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The effect of residual tumor on survival in patients with glioblastoma multiforme: A retrospective cohort study

Study Description:

1. Study purpose and rationale

Glioblastomas (GBM) are the most common of all primary brain tumors, resulting in 17,000 deaths annually in the United States. They account for 350,000 person-years of life lost yearly, and on average, decrease a patient's life expectancy by 21.3 years (Thuppal et al, 2006). The current standard of care is aimed at decreasing the morbidity and mortality of these tumors and includes surgery, chemotherapy, radiation and more recently, anti-angiogenesic therapy (Stupp et al 2009; Stupp et al 2005; Vredenburgh 2007) . Unfortunately, even using these agents in combination has a limited impact on outcome, with a median survival for patients with GBM of only 14 months despite optimal treatment (Stupp et al 2009; Deorah et al 2006; Ohgaki 2009).

When the diagnosis of a GBM is suspected, surgery is indicated to obtain tissue for a definitive diagnosis. When safe for the patient and technically feasible, aggressive surgical resection of the tumor mass (as opposed to biopsy) provides symptomatic relief, decreases the need for steroids, and may improve the quality of life of the patients with these lesions (Sawaya et al 1998; Ammirati et al 1987; Ciric 1987). Moreover, the majority of randomized controlled clinical trials require previous surgical resection as part of the inclusion criteria.

The evidence showing degree to which the extent of resection (EOR) of a malignant glioma impacts quality of life and survival remains equivocal. In contrast to the multicenter, randomized, clinical trial-based evidence supporting other therapeutic interventions for malignant gliomas (Stupp et al 2009; Deorah et al 2006; Ohgaki 2009),the efficacy for GTR is mainly supported by case-control or small studies that warrant conservative interpretation (Ammirati et al 1987; Ciric et al 1987; Kiwit et al 1996; Hess et al 1999; Lacroix et al 2001). While there are studies that address the prognostic importance of EOR in malignant gliomas (Stummer et al 2008; Laws et al 2003), none of them controlled for whether in fact the EOR was limited by the relevant functional anatomy or whether the tumor was potentially resectable but residual tumor was inadvertently left behind by the operating surgeon. There is a need to compare the prognostic importance of postoperative residual glioma in eloquent and non-eloquent brain areas, respectively.

In principle, the goal of surgery is to maximize the EOR. However, if the tumor involves functionally important (i.e. motor/sensory/language), deep seated, or bilateral

locations, only a portion of the tumor is frequently removed to minimize surgical risk. It is known that proximity to an eloquent area is a major predictor for neurological complications following resection of a parenchymal brain tumor (Sawaya et al, 1998) Alternatively, on some occasions, a portion of a tumor that is potentially resectable is not visualized during surgery and is discovered as residual on postoperative imaging. Data obtained from intraoperative imaging studies suggests that about 40% of all gliomas are amenable to gross total resection (GTR) based on their location, but without the use of intraoperative MRI only 27% are subject to GTR due to poor visualization of the tumoral tissue (Nimsky et al 2006; Schneider et al 2005). Determining whether EOR/GTR has true prognostic value has important implications for patient management and prognosis, as well as for health care expenditures. For instance, if GTR is proven to improve outcome, residual resectable portions of a tumor that are inadvertently discovered on a postoperative MRI should be resected with a second surgery prior to other treatments. In general, neurosurgeons do not currently return to the operating room to remove residual disease that is resectable. It has become a trend to expend large amounts of technological and financial resources in order to maximize the EOR at the initial resection, including techniques such as intraoperative MRI scanning; the use of 5-aminolevulinic acid, a fluorescent marker used for intraoperative tumor visualization; and awake intraoperative brain mapping of function to maximize tumor resection in and near eloquent brain areas (Stummer et al 2008; Nimsky et al 2006; Schneider et al 2005).

The current uncertainty about the efficacy of EOR/GTR poses considerable problems. If there is no improvement in outcome, the morbidity associated with an aggressive resection strategy in deep brain areas or in proximity to eloquent regions might lead to a decrease in survival and quality of life (McGirt et al 2009; Sawaya et al 1998). Similarly, the increase in operative time and the economic burden of techniques such as intraoperative MRI might not be justified. On the other hand, if there is a real improvement in outcome for those patients in whom GTR is achieved, by not performing a second resection in the presence of resectable residual disease, surgeons might be limiting interventions that can prolong the survival of their patients. For these reasons, there is an eminent need to compare the prognosis and morbidity associated with GTR versus subtotal resection, when the preoperative objective of surgery is GTR (when based on imaging the lesion seems to spare eloquent brain areas). This comparison should control for tumor invasion of eloquent areas in order to provide additional prognostic information.

