Neurosurgery's Impact on Neuro-Oncology—"Can We Do Better?"—Lessons Learned Over 50 Years

Adam M. Robin, MD*
Jacob A. Pawloski, MD*
James M. Snyder, DO
Tobias Walbert, MD
Lisa Rogers, MD
Tom Mikkelsen, MD
Houtan Noushmehr, PhD
Ian Lee, MD
Jack Rock, MD
Steven N. Kalkanis, MD
Mark L. Rosenblum, MD

Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA

*Adam M. Robin and Jacob A. Pawloski contributed equally to this work.

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Correspondence:
Adam M. Robin, MD,
Department of Neurosurgery,
Henry Ford Hospital,
K11 Clinic, 2799 W Grand Blvd,
Detroit, MI 48202, USA.
Email: arobin1@hfhs.org

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PART 1: THE BIRTH OF NEUROSURGICAL ONCOLOGY

Historical Perspectives and the Foundational Work That Paved the Way

Neurosurgeons of the late 19th and early 20th centuries encountered many obstacles. Most notable among them were an inability to accurately localize the surgical target and inadequate experience and techniques of working around the brain. Regarding intrinsic brain tumors, the early 20th century surgeon and neurologist collaborated, based on an early understanding of neurophysiology and neuroanatomy, to localize the lesion within the skull. Surgeons would often use large incisions and "brain needles" to help identify tumors not visible on the brain surface. With only rudimentary ether–based anesthesia and little effective hemostasis available, the first brain tumor surgeries were rushed and frequently fatal endeavors.[1] Often, the tumors could not be found at all.[2] The first textbook published on brain surgery was written by neurologist Starr,[3] wherein he described 50 brain tumor surgeries with a 46% recovery rate after successful localization of the tumor. Surgeons were often weary about delving into the unknowns of the intracranial space solely on the advice of the neurologist. Combining this with an initial surgical mortality rate greater than 40%, one can see why brain tumor surgery at the time was not viewed as an improvement on the natural history of the disease.

Only in 1905 do we mark the establishment of neurological surgery as a distinct subspecialty among surgeons in the United States.[4] Advances in operative techniques and improved understanding of surgery on the nervous system by Cushing[5] and others led to improved patient outcomes. Perioperative mortality decreased to 10% to 15% over the subsequent 20 years. However, difficulties with tumor visualization before and during surgery led to partial resection, subsequent edema, and bleeding, further increasing surgical risk. To mitigate this risk, surgeons frequently opted not to replace the bone flap and in some cases, surgeons advocated for simple removal of the bone flap as treatment, leading to debate over the role of so-called external decompression in early brain tumor surgery. Because of an inadequate means of controlling intracranial pressure, some postulated whether surgery made tumors grow. Little was known about the nature of intrinsic brain tumors. Bailey and Cushing[6] published the first histopathological classification of intrinsic brain tumors. Around the same time, the advent of ventriculography and neuroangiography helped lay the foundation for an era of brain tumor surgery that persisted well into the second half of the 20th century.[7,8] Important developments in anesthesia, the utilization of antibiotics, and the introduction of dexamethasone in 1962 to treat cerebral edema greatly improved the safety of brain tumor surgery.[9] Jelsma and Bucy[10] in a landmark publication reported a step-wise decrease in operative mortality from 48% in 1945 to 1949, to 22% in 1950 to 1961 and down to 2.9% after 1961 with the advent of pre- and postoperative dexamethasone administration. Early evidence also supported the intuitive idea that survival and functional outcomes were linked to the amount of tumor that could be removed, and external decompression alone rarely benefited the patient.[10–12]

Foster Kennedy humbly summarized the remaining challenges.[10]

> "He who cares for patients suffering from brain-tumour must bring to his problem much thought and stout action. There is need also of a formidable optimism for the dice of the gods are loaded!"

ABBREVIATIONS: NCE, noncontrast enhancing; **TMZ,** temozolomide.

PART 2: PICTURE CARE IN 1970

To understand how far neurosurgical oncology has progressed in the past 50 years and chart a course for the future, first picturing neurosurgical

care in 1970 will be helpful. Surgeons continued to deal with the problem of localizing the surgical target preoperatively. The ability to localize the tumor was based on the neurological examination, and the only images available to suggest the region and extent of a tumor were the radionuclide brain scan (Figure 1, left) and cerebral angiograms (Figure 1, right). Angiography would show distortion of normal neurovascular anatomy by a space-occupying mass, and in some glioblastomas, abnormal vasculature could be observed in part of the lesion.

