Surgical management of malignant gliomas - Challenges and strategies

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Introduction

Malignant gliomas continue to pose a serious challenge to neurooncologists in general and neurosurgeons in particular. Since the first report of an attempted glioma surgery by Godlee in 1884 (1), neurosurgeons have constantly grappled with this challenge. Advances in surgical techniques and adjuncts notwithstanding, prognosis remains dismal even today. The enthusiasm and optimism promised by current multimodality therapy is dampened by the stark reality of the inevitability of recurrence especially in glioblastomas. These issues have charged the minds of illustrious neurosurgeons in the past and continue to spur neurosurgeons even today. Neurosurgical oncology has been established as a speciality in its own right (2). In order to achieve optimal results the neurosurgeon has to think like an oncologist. Surgical management of CNS tumors differs in many respects from general oncosurgery principles. En bloc resections are the norm in oncosurgical practice. However such radical resections are rarely, if ever, possible in the majority of CNS tumors especially malignant gliomas. The brain and spinal cord are highly eloquent areas, where the risk of neurological deficits at the slightest insult is high. Most intra-axial tumors do not have a discrete plane of demarcation from normal parenchyma. Even where a plane does exist there may be admixed normal tissue, precluding a radical excision. The surgical access through the rigid bony skull is limited, often necessitating working through narrow corridors. Deep seated lesions further require traversing normal tissue to reach the site of the tumor. The normal parenchyma's low threshold to withstand mechanical pressure necessitates minimization of retraction. The safest route to a given lesion needs to be individualized based on a thorough preoperative assessment of imaging combined with sound knowledge of microsurgical anatomy. Thus strict principles of oncosurgery are difficult, if not impossible, to apply. They have to be modified and the neurosurgeon has to think like an oncosurgeon but with a neuroscientist's heart. Safe maximal resection remains the underlying tenet.

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Goals of Surgery

The aim of surgery is threefold- diagnostic (always), by providing tissue for histological typing; symptomatic relief (often) , by reducing the mass effect and/or re-establishing CSF flow; and curative (seldom), by eliminating/reducing tumor load. The last goal is indeed difficult in malignant gliomas and is more often than not substituted with "prolongation of survival". Surgery usually plays a combination of these roles.

Benefits of surgery

Surgery remains the mainstay of the treatment of malignant gliomas. Surgery has multiple roles to play and all together constitute the argument in favour of surgery. Unfortunately the role of surgery has been riddled with controversy surrounding mainly one single issue i.e. the survival benefit conferred by the extent of resection. So overwhelming is the preoccupation with this question that the other potential benefits of surgical decompression are overlooked (3,4) . To put things in perspective a critical analysis of the role of surgery is warranted.

The oncological benefits

In most solid tumors, radical excision with tumor free margins is the standard practice; the rationale being improved survival. This however is not possible in brain tumors and especially so the malignant gliomas which do not have a well defined plane of differentiation from normal tissue. Numerous studies have attempted to

address this issue (5-12). Very few randomized trials exist. The next best level of evidence would be well designed prospective studies. Analyses of these suggest that radical surgery does indeed improve survival. However, the extent of resection needs to be near total with strict radiological volumetric assessment. Reviews of these studies consistently highlight their inadequacies and deficiencies in design (heterogeneous patient population, ambiguity in histological grading, and non-uniform/ subjective assessment of extent of resection, to name a few factors), thereby feeding the controversy. Moreover the influence of extent of surgery seems to be offset by other more important variables such as age, performance status and evidence of necrosis which could bias the results of such studies. Most, however, support the benefit (though not significant) of surgical decompression, provided safety is not compromised (13). With modern microsurgical technique and surgical adjuncts morbidity (6-21%) and mortality (0-2.5%) is acceptable and possibly continually improving (14). The belief that radical surgery may increase the risks of neurological deficits even around eloquent cortex is fallacious (15,16). Proper preoperative planning and use of appropriate intraoperative adjuncts can ensure optimal results.

