Glioma Surgery: A Century of Challenge

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What I would like to do is discuss some of the challenges that have faced glioma surgery over the past century, in particular how those challenges have affected the outcomes of our patients. I think it is fitting that this meeting takes place in San Francisco, the first city in this country where a glioma operation was performed more than a century ago. Since that time, as we know, there have been lots of advances in medicine—certainly in our specialty and in neuroimaging—that have made it easier and safer to operate on these kinds of lesions.

It was in the 1980s when the field really evolved within a perfect storm of imaging, stereotactic localization, and microsurgery, leading Pat Kelley to develop the important concept of volumetric stereotactic resection of gliomas. Since that time, we have had lots of advances that we have taken into the operating room that allow us to do maximal, safe resections for patients with gliomas in all different locations. The other thing we have done with surgery is to become very clever at delivering adjunctive therapies into various aspects of the tumor safely and precisely.

Yet, we have to step back as a specialty and ask the very fundamental question, ''What evidence exists that any of these surgical outcomes have improved glioma outcomes''? Only 1 study has been done in the glioma field as a randomized prospective study that showed a gross total resection is desired and that, if 5-ALA is used to do it, you can double the 6-month progression-free survival and improve overall survival significantly.[1] The big challenges that we have had as neurosurgeons doing glioma surgery are to better define the extent of the tumor, to understand the biology of the disease, and then to determine the functionality of the tissue in which we work. We have met these challenges with new imaging paradigms. As a specialty, we have done a very good job in the last decade or so of linking navigation-based biopsies with these imaging paradigms to create what I think is a magnificent set of surrogate imaging biomarkers that tell us so much about the disease before we even get into the operating room.[2] For example, a patient previously operated on had a very subtle enhancing area within a low-grade glioma. The patient was followed up in the clinic and was completely asymptomatic, but we started to see some changes on the anatomic images. We obtained all the physiological studies and saw an increase in cellularity, a disruption of the architecture around this tumor indicative of invasion, an increased cerebral blood volume in the tumor, and a leaking of the vasculature, all on the background of a high choline index indicative of proliferation in a hypoxic fraction based on the lactate spectra. The imaging told us this was going to be a glioblastoma, but we knew exactly where to take this specimen from, which is a significant advance in the field. We have been mostly in a 2-dimensional era with magnetoencephalography and functional magnetic resonance imaging, and we have used anatomic studies with diffusion tensor imaging to determine subcortical pathways, yet the future is about understanding in a 3-dimensional way how different areas of the brain connect with each other, so-called network connectivity. Based on the fact that we can identify and measure the oscillatory patterns of different brain regions preoperatively and relate them to each other mathematically and based on the time frame in which that happens, we can determine what areas are functional, and therefore connected, and what areas are not, which we can readily remove during surgery.[3] Another area that is going to advance over the next several years is the higher-field-strength magnets; we will have in vivo spectroscopy like we have never seen before. This is based on some of the work that we and others have done with ex vivo nuclear magnetic resonance spectroscopy in which we take biopsies and look at those samples out of the operating room. We can see a whole set of new surrogate metabolic markers for progression profiles in gliomas, and we are going to be able to see this in vivo before we go into the operating room. The molecular biology of the tumor is fair game as well; we can now use a surrogate marker for an IDH1 mutation, which is so important for low-grade gliomas, by spectroscopically identifying the oncometabolite of the mutation, 2- hydroxylglutarate. Drug resistance is also on the horizon. We have been looking at this experimentally in animals, and we can show, for example, that Temodar, which works through DNA damage and activation of mismatch repair, actually processes that damage through changes in pyruvate metabolism. C13 pyruvate conversion to lactate is now possible to see spectroscopically. So we are going to be

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able to know before we even give patients Temodar whether they are going to respond to that agent.

I think we all would agree that we have made some significant advances from bench to bedside. But the real issue is whether we have affected patient outcome. I would argue that translationally those advances have not been as robust as we had once hoped they would be. Yet we certainly have learned a lot about the molecular biology of this tumor, from what we knew 15 years ago to the very elegant and sophisticated TCGA data.[4] For example, in glioblastoma, 80% of all those tumors have 3 core pathways that are dysfunctional during development and progression, and there are all these targets now that we can go after pharmacologically, which is exactly what we are doing with phase I and phase II clinical trials.

So what is the standard of care for a patient with a newly diagnosed glioblastoma? What are you going to tell this patient? The patient will have a 14.6-month median survival and a 2-year survival of 26%. If the patient is fortunate enough to have an methyl guanine methyl transferase promoter methylation, then Temodar is going to work better, and the 2-year survival is then 46%. That is clearly an advance, but where do we go from here? We take the exciting data that come out of the relapsed population of patients showing very nice response rates to Avastin, an antiangiogenic agent, and we build on that platform of radiation and Temodar. Then we do something that we have not done very well in the past: We stratify patients on the basis of their clinical risk factors, their promoter methylation status, and their molecular profile.