Large craniotomies would be performed over the suspected region containing the tumor, and a large dural opening was made. While the brain started to swell, the cortex was incised and an Elsberg cannula was passed into the brain substance until one could feel a difference in brain consistency. Once the tumor was suspected, the lesion would be biopsied using handheld retractors. If a tumor was confirmed, a rapid removal was attempted while controlling bleeding with a bipolar forceps and gentle compression. Subtotal resection was common, and patients were often clinically worse in the immediate postoperative period.

The estimated extent of resection was subjective and generally based on the surgeon's observations. Adjuvant therapies were also limited. Brain swelling was managed with urea or mannitol and corticosteroids. Although there was some suggestion of effectiveness, the utility of radiation or chemotherapy was yet to be established or implemented into standard practice.[13] The postoperative administration of whole brain radiation therapy was common a couple of weeks thereafter. To summarize, a patient diagnosed with a brain tumor in 1970 would be offered surgery based on only indirect tumor localization, and if they had most of the tumor resected, they could expect an average survival of 6 to 9 months. Those who aspired to improve the care of patients with brain tumors were still outpaced by a disease that was yet to come into full focus.

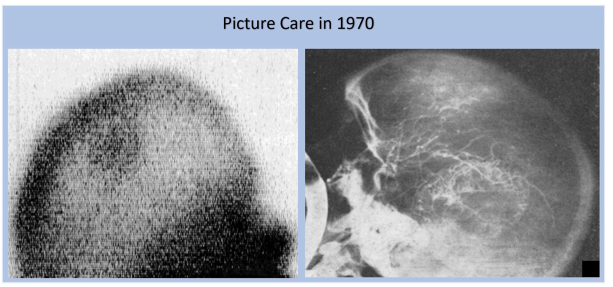

FIGURE 1. *Picture care in 1970. Radionucleotide scan in a patient with a brain tumor (left). Cerebral angiography in a patient with a temporoparietal glioblastoma (right). Abnormal vasculature is seen in part of a glioblastoma.*

PART 3: DECADES OF ADVANCEMENT

True advances, especially disruptive innovations, are frequently met with skepticism. In 1971, Godfrey Hounsfield introduced the computed tomogram (CT) scan. The neuroradiologist at the National Neurological Hospital at Queen's Square in London "explained to Hounsfield that with pneumoencephalography, plane tomography, and angiography there was no existing brain lesion that could not be diagnosed by imaging already. There was no obvious clinical use for a CT machine as tomograms in general weren't really all that useful. He was sent packing." [14] It was not until 1973 to 1974 that the EMI CT scanner became readily available that true advancements in surgery were enabled. This localization advance also promoted the development of regional postoperative radiation therapy later in that decade.

In 1971, Paul Lauterbur conceived of nuclear magnetic resonance (NMR) imaging but was met with the same skepticism as Hounsfield. Lauterbur's discovery would ultimately lead to the first commercial MRI scanners a decade later. "Lauterbur filed a preliminary patent disclosure, but he received advice from all sides that MRI had no imaginable commercial use. He would need to spend money to file the actual patent and allowed the 1-year deadline to pass without filing. He published the method in Nature after successfully appealing an initial rejection by an editor who felt this would be of limited specialist interest only." [14] The first commercial MRI scanner was introduced in 1980. Identification of tumors and surgical localization improved remarkably when MRI technology advanced and was used commonly in 1984.

However, neurosurgeons began to realize that even the most effective surgeries would need to be aided by equally effective postoperative care and adjuvant therapies to improve outcomes for malignant gliomas. The first effective adjuvant therapies were beginning to take shape, fostered by the foundational work of the Brain Tumor Cooperative Group in the 1970s led by Walker and Wilson. Bischloroethyl nitrosourea (BCNU) and radiotherapy in combination extended the median overall survival from an unacceptable 4.2 to 10 months in their randomized study.[15,16] Introduction of adjuvant oncological therapy was a major step forward and further improved survival for patients with glioblastoma multiforme (GBM). However, further advancements in subsequent decades proved incremental. Oertel et al[17] demonstrated that the overall prognosis of patients with GBM did not change significantly between 1978 and 1995, leading neurosurgeons and oncologists to ask themselves, can we do better? Temozolomide (TMZ), a better tolerated oral alkylating therapy, in combination with fractionated radiation and further adjuvant temozolomide, also known as the "Stupp regimen," has become the standard of care since 2005 and offered another incremental increase in survival.[18] Further demonstrated survival advantage has been conferred by the addition of tumor treatment fields to the Stupp regimen in select patients.[19,20]

With growing accessibility of MRI, tumor volumes before and after surgery could be better studied and mounting evidence for complete tumor removal further informed neurosurgical decision-making. In 2001, Lacroix et al[21] identified that among 416 patients, obtaining a near gross total resection >98% conferred a

median survival advantage of 4 months (median overall survival 13 months) and any resection >90% conferred some meaningful survival over those with lesser resections. Sanai et al[22] added to our understanding, finding that there was a significant survival advantage conferred with any extent of resection >78% and the improvement was incremental, leading to a median survival of 16 months in those who achieved gross total resection. These results were echoed among other neurosurgical groups, and it became evident that the postoperative MRI shortly after surgery was necessary to determine the extent of resection accurately and