Radiologically (on MRI) two patterns of glioma growth have been described (17) - a central solid tumor tissue constituting the enhancing core and a diffuse invasive peripheral non enhancing T2 abnormal infiltrating tumor tissue zone. All malignant gliomas can be conceived to comprise of these two components in various proportions. Every neuro-oncologist knows how difficult it is to interpret the non enhancing T2 signal changes. Clinicopathological studies have shown that beyond the central mass of visible tumor, there exist invisible tumor cells scattered amidst the normal cells(18-20) .These so called small anaplastic cells are not only morphologically different from the main tumor mass cells, but are also biologically different. In vivo studies have shown that that local cell proliferation and diffuse invasion are both early events in gliomagenesis and begin simultaneously (21) .It would thus seem that right at the outset, two distinct sets of tumor cells are produced-one with a high proliferative potential, and the second with a propensity to invade. Thus, there appears to exist a dichotomy as regards the biological properties of tumor cells in a GBM. Moreover it seems that this dichotomy may be mutually exclusive with two distinct subsets of tumor cells within any given GBM - the central tumor-mass containing rapidly proliferating cells (presumably incapable of invasion), and a surrounding zone of mitotically inactive, non cycling cells capable of invasion but not able to proliferate(22). It can be envisaged that the central proliferating core which produces a macroscopic mass lesion is the one which usually produces symptoms, and is often the component targeted and eliminated by local therapy (including surgery). Radical removal of this core should be attempted and this is the component of interest radiologically when describing the extent of resection. However, the infiltrating zone beyond this (even beyond the visible T2 abnormality on MRI) remains untreated with local therapy. This remains the challenge to the neurosurgeon. Adjuncts such as navigation and intraoperative imaging cannot overcome this limitation. Whether the use of biological intraoperative imaging techniques (such as fluorescein based techniques) address this component is unclear and needs further elucidation. The very fact that even hemisperectomy which has been attempted in the past has been unable to really solve this problem indicates the extent of the challenge on hand in controlling these cancers (23).

This preoccupation with the survival benefit of extent of surgery must end. It is only logical and intuitive to think that a better (more radical) surgery would be more beneficial. Though it may sound sacrilegious, perhaps it is not wrong in wondering whether randomized clinical trials are really needed to prove that. Such a trial would need to compare surgery with no surgery in patients with malignant gliomas. Underlying the very fact that there are no randomized trials looking at extent of surgery in gliomas is the admitted ethical difficulty in conducting such trials. No ethics committee would approve such a study, and for that matter no investigator would probably conceive such a trial. This itself is testimony to the fact that SURGERY IS USEFUL. We need to look beyond just survival advantage. The prognosis of gliomas is so dismal, that even with adjuvant therapy overall survival

is only marginally better. Agreed that overall survival is the gold standard for any cancer therapy; but given the facts, progression free survival and time to progression are also important endpoints. Even if surgery does not improve overall survival, it has other proven benefits.

Establishment of histological diagnosis

This remains the primary and in certain cases the only role of surgery. Unlike most other subspecialties in oncology where a tissue diagnosis is available (and mandatory) prior to commencement of therapy, the initial diagnosis of a glioma (and for that matter all brain tumors) is essentially based on radiology. Seldom is a biopsy obtained initially (24). Often if a biopsy (stereotactic or open) is attempted it is in all probability the only form of surgery feasible in the patient. This is usually the case in lesions which are small and/or deep seated and in intimate proximity to significantly eloquent areas in the brain, or in patients who are unfit for major surgery. Biopsy is also indicated if the radiology is highly suggestive of a lymphoma or a non-neoplastic process. Despite advances in radiology especially MRI, brain tumors and tumor-mimics are notorious for defying standard definitions and hence a tissue diagnosis is so vital (except perhaps in brainstem gliomas). Given the intratumoral heterogeneity of gliomas, sampling of larger amount of tissue allows a more confident histological assessment of tumor type and grade minimizing the risk of undergrading. False negative rates as high as 10% and discrepancy rates as high as 38% have been reported (3). This underlines the need to retain and submit as much of pathological tissue as is possible even during surgical decompression. Banking of tissue also allows for subsequent molecular testing and is an invaluable biological resource.

