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The Treatment of Anaplastic Astrocytoma and Malignant Glioma - A Review

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INTRODUCTION

Axial tumours of the brain are classified according to their cell of origin. Those with the astrocytes and other glial cells as the cells of origin may be called astrocytomas if arising from astrocytic cells recognisably, ependymomas if arising from the ependymal lining cells and neuroblastomas if arising from the neuronal cells. Of these the astrocytomas are most common and for which treatment is deemed to be most inadequate. Astrocytomas may arise in any part of the brain that has glial supporting tissue. These spread in the brain by mainly an infiltrating method making them hard to remove without adjacent normal tissue. Symptoms are caused by either local irritation causing epilepsy, interference in normal function by causing paralysis or sensory deficit or other deficits according to location in the brain and by mass effect more commonly giving the symptoms of headache, nausea and vomiting. Prolonged raised intracranial pressure may lead to deterioration and then loss of eyesight due to optic atrophy. More acute rise in the intracranial pressure as may be caused by rapid growth, intra tumoural haemorrhage, associated brain oedema and by interference in the normal CSF circulation may cause death rapidly. Neurosurgery has a role in the diagnosis by tissue sampling, reduction in intracranial pressure and reduction in tumour cell load.

REVIEW LITERATURE

Ever since the days of Cushing the role of surgery in Glioma has been hotly debated. However, surgical endeavours have continued and patients have been subjected to surgery in the pursuit of various goals. The presently defined roles of surgery are firstly to obtain a tissue characterisation of the intrinsic tumour of the brain. A second objective is to reduce mass effect, which may be causing neurological deficit or more commonly headache. A third objective is to reduce tumour bulk so that other adjunctive therapies such as radiation and chemotherapy may be more effective. A decision is also taken for surgery to buy time so that other therapies by given a chance to take effect.

The role of this article will be to examine the various treatment options especially the role of surgery in the light of the evidence available in the current literature. At the outset it may be mentioned that a major difficulty in these lesions is the determination of the superiority of one surgical regime over another due to the lack of randomised clinical trials.

Biopsy alone followed by radiotherapy has been the favourite option of many surgeons and neuro-oncologists. The reason has been a personal belief in some instances and the observation even after imaging studies that final prognosis in malignant glioma is not affected much by the other surgical options then available[1]. This has also been in decline for some reasons. The advent of CT scanning led to a prediction of the histological status of many of these lesions and although not accurate completely[2] provided a useful alternative to a surgical procedure with its inherent complications such as postoperative haemorrhage and risk of increased neurological deficit[3]. In some cases it led to a biopsy alone other than a meaningless attempt at excision[4,5]. The increase in the definition and resolution of the later CT scanners and the advent of MRI scanning increased the accuracy of such predictions, so much so that at least in the larger lesions it has been possible to accurately characterise a lesion[6,7]. This approach has its proponents for another technical reason. Malignant gliomas are well known for their propensity to have different histological characteristics in different parts of the lesion. The behaviour of the lesion is always that of the more malignant component. A biopsy especially a needle biopsy supplying a small core of tissue samples only a small part of the lesion, thus leading to an erroneous diagnosis in many instances[8]. Also there is a diminishing need

for demographic data about survival and incidence in a community at least in the West[9-11]. The incidence in most countries for primary brain tumours hovers about 8/100000 per year[12]. Also in our community the fragmentary data available makes it unnecessary to do this just for scientific and research purposes. Biopsy has a greater role to play in the deep seated lesion around the pineal, brainstem and the thalamic region[13].

The alternative approach is to perform a tumour resection. There is reduction in tumour cell load by this approach. A benefit may be a reduction in the total amount of steroids necessary for the patient.. Mass effect may be reduced both by a subtotal resection and by an attempted total resection[14,15]. The proponents of subtotal or intra-tumoural resection point out that the complication rate of such a resection is much lower than an attempted total resection. Also most of the gliomas have a " pseudocapsule" around their periphery which is delineated by the enhancing line in the CT scan or the MRI scan. However this is generally surrounded by oedema[16]. Biopsy and postmortem studies have shown that the malignant cells extend into these areas[17] and so the "total resection" is merely a misnomer and may just be called complete radiological or macroscopic resection. As noted by Kelly the tumour cells tend to spread far beyond the radiological tumour front and extension of the resection margin into these areas would of necessity entail neurological deficit. Tumour recurrence is therefore inevitable[18].