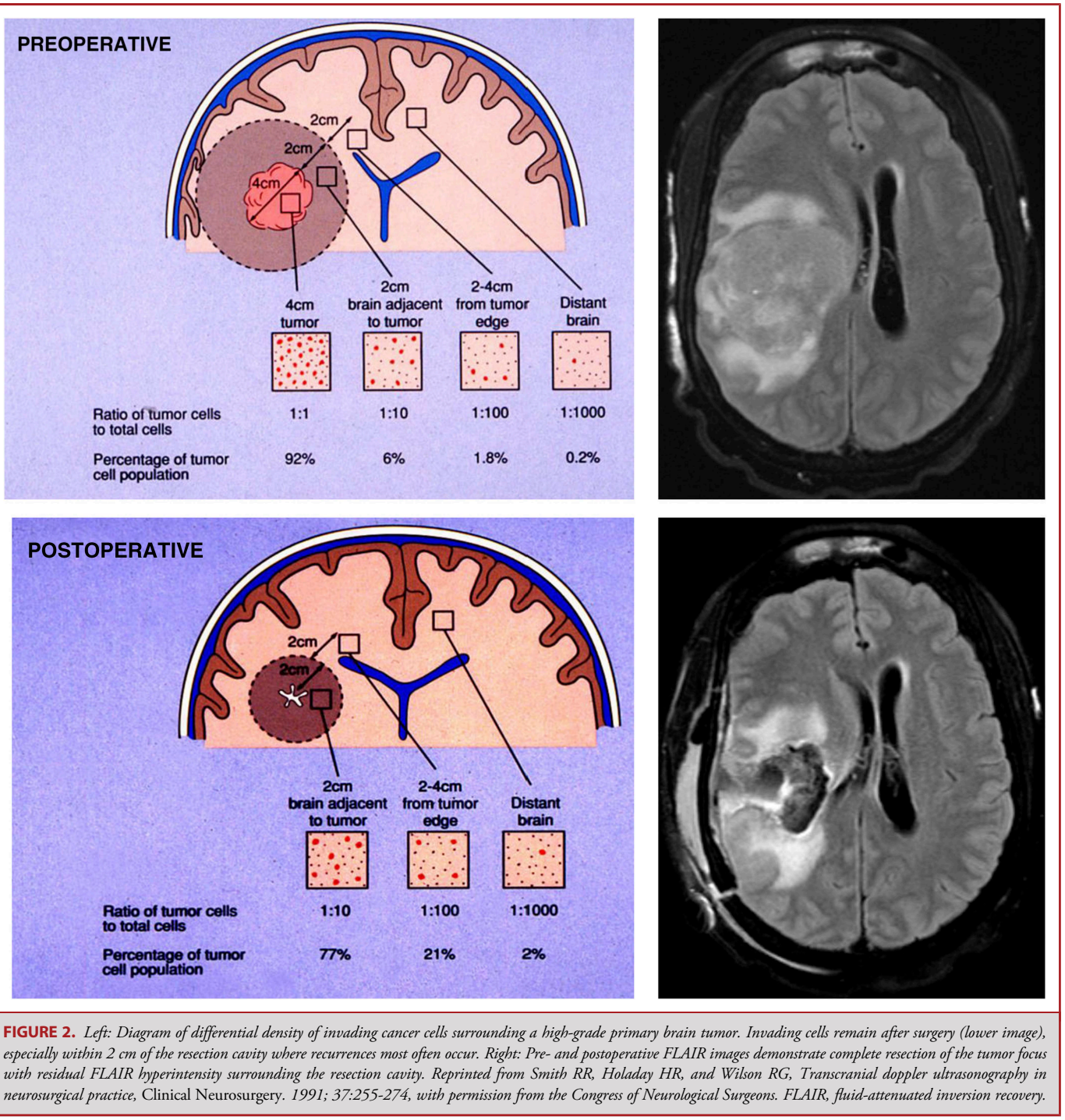

FIGURE 2. *Left: Diagram of differential density of invading cancer cells surrounding a high-grade primary brain tumor. Invading cells remain after surgery (lower image), especially within 2 cm of the resection cavity where recurrences most often occur. Right: Pre- and postoperative FLAIR images demonstrate complete resection of the tumor focus with residual FLAIR hyperintensity surrounding the resection cavity. Reprinted from Smith RR, Holaday HR, and Wilson RG, Transcranial doppler ultrasonography in neurosurgical practice,* Clinical Neurosurgery. *1991; 37:255-274, with permission from the Congress of Neurological Surgeons. FLAIR, fluid-attenuated inversion recovery.*