Symptomatic relief

Undoubtedly surgical decompression relieves the mass effect (local as well as generalized raised intracranial pressure) and restores CSF circulation. This translates into immediate symptomatic relief (both global as well as local symptoms) and reversal of neurological deficits which may be life-threatening at times (3). The response to preoperative corticosteroid medication has been often used as a surrogate marker to predict the likely benefit of decompressive surgery. Again, near total excision (when possible) provides better relief. In fact subtotal/partial resections may be counterproductive. Alluding to the tumor dichotomy described earlier, it is the removal of the central mass-producing core which results in the symptomatic relief obtained after debulking surgery. Incomplete removal of this core may elicit a kind of tissue reaction (reaction to injury) which may result in aggravation of edema/and or tissue hemorrhage translating into neurological morbidity which correlates with clinical experience in subtotal resections (15,25). Clinical recovery and improved performance status may enable a previously unwell patient to be eligible for and benefit from adjuvant treatment. Improvements in quality of life are also important considerations, and cannot be overlooked (26).

Surgical decompression/excision also helps reduce steroid dependence. So often do patients become steroid dependant, especially in the recurrent setting. Surgical decompression allows for stabilization of the neurological condition allowing reduction in steroid doses without aggravation of the symptoms. Surgery can also improve seizure control, allowing patients to be weaned off potentially toxic medications. Of course, the epileptogenic focus has to be eliminated and ideally would require intraoperative corticography to ascertain this. This issue is of more relevance in low grade gliomas where seizure control is the primary goal of surgery.

Facilitating other therapies

Reduction in residual tumor burden (especially the central, inaccessible, hypoxic, radioresistant core) ensures better efficacy of subsequently administered radiotherapy. Radiotherapy works best when the residue it has to contain is minimal.

With the realization that malignant gliomas are essentially local diseases, therapy to limit local recurrence is gaining increasing importance. To be effective local therapies need to be able to home in on the site of tumor preferentially and subsequently precisely and specifically target the tumor cells. The interaction of biological advances and newer

nanotechnology has provided powerful tools to target these tumors precisely at the molecular level. The neurosurgeon then is essential in deploying these locally directed therapies such as chemotherapy-impregnated wafers, convection-enhanced drug delivery catheters, drug impregnated microspheres and other many such experimental devices/implants (27, 28).

Promoting research

There is a growing need felt for studying the molecular behavior of malignant gliomas, resulting in a clamour for more tissue material. Tissue banking is vital and surgery provides tissue which can be used for ongoing and future research. Hopefully translational research will help us answer the many questions we face today.

Surgical technique and technical adjuncts

As with all neurosurgical procedures, surgical extirpation of malignant gliomas requires a combination of technical expertise and knowledge combined with a judicious use of technical adjuncts; with neither capable of substituting the other. It is no longer acceptable to simply debulk with palliative intent accepting defeat even before the commencement of therapy. It is the .moral and ethical responsibility of the neurosurgical oncologist to provide the optimum treatment available. Various technical adjuncts are at the disposal of neurosurgeons. (29).A sound knowledge of basic microneurosurgery is imperative. The use of the surgical microscope has become routine (30). It affords improved illumination, magnification and stereoscopic view at a depth, enhancing the view and facilitating performance of more radical and complex surgeries safely. Elaborate techniques of microneurosurgical dissection have been described (31,32), and should be part of every neurosurgeon's armamentarium. These techniques though effective may be difficult to use when the tumor is subcortical and invisible to the naked eye (even under a microscope). Crude visual and tactile cues to localize the tumor may have deleterious effects. Even when the tumor is localized there may not be a clear plane of demarcation from the adjacent normal parenchyma. Separation of the tumor mass may be difficult. Traction to the at-risk surrounding cortex is to be avoided at all costs. Fortunately the availability of various technical adjuncts for visualization of the tumor as well as its debulking has facilitated the neurosurgeon's task.

