Does Extent of Resection of a Glioblastoma Matter?

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Glioblastoma (GBM) remains a deadly and incurable disease despite decades of intensive investigation. The development of novel surgical techniques and medical therapies has produced incremental gains in the length and quality of survival of patients with GBM. For example, it has been shown in prospective, randomized trials that chemotherapy, given as a surgical adjunct (eg, Gliadel) or in combination with and adjuvant to radiation therapy (eg, Temodar), has provided survival benefit.[1-3] There have also been notable advances in surgical techniques. Advances in routine and functional imaging, routine use of image-guided navigation techniques, use of novel intraoperative tumor visualization modalities, and use of intraoperative functional monitoring when indicated by tumor location permit neurosurgeons to remove enhancing tumor more completely while maintaining excellent outcomes in terms of neurological function.[4-7] Data show that the use of some of these techniques is associated with complete resections of enhancing tumor more frequently, and other articles in this volume have presented details on these studies. Whether improved extent of resection contributes to patient survival remains controversial, however, because there are no data from prospective, randomized studies demonstrating an association between extent of resection and survival in GBM. Retrospective studies, no matter how large or well designed, are unavoidably subject to difficulties with patient selection and bias. So, does the fact that we do not have evidence from prospective, randomized trials mean that the extent of resection does not matter? Conversely, can we use our retrospective evidence to definitively state that a complete resection of enhancing tumor is the goal for all patients?

THE STATE OF THE EVIDENCE: 2012

Other authors have provided detailed reviews of the evidence linking extent of resection to outcome for patients with GBM, so a comprehensive review of the evidence is not repeated here. There is consensus, however, that Class 1 evidence to address this issue does not exist. Some of the most often cited retrospective studies seem to indicate that there are quantitative cutoffs, in terms of percentage of resection when evaluated with volumetric techniques, that are of prognostic value.[8,9] The only prospective study to evaluate survival as the primary outcome measure was underpowered and compared only stereotactic biopsy with any extent of resection; it does not inform us as to the value of progressively more tumor resection.[10] To date, published evidence on the use of the surgical imaging adjunct 5-aminolevulinic acid (5-ALA) demonstrates a progression-free survival benefit associated with increased extent of resection but not an overall survival benefit.[5]

A HISTORICAL PERSPECTIVE

The philosopher Georges Santayana (1863-1952) wrote, "Progress, far from consisting in change, depends on retentiveness. When change is absolute there remains no being to improve and no direction is set for possible improvement: and when experience is not retained, as among savages, infancy is perpetual. Those who cannot remember the past are condemned to repeat it."[11] We in neurosurgical oncology are not the first to face the problem of determining whether surgical goal of a "complete" resection is of clinical value. In his "biography of cancer," Siddartha Mukherjee, MD, tells the story of the evolution of surgery for breast cancer.[12] In the early 20th century, surgical mastectomy was the only treatment modality available to treat breast cancer. The concepts of tumor metastasis and staging were not yet developed, and although mastectomy was widely used, surgeons were frustrated by their inability to reliably provide lasting benefit to their patients. Indeed, with the goal of trying to achieve more consistent, lasting survival benefit, some surgeons pursued the doctrine that a more extensive surgical resection was better. One of the pioneers of the so-called radical mastectomy was William Stewart Halsted, MD (1852-1922), who was surgeon-in-chief of the Johns Hopkins Hospital from 1890 to 1922. Under Halsted and his disciples (including Harvey Cushing, MD), a radical mastectomy started with resection of the breast and underlying pectoralis major but then was extended to include the clavicle, ribs, and axillary lymph nodes. With use of these more radical approaches, the local recurrence rates were lowered to an unprecedented level of $< 10\%$. However, 3-year overall survival remained only about 50% and not appreciably different from what it had been with mastectomy alone. The cost of these major anatomic resections, however, was tremendous in terms of morbidity and quality of life. As the concept of cancer metastasis developed, subsequent work showed that patients who had tumor present in their lymph nodes at the time of surgery had a 100% 3-year mortality, whereas those who did not have tumor present had a 100% 5-year survival. Although these new data raised the question of whether extent of resection for

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breast cancer was of value, the standard of radical mastectomy for all patients with breast cancer remained in place for decades.

An alternative approach to treating breast cancer was initially proposed by the London-based surgeon Sir Geoffrey Keynes (1887-1982) and introduced in the United States by George Barney Crile, MD (1907-1992). These surgeons pioneered the use of limited tumor mass extirpation (lumpectomy) followed by local irradiation. Independently, they demonstrated survival rates similar to those observed after radical mastectomy but without any meaningful disfigurement and with better quality of life. Crile attempted to launch a prospective, randomized trial of lumpectomy vs radical mastectomy, but this idea failed to gain traction in the United States. One can imagine that the arguments against a randomized trial were similar to those we hear today: It would be unethical to offer such a minimal surgery when radical mastectomy is the "standard"; surgeons will refuse to randomize patients; and without blinding there will be unavoidable bias. It took several decades before another surgical oncologist, Bernard Fisher, MD (1918-), formed the forerunner of today's National Cancer Institute cooperative research groups, the National Surgical Adjuvant Breast and Bowel Project, which launched a prospective, randomized trial to evaluate radical mastectomy vs lumpectomy with or without adjuvant radiation therapy for patients with newly diagnosed breast cancer. There was resistance in the surgical oncology community to this trial, and it took >10 years to fully enroll. In the end, however, >1700 patients were studied and the results were clear: The rates of local recurrence, distant metastasis, and survival were statistically identical for all 3 arms, but the morbidity and surgical mortality rates were much higher for the radical mastectomy arm.[13] The impact of this trial was immediate, and the routine practice of radical mastectomy was abandoned.