prognosticate survival.[23] In addition, larger glioblastomas at diagnosis did not necessarily portend a worse prognosis than smaller tumors, and the residual volume after surgery and the extent of overall resection were found to be independent predictors of improved overall survival.[24,25] As the data advocating for maximal tumor removal came more sharply into view, data suggesting that new postoperative deficits led to a significant decrease in overall survival accompanied it.[26] Duffau and Mandonnet[27] described the concept of the oncofunctional balance, in which the value of further resection must be weighed against the potential harm to the patient, survival benefit, and quality of life. Yong and Lonser[28] went on to refine this concept in the context of surgical decision-making and the risk of making the patient with a brain tumor clinically worse. Thus, within the last decade, we have realized that effective treatment of a patient with brain tumor requires safe, maximal resection of the contrast-enhancing disease, when possible, but without causing new neurological deficits.[26–29]

As a means to achieving this result, many tools have been added to the surgeon's armamentarium with the goal of safer, more effective surgery. Neuronavigation, ultrasound, and 5-aminolevulinic acid fluorescence improve on our ability to visualize the tumor intraoperatively. Diffusion tensor imaging, awake craniotomy, and neuromonitoring have allowed surgeons to make safer cuts, actively avoiding the most eloquent cortical areas and subcortical fiber tracts. A meta-analysis of intraoperative neurostimulation for brain mapping demonstrated improved extent of resection and a significant decrease in permanent neurological deficits.[30] Greater insight into neural circuitry and the neurobiology of the mind, increased computer processing power, and progress in machine learning allow for optimized preoperative planning and preservation of critical neuroanatomy.[31,32] Intraoperative MRI has been installed in many comprehensive tumor centers, allowing surgeons to reassess the residual tumor and account for brain shift from the surgery, significantly increasing the likelihood of achieving a gross total resection.[33] Minimally invasive laser ablations can now offer safe cytoreductive benefit for tumor foci that would have been unfavorable targets for open surgery.[34,35] Similarly, neuronavigated, minimally invasive brain retractors placed along critical structures rather than through them allow for microsurgical resection of deeply seated lesions previously believed of as inoperable.[36]

Despite complete resection of the observed solid tumor and adjuvant therapy, high-grade gliomas are characterized by their relentless progression. The likelihood of recurrence is related to various aspects of the tumor's biology and our current treatment paradigms. There are infiltrating tumor cells outside the contrast-enhancing portion of lesion, which are difficult to visualize with current technology and in many cases, more difficult to access surgically (Figure 2). There is a growing body of evidence focused on so-called *supratotal* resection of brain tumors. Li et al[37] demonstrated that in a single-center cohort, the median survival could be increased from 14 to 20 months with resection of all the contrast-enhancing disease and >53% of the noncontrast-enhancing (NCE) disease. Molinaro et al[38] demonstrated that in certain subgroups of patients, the aggressive resection of >90% of NCE disease conferred significant increases in overall survival up to a median of 36 months. We are beginning to understand that the benefit of supramarginal resection is also partly affected by the degree of invasiveness of the tumor. Using mathematical models of diffusivity, diffuse tumors with a larger portion of fluid-attenuated inversion recovery (FLAIR) relative to contrast enhancement were shown to benefit from the most aggressive NCE resection compared with nodular tumors with relatively smaller areas of perilesional NCE disease.[39] Although the preponderance of currently available evidence suggests that greater resection of NCE disease may be beneficial to patients, in a recent systematic review, the authors suggest that there are insufficient data and methodology for a broad recommendation in favor of supratotal resection.[40] As we move toward more aggressive resections, a more nuanced understanding of brain networks and fiber tractography combined with effective utilization of superficial and subcortical stimulation will be essential to prevent new neurological deficits and minimize the morbidity of surgery on our patients.[29–31]

PART 4: PRECISION MEDICINE: THE NEXT DISRUPTIVE INNOVATION

Molecular Biology Advances Lead to Molecular Therapeutics

Perhaps most disruptive of the recent innovations in neuro-oncology are the collective biomolecular advances that have yielded greater understanding of GBM biology. Although median survivals have increased steadily over the past 20 years, there remains wide variability when examining the survival of individual patients. Some patients may respond extraordinarily well to their adjuvant TMZ, whereas others with a seemingly equivalent tumor and treatment go on to suffer from aggressive disease and recurrence. The fifth edition of the World Health Organization classification of tumors of the central nervous system published in 2021 well reflects the advances in our understanding of disease biology and illustrates the role that molecular diagnostics have come to play alongside more traditional immunohistochemistry.[41] Identification and characterization of specific GBM molecular features has implications for diagnosis, prognosis, and prediction of treatment response and increasingly can inform our surgical objectives as well, ushering us into the molecular era of neuro-oncology.[42–44]

