaling alterations, and RB signaling pathway abnormalities. Aberrations in these 3 pathways amount to > 80% of the defined genomic alterations seen in glioblastoma. From these 3 aberrant pathways come a number of key gene amplifications and deletions that will provide the next generation of therapeutic targets. The value of having this information lies in the use of this knowledge to develop a robust clinical trials portfolio in conjunction with industry and pharmaceutical companies. Thus, another aspect of achieving success in surgical neuro-oncology is to provide the tissue from the operating room that is used by researchers to conduct translational research and to develop strong relationships with industry and pharmaceutical companies that are developing signal transduction inhibitors. The neuro-oncology group often participates in cooperative group studies such as the Adult Brain Tumor Consortium or the Pediatric Brain Tumor Consortium to implement these studies in the phase I and II setting. This also requires a very strong biostatistics and bioinformatics core dedicated to neuro-oncology.

An excellent example can be defined on the basis of how much progress has been made in the treatment of glioblastoma. Previous studies have demonstrated approximately a 20% 2-year survival for high-grade gliomas when any form of chemotherapy was added to radiation therapy. Subsequent work by Stupp and colleagues[20] demonstrated that for newly diagnosed glioblastoma treated with Temodar and radiation, the 2-year survival could be expected to be as high as 26%. However, when information regarding the methylation status of the methylguanine-methyltransferase (MGMT) repair enzyme is included in this analysis, it appears that the 2-year survival rate expands to 46% in those patients who have a methylated MGMT promoter region who also receive Temodar and radiation therapy.[21] Thus, we have made significant progress in our ability to improve the outcome of patients with glioblastoma. Moving beyond Temodar, we are now in the age of targeted therapeutics in which a significant number of tumor- and endothelial cell-related antigens can be targeted with small therapeutic agents or monoclonal antibodies.[22] Perhaps the most glaring example of how this has succeeded is the work with Avastin, a monoclonal antibody that sequesters the vascular endothelial growth factor ligand before it finds its way to the receptor. Therefore, patients who receive this drug do not have to have a disrupted blood-brain barrier.[23] Avastin was approved for recurrent glioblastoma after demonstrating a 6-month overall survival of 77% for those patients with glioblastoma multiforme. Avastin is currently being evaluated in newly diagnosed patients with the same tumor. One of the side effects of Avastin appears to be the promotion of an invasive phenotype with extended use.[24]

Thus, there have been many successes with these new targeted therapies such as with the antiangiogenesis strategies and the use of mTOR inhibitors. However, there have been relative failures with the use of agents targeting the epidermal growth factor receptor.

Defining excellence in surgical neuro-oncology also means dedicating time and effort to neuro-oncology research. This includes the acquisition of peer-reviewed funding from agencies such as the National Institutes of Health. We must publish our work in high-impact peer-reviewed journals and present important discoveries at national and international meetings. Neuro-oncology surgeons are also encouraged to participate on scientific review boards and advisory councils to be at the table when decisions regarding funding for research are being made. It is also essential to define excellence in education both in the training of residents and fellows and by continuing medical education activities. This should be done on a routine and lifelong basis. It is critical for us to train the next generation of neurosurgical oncologists to participate in a multidisciplinary team approach to the patient with a brain tumor. Our residents and fellows should be able to assess the medical literature so that they can accurately inform patients and their families about treatment decisions. We have to be able to mentor the next generation on how to become productive clinician-scientists who understand the role and importance of translational science, clinical trial design, and biostatistics. In addition, it is critical to teach the younger neurosurgical generation how to appreciate quality-of-life issues involving patients and caregivers. It is critical for patients to feel satisfied with the care that they receive, and the way to achieve this is to provide outstanding communication to patients, caregivers, and other health professionals involved in the care of the patient, ie, feedback to referring physicians. We need to provide easy access to all the personnel who work in the multidisciplinary team so that patients can have their health questions answered both preoperatively and postoperatively. Finally, we must provide patients with the relative ease of navigating the system to achieve excellence in everyday care, including coordination of clinic appointments and preoperative and postoperative assessments.

Thus, we have an excellent format, based on this discussion, for defining excellence in surgical neuro-oncology. However, it is critical that to achieve excellence, we as surgeons must strive to excel each and every day when caring for our patients with brain tumors.

Disclosure

The author has no personal financial or institutional in any of the drugs, materials, or devices described in this article.

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