1. Adjuncts to tumor visualization/ localization and margin delineation

a. Stereotactic localization. Use of frame based and frameless stereotactic devices (neuronavigation/image guided surgery) allow for accurate localization and delineation of tumor extent. The use of neuronavigation has become integral to the management of brain tumors, the main advantage being accurate siting of a limited craniotomy (minimally invasive) and localization of tumor especially in relation to the relevant important surface anatomy (eloquent cortex, draining veins, prominent sulci, etc). (33,34) However, the main drawback of navigation systems is the intraoperative brain-shift due to decompression and CSF drainage intraoperatively. This results in loss of registration and limits the accuracy of this technique (34). Computer assisted stereotactic volumetric resection of tumors is another computer assisted technique with similar applications (35).

b. Intraoperative imaging: Intraoperative MR allows exact delineation of tumor extent intraoperatively in near-real-time, eliminating the problems with brain shift. Various types of IOMR platforms are available, each trying to balance ease and convenience of surgery with optimum image resolution (36-38). The combination of IOMR with navigation has superior results. This technology is however prohibitively expensive and not available freely. A more easily available and cost effective option is the use of intraoperative ultrasound, a technology which is highly underutilized. The IOUS has been available much before neuronavigation and IOMR came into use (39). Low resolution and the relative user-unfriendliness of the US coupled with the glamour and probably aggressive promotion of the newer technology has relegated the IOUS to the background. However, with advances in technology in US and improved image resolution with newer digital machines, neurosurgeons are rediscovering this tool (40,41). Importantly it provides real-time image guidance. Combining US with navigation

(sononavigation) allows one to complement the other and enhances the efficacy of each (42). This could probably result in a powerful intraoperative image guidance tool, at a fraction of the cost of IOMR. This is of considerable interest to developing countries where IOMR is inconceivable even at tertiary care centres.

c. Neuro-endoscopy is established as a means of minimally invasive approach to a host of regions; especially for intraventricular and the skull base tumors (43). Skills for handling the instruments as well as hand-eye coordination are extremely important. Endoscopic assisted microsurgery utilizes the endoscope to enhance routine microsurgical techniques and is an invaluable surgical adjunct.

d. Recently, interest has arisen in intraoperative fluorescence imaging to visualize microscopic tumor tissue. Various techniques of fluorescence-guided resections have been proposed (45,46). Though the proof-of-principle has been established, further studies to establish clinical relevance and efficacy are required.

e. The aforementioned anatomical localization and visualization tools cannot unfortunately predict the functional nature of the tissue being handled. Given the wide variations in Individual anatomy, reliance on surface landmarks and/or atlases to localize eloquent areas is very inadequate. Intraoperative electrophysiological monitoring is preferable when working in and around eloquent areas. Monitoring and stimulation techniques for cortical, deep white matter and cranial nerves are an integral component of microneurosurgical procedures in these vital areas (47).

2. Adjuncts to tumor debulking

Mechanical methods such as suction (for soft tumors) and fragmentation using tumor forceps remain the mainstay of internal decompression piecemeal resection of most tumors. Since the initial description of microneurosurgical instruments, technology has been refined and more precise, light-weight yet robust instrumentation is available (48,49). Gentle and careful microsurgical dissection of arachnoid and tissue planes are essential to minimize morbidity. Use of adjuncts such as ultrasonic aspiration and lasers for certain tumors facilitates debulking. As mentioned earlier, it is important to preserve as much tissue as is possible for research purposes.

Conclusions

Neuro-oncology has evolved into a specialty in its own right. It is obligatory for a neurosurgeon practicing as a neurosurgical oncologist to be abreast with the current evidence in treating patients with brain tumors. Rather than despair at the prognosis of malignant gliomas [which is more a function of the biology of these intriguing tumors rather than the efficacy (or lack of it) of surgery]; the neurosurgical oncologist must equip himself with the evolving advances in surgical techniques and utilize all the adjuncts possibly at his disposal to effect the maximum benefit possible. Active participation in translational and clinical research is mandatory to provide direction and relevance to the explosion of information and insights that basic research is throwing up.

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