Much effort has been invested in identifying and characterizing specific mutations that may serve as therapeutic targets in primary or recurrent glioblastoma including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), the tyrosine protein kinase mTOR, fibroblast growth factor receptor (FGFR), the proto-oncogene BRAF, and other genes.[45] Although it is known that tumors with a methylated methylguanine-deoxyribonucleic acid methyltransferase (MGMT) promoter region will have an enhanced response to temozolomide and better

prognosis, presumably because of downregulation of the MGMT gene transcription by hypermethylation, this has not translated into new therapies for patients.[19,46] To date, VEGF inhibition with bevacizumab is the only targeted approach that can improve progression-free survival in recurrent GBM, but disease recurrence remains nearly inevitable.[47–49] GBM exposed to VEGF inhibition may respond initially, but the tumor cells that remain can cause recurrence by upregulating other angiogenic pathways or activating pathways that enhance invasiveness of the tumor cells without requiring angiogenesis.[47] It is likely that by targeting 1 pathway directly, we may cause a temporary regression, but at the same time, induce an alteration in the tumor state and microenvironment that enables recurrence.[50] Tumor temporospatial heterogeneity and subclonal populations thus enable the development of evasive resistance to any single directed therapy. When considering a potential cure for glioblastoma, we are not likely to achieve this with a single silver bullet; rather, the treatment will likely consist of a collection of therapies, all focused at different areas of the tumor molecular biology.

At present, there remain several biological issues to address before molecular therapeutics can reach its optimal goal and potentially become standard of care (Table 1). Research should focus on the most prevalent and actionable molecular alteration in a patients' tumor. The issues of tumor heterogeneity, tumor stem cells, and the invading tumor cell need to be addressed. In addition, the inevitable resistance development in the tumor cell population and the common normal tissue toxicity observed in clinical trials need to be understood and, if possible, avoided.

The question of which genetic or epigenetic alterations are important remains unanswered. Genetic and epigenetic changes that occur within the tumor microenvironment in response to chemotherapies are also problematic.[51] The Glioma Longitudinal Analysis Consortium is focused on characterizing the molecular alterations that occur during the course of the disease from diagnosis through recurrence.[52] The group has shown that 70% of tumors had an increased mutation burden at the time of recurrence.[53] They also demonstrated that treatment with alkylating agents such as temozolomide can induce hypermutation states in glioma and that environmental and treatment-related selective pressures can produce more aggressive tumor cell subpopulations linked to disease progression and decreased survival.[52] Using a pan-European cohort of 176 paired primary and recurrent GBM isocitrate dehydrogenase gene (IDH) wild-type samples, Draaisma et al[54] observed changes in mutation status for all oncogenes that they examined.

TABLE 1. Remaining Biological Problems for the Development of Molecular Therapeutics

1. Which molecular abnormalities observed (genomic, epigenomic, or both) are important?
2. Tumor heterogeneity—in space and time
3. Tumor stem cells—are they the key target?
4. The invading tumor cell—altered sensitivity to treatment?
5. Combating resistance development—it's inevitable!
6. Normal tissue toxicity—systemic and brain

TABLE 2. Developing Therapeutics to Specific Molecular Targets

1. Develop relevant preclinical models
2. Confirm brain delivery in humans
3. Confirm in vivo antitumor activity (identify surgical trial opportunities)
4. Encourage industry and governmental support for therapeutic cocktails

Early evidence suggests that recurrent GBM can respond to personalized treatment based on repeat tissue characterization at recurrence in selected patients and there are data in support of histology-agnostic targeted therapy for other malignancies increasingly published over the last several years.[55–57] Patients and treatment teams may be missing a valuable opportunity for tissue characterization at the time of progression or recurrence, particularly given the favorable safety profile and accuracy of current minimally invasive biopsy techniques. Recurrent GBM often harbors molecular features distinct from their primary counterparts.[51,58,59] Molecular evolution of IDH wild-type glioblastomas affects survival and can inform precision medicine trial design.[54] Obtaining multiple tissue samples from primary and recurrent GBMs, particularly after chemotherapy, will enable further investigation into the alterations to the tumor microenvironment by treatment and aid in discovery of molecularly targeted therapies.

To develop precision therapeutics to specific molecular targets, several prerequisites are likely to be critical (Table 2). Preclinical models in the laboratory will be necessary. Confirmation of drug delivery into the human brain tumor will be important. Confirmation of anticipated in vivo antitumor activity is paramount. To develop therapeutic cocktails of multiple agents that target different molecular abnormalities, industry and governmental support will likely be needed.