This study will add a significant contribution to the field by providing a multicenter evaluation of the significance of EOR on outcome, controlling for eloquence. This is an important step to improve the evidence-based surgical treatment of malignant gliomas.

2. Study design and statistical procedures

This study will be a retrospective, multicenter observational study. The study involves the creation of a database consisting of patients' pre and post-operative MRI scans, and

clinical information including age, date of death, Karnofsky Performance Score (KPS), adjuvant treatments, and any re-operations.

In order to detect a difference of 20% in the proportion of patients alive at 1 year in each of the two groups, 107 patients will need to be included in each group to be analyzed using the chi square test. To ensure adequate numbers, we will study a total of 400-500 patients with the understanding that approximately half of the patients will have received a gross total resection.

3. Study Procedures:

Patients enrolled in this study will have already undergone craniotomy for resection of glioblastoma multiforme. There are no interventions or change in treatment that these patients will undergo, as this is a retrospective study in which patient data and imaging has already been collected.

4.Study drugs or devices

None

5. Study questionnaires

None

6. Study subjects

Study subjects will be patients with grade IV glioblastoma tumors who presented to participating surgeons at CUMC and affiliated institutions between 2004 and 2010 for management of their disease. Patients will be over the age of 18 and under the age of 65. Other patient characteristics such as gender and ethnicity will not be specifically selected for.

7. Recruitment

A list of patients with pathologically confirmed glioblastoma at CUMC, University of Washington, and other participating institutions will be prepared by study coordinators at each site. The clinical information, including adjuvant therapy, re-operation, and survival will be collected, as well as pre- and post-operative MRIs.

8. Informed Consent

The investigators believe that a waiver of documentation of informed consent is appropriate in this case, as it meets the criterion that "That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context."

9. Confidentiality of Data

Data obtained in this study will be coded to protect patient confidentiality. Upon enrollment in the study, the patient will be assigned a random ID by the research coordinator at that site. The original patient IDs will be kept by the research coordinator at that site, in a password protected document on a hospital computer. The research coordinator who will review the chart, and access new imaging, and upload it into the internet-based platform using the assigned patient ID. Only the participating surgeon or research coordinator at each center will have the information on the identity of each patient, and the corresponding ID.

10. Privacy Protection:
The confidential information for each patient such as the identity and contact information will only be available to the clinical team (participating surgeon and nurse practitioner) who would already have access to it based on their clinical duties. The only exception to this is when an institution has a research coordinator that was not involved in the care of that patient. In that case, the research coordinator should be trained in HIPPA compliance.

11. Potential risks
There are no potential risks associated with this study, as it is retrospective.

12. Data Safety and Monitoring
There is no risk associated to this study as it is observational and retrospective in nature. The only risk is a violation of HIPPA compliance, which will be avoided as all research personnel will have HIPPA training.

13. Potential benefits
The potential benefits of this study are a greater understanding the effect that the extent of resection might have on outcome, with a focus on the significance of residual disease in eloquent brain versus non eloquent residual. This might help support the need for aggressive resections, re-operation and or additional surgical tools such as intraoperative imaging to maximize EOR. Alternatively, this study could provide evidence to perform conservative debulking if no difference in survival is noticed between GTR and residual disease in non-eloquent brain.

14. Alternatives
N/A

15. Research at External Sites

The study will have a period of testing and optimization at CUMC. At a later stage, additional centers will be recruited, and each center will submit an IRB to comply with the study design and conditions presented here. These IRBs will be presented and

approved by the Columbia University IRB as well. The original consent form approved by the Columbia University IRB will be used at external sites.The funding will be distributed among participating centers to cover the costs of the research coordinator and administrative fees. Additional funding will be employed for data analysis.

16. Columbia as the leading Institution

Each medical center will submit an independent IRB in order to participate in this study. These IRBs will also be reviewed at Columbia. Similarly, each center will be required to have the same written informed consent for patient enrollment, a similar data handling protocol and to assure compliance with HIPPA.

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