As surgeons, we have done a good job promoting the fact that the extent of resection affects outcome. Most studies to date are not volumetric, but 4 studies are volumetrically based. I think the most important one that we are all aware of in the last decade is the study that came out of M.D. Anderson[5] that showed that if we operate on a patient with glioblastoma, the best option for that procedure is to get a 98% extent of resection. Now, what that study did not show us is, What happens if we do not get to 98%? What is the next best level to get to? A study that is going to answer this question comes out of my group at the University of California at San Francisco on 500 newly diagnosed glioblastomas that is about to be published[6] that shows once again that the extent of resection is a critical factor as it relates to outcome. It also shows us, much like the M.D. Anderson study, that we have to be fairly aggressive; 95% extent of resection is better and gives the best result based on the RPA risk stratification process. But it also shows us for the first time that if we do not get to 95% resection, we still get a survival benefit beyond 78% resection. So we have to recalibrate the way we think about this disease from this all-or-none mindset to an all-or-most strategy. Thus, if we cannot get 95%, then we can still benefit the patient by getting $>$ 78% resection of the tumor.

What about grade III tumors? We showed in the last decade that the deletional status of 1p19q is very critical. But what our colleagues from North America and Europe showed us as time went on is that this was not really a chemosensitivity marker. In fact, this was a marker of biology; therefore, it has nothing to do with the response to radiation or chemotherapy. So we build on that platform. We take the 1p19q status, we stratify based on that, and then we randomize both in this country and in Europe to different combinations of Temodar at the time of radiation and beyond radiation to tell us whether the next best strategy for the grade III tumors is going to be something different from what we have now. Remember that original work was based on PCV; now we are going to learn about Temodar. The other point I want to make is that as surgeons we have to keep in mind that 5 studies in the last decade have shown us that the extent of resection is critical for this and for glioblastoma. So keep in mind that, when the frozen section comes back as grade III, we need to complete an aggressive resection and try to go as far as we can to remove the lesion.

Let us end with low-grade gliomas because I think we should consider these gliomas in a completely different way if we want to understand how to deal with patients with low-grade gliomas. The European Consortium did this very well in the early 2000s when it came up with a set of clinical prognostic factors such as age, histology, and tumor size as factors that define risk for this disease. What that study did not show us is what the prognostic significance is for the extent of resection. Jump forward now 6 years. Many of you, whether you know it or not, participated in this study. This was a prospective clinical trial from the Radiation Therapy Oncology group published in the *Journal of Neurosurgery*[7] showing what we already knew about histology and size, but it showed us for the first time that extent of resection was a very important prognostic factor. In fact, the group produced a very nice set of risk profiles for this disease based on what happened after the surgical procedure and how risk is defined. Yet at the same time, we have published an article on $>$ 220 cases of low-grade gliomas with volumetrically determined extent of resection.[8] We showed that size was important, of course, as well as extent of resection. In fact, in 2008, this was the first study in our field to demonstrate that if you get a complete resection radiographically, the likelihood of the 10-year survival was very close to 100%. That is not progression-free survival; that is overall survival. The other interesting thing we learned is that surgery affects the natural history of this disease; it reduces the risk of malignant transformation. A Hopkins group showed the same exact thing 2 years later on univariate and multivariate analyses.

Another point to make about extent of resection is seizure outcome. This is a big problem for all of our patients. It turns out, based on a study that we published a few years ago with $>$ 330 patients with low-grade gliomas, that if we

achieved a gross total resection, the patient was 16 times more likely to be seizure free than if he or she had anything less than a gross total resection, regardless of anticonvulsants and regardless of the seizure situation preoperatively.[9] We also realized that eloquence was an important risk factor. We combined eloquence with functional status, age, and tumor size. We assigned a point to each of these so that we could look at a scan preoperatively and determine whether the patient was low or high risk. We looked at those data and saw, regardless of extent of resection, that survival progression could be predicted preoperatively from these 4 criteria, and then we took that out into the community into 3 other institutions and did an external validation of that study.[10,11] Two years later, we published the compendium article and showed, indeed, that eloquence was related to extent of resection based on demonstrating that the patient's tumor is in an eloquent area and when not offering the patient mapping, the extent of resection is smaller, the 5-year survival is less than in the patient who you think is in one of those areas that is not so eloquent in which a more aggressive extent of resection can be done. So eloquence is a very key factor to the extent of resection and outcome.[12]

So where do we go from here with this disease? If you have a low-risk patient who is 40 years of age or younger and has a complete resection, you do not need to do anything more. Just sit tight and do scans every 3 or 4 months. If the patient has three of the criteria that define the tumor as high risk and based on the low-grade glioma response to Temodar, the neurooncology community is advocating that we do not sit tight and that we treat them with RT and Temodar. That study has been done, and we will know the results in 2013.

Finally, what do we know about the disease from a molecular point of view? Just as methylation of methyl guanine methyl transferase is important for high-grade tumors, methylation of the phosphatase and tensin homolog (PTEN) suppressor gene is key for this disease. In fact, it is seen in 50% of patients who have a low-grade glioma. The methylation status reflects a prognostic factor based on the fact that, if PTEN is methylated, the patient will progress earlier and consequently the tumor will transform. So we know a lot about the PTEN pathway. The good news is that pharmacologically we can block it. This is translational medicine at its best; we find the pathway and have something that we can block it with, and we can put that into a clinical trial. This is exactly what we are doing now for these patients, along with all these other areas of clinical research.

Thus, I think we have made a great deal of progress. It has been slow and frustrating at times. We have to keep going back to the operating room every day and do the best we can to achieve a maximal, safe resection in preparation for the next phase of treatment for patients with gliomas.

Disclosure

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

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