The evidence that decrease in tumour load helps survival is available[19-21]. However as previously noted there has been a debate about the safety and efficacy of the attempted " total removal of glioma". The reason is the proximity of many of these to vital functional centers such as the language centres and the motor areas. Wandering out of tumour into these areas may have disastrous effects. While some papers point out that there is no difference in the morbidity and mortality after attempted total resection as compared to subtotal resection, the consensus seems to be arising that the decrease should be maximal for radiotherapy and subsequent chemotherapy to favourably affect survival[22].

Notwithstanding concerns about deficit, there is newer data available showing that the greater the resection the better is the postoperative survival and the better is the postoperative functional state[23-27]

Help is at hand for the neurosurgeon now. Language function deterioration by far the most important neurological problem encountered after surgery has been studied in detail and conclusions are that " complete macroscopic excision" may be carried out safely with the help of modern technology[28]. Technological advances have made it possible to have functional mapping of the vital areas by Magnetic Resonance Imaging and fusion with anatomical images guides the neurosurgeon. The application of the principles of the stereotactic frame into the production of frameless intra-operative image guidance systems has been a great help[29,30]. More help is available with the fusion of the CT scans and MR images and intraoperative MR Imaging so that a greater accuracy is available[31-33].

The studies although numerous are unanimous on one point. Surgery is not the therapy which is the major determinant of longevity following the diagnosis of glioma. The key factor is radiotherapy. Radiotherapy is the single most important factor affecting survival[34-38]. This has led to innovative methods using the help of surgical techniques. The "radium bomb" , interstitial brachytherapy was used by Cushing and then fell out of favour[39]. It has been revived may times over the years especially being used in recurrent malignant glioma[40]. However the useful increase in survival has not been documented. Chemotherapy is the next line in the armamentarium against the gliomas. It however is generally used for recurrent gliomas. The nitrosoureas and platinums, either as single agents or as combination chemotherapy, appear to be the most active agents in this disease although few, well designed chemotherapy trials are available for analysis. There is an increase in survival but whether it is deemed worthwhile is open to question[41].

Other innovative methods such as photodynamic therapy with surgical help and sensitisation of glioma cells have been tried with moderate success. In this procedure an intravenous photosensitiser is administered with greater binding to malignant cells and then at surgery there is exposure of the tumour area to light of a certain wavelength leading to a greater damage and reduction in tumour cell load by vascular and direct cellular mechanisms[42-44]. Another innovative method used recently using retroviral mediated cell apoptosis may hold promise[45,46]. The blood brain barrier is the main problem with the delivery of

chemotherapy to the malignant glioma. Although therapies such as hyperthermia during the administration of chemotherapeutic agents have been tried none has been of much use[47]. Now the development of gliadel wafers with the impregnation of carmustine (CCNU) and direct implantation into the tumour resection bed is being investigated with Phase II trials. Moderate success is being achieved here[48].

What does the future hold for glioma treatment ?. For the foreseeable future the following procedure holds promise with the best long term survival and function. A glioma patient undergoes surgery using an intraoperative image guidance system coupled with realtime MRI/CT after functional mapping of the brain preoperatively using functional MR/PET imaging. At the time of surgery the tumour bed is lined with a non neurotoxic chemotherapeutic agent which slowly releases cytotoxic substance into the affected area. This chemothearapeutic agent is a targeted one. An alternative treatment would be the use of monoclonal antibodies to sensitise the lesion so that an intelligent vector may attack the tumour cells wherever they are.

However surgery is likely to play a role in the treatment of malignant glioma for the foreseeable future.

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