RELEVANCE TO GBM?

Is this historical perspective relevant to our understanding of the role of surgery for patients with GBM? One defining issue, from a surgical perspective, in patients with breast cancer is whether the disease has metastasized beyond the breast. Those without regional or distant metastases are likely to have a prolonged survival with "local" treatment (ie, treatment of the tumor mass and immediately surrounding tissue alone). Those with widely metastatic disease will not benefit from more extensive surgical resections. Unlike breast cancer, GBM does not "metastasize" outside of its organ of origin, the brain. A second key issue with respect to the debate about extent of surgery for breast cancer was the radicality of resection. A radical resection was defined as the organ of origin of the cancer, the breast, along with adjacent but anatomically distinct structures (eg, muscles, ribs, lymph nodes). Surgery for GBM almost never includes removal of adjacent anatomic structures (eg, cranial nerves, major vessels, skull).

Although it is true that the evolution of surgical oncology for breast cancer cannot be literally applied to our approach to surgery for GBM, many of the underlying principles are quite similar. We do not generally recognize GBM to be metastatic in nature because it does not spread outside the brain. However, GBM is well recognized to be locally invasive; tumor cells are present within normal, functioning brain many centimeters away from the enhancing tumor mass. Although we describe a gross total resection (or, more clearly stated, a complete resection of the enhancing tumor[14]) to be the surgical ideal, it can in no way be compared with a pathologically defined margin-free lumpectomy that is the convention for breast surgery. Patients with GBM always have unresected tumor cells present after even the most extensive surgery, and similar to the impact that metastasis plays in defining outcome in breast cancer, the poor survival outcomes we observe are the inevitable consequence.

The issue of the impact of radicality of resection on the morbidity, surgical mortality, and quality of life observed in breast cancer surgery also applies to neurosurgical oncology. Although radicality is defined anatomically in breast cancer, it needs to be defined by functional anatomy in GBM surgery. At one extreme, Walter Dandy, MD (1886-1946), attempted hemispherectomy for patients with GBM and, despite the obvious cost in function, failed to see a meaningful survival benefit.[15] Newer tools, including functional magnetic resonance imaging (MRI), diffusion tensor imaging, electrocorticography, and awake functional monitoring, allow the neurosurgeon to remove enhancing tumor closer to important functional anatomy, thereby increasing the extent of tumor resection. However, these same tools, along with additional imaging methods such as intraoperative MRI, 5-ALA administration for fluorescence-guided surgery, and image-guided navigation, also serve to increase the risk of meaningful neurological deficits after surgery.[16] Not only can surgically acquired neurological deficits lead to reduced quality of life, but retrospective evidence suggests that these deficits are associated with a decreased survival.[17] In the end, it may well be that for some patients whose tumors are remote from functionally significant cortex and white matter, maximizing the extent of resection (perhaps even beyond the enhancing margin) is associated with a survival benefit of a meaningful magnitude. However, the same may not be true for patients whose tumors are immediately adjacent to, or grossly invading, functionally significant areas of the brain. For these patients, the likely more relevant factor is the surgeon's judgment and ability to balance the competing effects that extent of resection and surgically induced neurological deficits have on outcome.

MAKING SURGERY MORE EFFECTIVE FOR GBM

It is unlikely that the development of newer techniques beyond the ones we have available today, including intraoperative MRI and 5-ALA tumor fluorescence, will have a meaningful impact on the goal of increasing the extent of resection of GBM. Even without the techniques of intraoperative MRI and 5-ALA, the M.D. Anderson group reported $>98\%$ resection of enhancing tumor in nearly 50% of their patients; the median extent of resection for the others was 88%.[8] Perhaps for a small subset of patients, one

can imagine that the benefit of even more radical resections beyond the enhancing margin will be explored, but for most patients, extending resection into areas of fluid-attenuated inversion-recovery abnormality on MRI will inevitably be associated with functional loss, so resection of 100% of enhancing tumor likely is a real ceiling in GBM surgery.

Nevertheless, neurosurgeons can play an important role in advancing our ability to treat patients with GBM and other brain tumors in a number of other ways. Neurosurgical oncologists are critical gatekeepers for translational research. The tissue that we obtain, when properly prepared and preserved, is invaluable for research focused on the genomics, proteomics, and metabolomics of cancer; the development of new prognostic markers; the evaluation of the effects of drug treatment; and the establishment of cell cultures that are needed for basic biology research and therapeutic development. Furthermore, because GBM is a locally invasive disease, there are opportunities for neurosurgeons to participate in the development and application of novel, surgically delivered treatment strategies. It has been almost 2 decades since the first surgeon-delivered local chemotherapy system was approved by the Food and Drug Administration, and although the clinical impact of that approach has been modest, the opportunity remains for surgeon-led development of new local and regional therapeutics.

CONCLUSIONS

No matter the extent of resection, surgery for GBM cannot be viewed as curative. At best, the survival benefit associated with more radical resection may be modest and needs to be balanced carefully against the negative impact that neurological deficits have on both the length and quality of survival. Hence, the pursuit of more radical brain tumor resections is best performed by neurosurgeons who are well versed in the techniques of preoperative and intraoperative functional mapping and monitoring. Further debate based on retrospectively acquired data is not likely to be informative; prospective clinical trials are the only way to definitively demonstrate the value of new techniques to increase the radicality of surgical resection. Ultimately, the greatest impact that neurosurgeons can have on advancing the survival of patients with GBM is more likely to come from their involvement in therapeutic development and delivery rather than in the development of new techniques for tumor resection.

Disclosure

Dr Vogelbaum has submitted patent applications for and is leading the commercial development of devices for surgically mediated drug delivery to the brain. He has also received honoraria from Merck, Pharmaco-kinesis, and Neuralstem.

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