As is true in other tumor types, glioblastoma cells undergo epigenetic changes and develop areas of hypermethylation around specific deoxyribonucleic acid (DNA) promoter regions, resulting in altered gene expression.[60,61] Abnormal methylation of conserved cancer cell DNA regions in promoters known to regulate gene expression (CpG islands) in cancer cell DNA has been identified as a key epigenetic signature that is often unique to different cancer types.[62] Glioblastoma cells shed DNA into the blood stream, and altered methylation patterns have been studied in plasma cell–free DNA. CNS tumors including glioblastoma have been accurately categorized based on DNA methylation profiles acquired from serum samples.[63,64] This area of active investigation has potentially significant clinical utility, with the potential for minimally invasive diagnosis and characterization of a tumor or recurrence through a simple blood draw, the so-called liquid biopsy.

There is growing recognition of spatial and temporal tumor heterogeneity, not only in primary brain tumors but also increasingly in brain metastases.[51,58,59,65] These findings have implications in clinical trial design because driver mutations present in primary tumors at diagnosis may be absent in the metastatic tumor. Moreover, clinically actionable driver mutations not found on initial analysis of

the primary tumor site may be present in up to 50% of metastatic brain tumors, further underscoring the role for biopsy of recurrent or metastatic disease sites over time to help guide treatment.[55,66,67]

The complete realization of precision medicine will likely involve a cocktail of different targeted therapies with the hope of transforming a patient's cancer from an aggressive and terminal illness to a chronic disease, which has been successfully performed with patients harboring the human immunodeficiency virus.[68] Patients diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome in the 1980s had an average survival measured in months, whereas those who receive the diagnosis today can live a full and healthy life. We can hope that this day will come for patients suffering from glioblastoma as well. As we guide patients on increasingly longer journeys living with their disease, hope itself can be a powerful tool.

PART 5: HOPE SPRINGS ETERNAL

Comprehensive Brain Tumor Centers and the Patient Experience

Patients routinely describe the moment of a brain tumor diagnosis as one of emotional extremis associated with feeling of shock, panic, and difficulty in processing the information.[69–72] Much effort over the past 50 years has been dedicated to providing these patients with new and advanced ways to study and treat their cancer. Amid this era of rapid scientific advancement and progress in the field of glioblastoma management, it is important that we continue to consider the disease through the eyes of the patient. A physician's ability to convey truth while also instilling hope may be as important to the patient and their family as the medical care they receive.[71,73] Patients need to be supported through the continuum of their disease process, not just the perioperative period. To achieve these goals, an emphasis should be placed on establishing and strengthening collaborative centers for the management of brain tumors.[72]

Institutional tumor boards involving neurosurgeons, neuro-oncologists, and radiation and medical oncologists are essential for ensuring that patients are receiving the best possible care, but caring for patients with brain tumors requires much more than surgery, radiation, and chemotherapy (Figure 3). In his keynote lecture to the 1988 Congress of Neurological Surgeons, Rabbi Harold Kushner, the author of *When Bad Things Happen To Good People*, noted that "patients with cancer are most afraid of fear and abandonment." [71] Although our patients with brain tumors do not often experience pain, they and their families too frequently can feel abandoned, especially late in their disease progression. Comprehensive brain tumor centers are increasing in number, with the focus of providing patients with a holistic and supportive network of physicians, nurses, care navigators, clinical trials teams, psychological support and case management resources, and other dedicated staff to provide support for patients throughout their continuum of care. Nurse navigators who are available for questions and communicate between physicians and patients improve the quality of life for the patient and their family and protect patients from the fear of abandonment. Support groups help provide a bulwark against the isolation and stress that often accompanies the role of a caregiver to a patient with brain cancer. The Hermelin Brain Tumor Center is but one example of such comprehensive brain centers.

Paramount to the patient's struggle is the ability of the physician to maintain an atmosphere of hope, even in the face of a grim prognosis. Our patients have taught us that from their perspective, this is as important as any surgical treatment that we can offer.[71,72,74] Psychosocial support should also be focused on those closest to the patient, who often bear the burden of care, while their own health and well-being suffer. Caregivers faced with feelings of helplessness, isolation, and financial difficulties should be assisted by providing frequent and timely communication and support resources. In fact, increasing caregiver centers are springing up within comprehensive brain tumor centers around the country.[75] Collaborations between patients, caregivers, and brain tumor center staff such as patient and family advisory councils can provide an important mechanism for continuous quality improvement within the comprehensive brain tumor center. We have found patient and caregiver feedback to be an invaluable resource to our own comprehensive brain tumor center.

PART 6: LESSONS LEARNED OVER 50 YEARS

Can We Do Better?

The role and impact of a neurosurgical oncologist has evolved tremendously over the last 50 years, yet we are still faced with the same question, "Can we do better?"

The way forward should focus on achieving several separate goals as a consequence of lessons learned over the past 50 years (Table 3). Surgically, we should strive to develop techniques to achieve the maximal cytoreductive effect without causing untoward neurological deficits in the patient. We should be most aggressive with low-grade gliomas because these tumors offer the highest likelihood of long-term benefit and probably harbor fewer and less widespread invading tumor cells. After surgery, we need to focus our efforts on understanding the molecular biology of each tumor. By further developing systems to store and annotate tumor and serum samples, we can contribute to the emerging science of molecular diagnostics and precision therapeutics for brain tumors.[76] We should obtain specimens from multiple tumor regions and, when clinically appropriate, from invaded brain to enable studies of invading tumor cells. Because of the cellular complexity of solid tumors, which contain normal brain elements and infiltrating immune cells along with the tumor cell component, studies of isolated tumor cells should be encouraged. Perhaps the invading cells have a novel target to which therapeutics can be directed. When developing treatments, this research should consider normal tissue toxicity and tumor cell sensitivity. The development of targeted, personalized therapies is the next and most promising frontier in glioblastoma treatment.

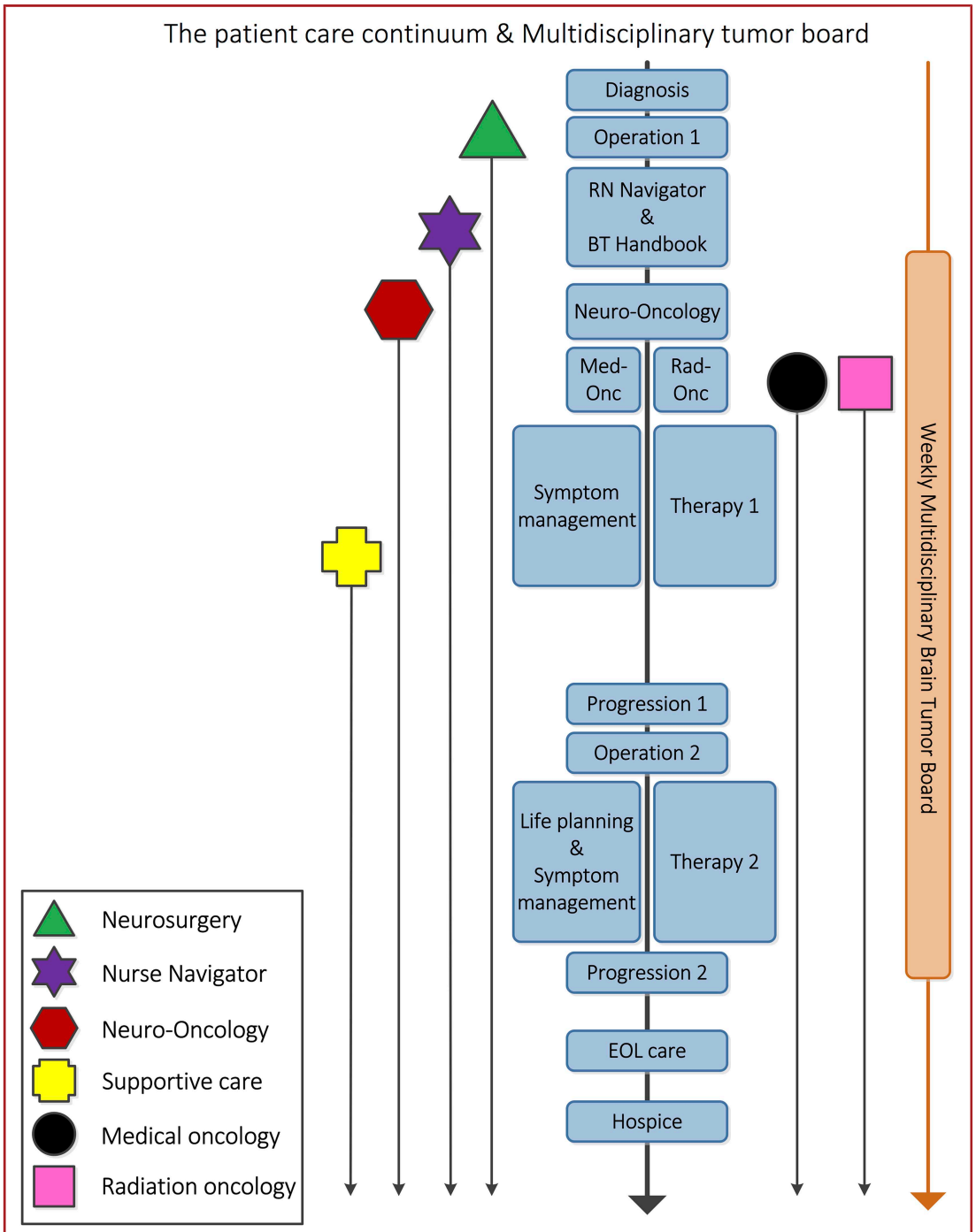

FIGURE 3. *A schematic representing a comprehensive multidisciplinary continuum of care model for the patient with a brain tumor. Reprinted by permission from Copyright Clearance Center: Springer Nature,* Journal of Neuro-Oncology, *Through the patient's eyes: the value of a comprehensive brain tumor center, Robin AM, Walbert T, Mikkelsen, et al, 2014.*

Patients with brain tumor, when possible, should be directed to comprehensive brain tumor centers so that they can have access to leading-edge therapies and the support services and continuum of care that the tumor center provides. Contributing to research endeavors and participating in clinical trials gives patients and clinicians hope. It is also important to

TABLE 3. Lessons Learned Over 50 Years in Surgical Neuro-Oncology

Surgical goals
• We cannot remove every last tumor cell, but the fewer cells remaining, the better
• Do not cause deficits
• Use minimally invasive technologies if possible
• Be most aggressive with lower-grade gliomas
Evaluating the tumor molecular profile
• Develop an optimum tumor banking system to collect tissue and serum/blood
• Obtain specimens from multiple tumor regions and invaded brain
• Study isolated tumor cells (eg, single cell RNA sequencing)
• Study invading tumor cells—will we find a novel target?
Research efforts
• Supporting research and clinical trials gives the patient and us hope
• Focus on normal tissue toxicity, not just tumor cell sensitivity (as often performed in the past)
• Cancer research is a potent philanthropic stimulus to support all needed efforts
The patient is our most important consideration
• Comprehensive, multidisciplinary tumor boards and programs are optimal
• The care team is as important as us (especially the neuro-oncologist and nurse)
• Communicate throughout with the patient and family—avoid a fear of abandonment
• Improve system processes to lessen anxiety and ensure up-to-date treatment
• Our words mean a lot, our attitude is obvious, give them something to hope for

recognize that cancer research is a potent philanthropic stimulus that can yield important funds to help support all the goals mentioned in this article.

Throughout this important work, it is critical to view this devastating disease through the eyes of the patient. Many patients remember the precise wording and circumstances surrounding the moment of their brain tumor diagnosis for the rest of their lives. That moment is an opportunity for the neurosurgeon to have a tremendous, positive impact on our patients and their families. It is the challenging yet rewarding job of the neurosurgeon to be informative and honest with the patient, while reassuring them that they will be cared for, lessening their anxiety and providing realistic hope. When delivering a new diagnosis, start the conversation by calming the patient's and family's fears, then review the diagnostic findings, and discuss the science. Prognoses are based on an average of survival statistics and mathematical estimations, but every patient is different. Assure them of up-to-date treatment. Build the relationship between the care team and the patient family and focus on their responses and questions. Improvements in care processes are possible along the care continuum. For example, when possible, at the follow-up clinic visits during treatment, the repeat imaging can be performed and the results can be shared with the patient the same day. This simple process improvement can significantly lessen anxieties for both the patient and their family. Finally, we need to be aware that the words we use explaining the situation to the patient mean a lot, and our attitude is obvious to all. We must provide patients with the truth, but above all, give them hope.[71]

For glioblastoma, the role of neurosurgeons from the 1970s to 2020 was based on 3 objectives: obtain a tissue diagnosis, remove as much tumor as safely possible, and play a role in tumor boards. However, it is important to realize that with new capabilities, our role has expanded (Table 4). Neurosurgeons in 2021 and beyond need to also obtain tissue for molecularly directed precision therapeutics, consider safely obtaining a tissue biopsy at the time of recurrence for guiding next-line therapy selection, and play an active role in the development of comprehensive brain tumor centers. In summary, neurosurgical oncologists should be innovative and open to change, aggressive (within limits), enablers of scientific advances, compassionate and supportive, and leaders in the multidisciplinary neuro-oncology team. Why are these things

TABLE 4. The Role of a Brain Tumor Surgeon: 1970 to 2020 vs 2021+

Role of a neurosurgeon (1970-2020)	Role of a neurosurgeon (2021+)
• Obtain a tissue diagnosis	• Obtain a tissue diagnosis
• Remove as much tumor as safely possible	• Obtain tissue for molecularly directed precision therapeutics
• Play a role in tumor boards	• Remove as much tumor as safely possible
	• Play an increased role in tumor programs
	• Consider safely obtaining tissue at recurrence for new therapeutic selection

important? Because the future of neurosurgical oncology is in our hands, and the future can be bright.

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