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Overview

Current Concepts in the Surgical Management of Glioma Patients

C. Watts [*,†], S.J. Price [*], T. Santarius [*]

[*] University of Cambridge, Department of Clinical Neurosciences, Division of Neurosurgery, Addenbrooke's Hospital, Cambridge, UK

[†] Department of Clinical Neurosciences, Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK

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Abstract

The scientific basis for the surgical management of patients with glioma is rapidly evolving. The infiltrative nature of these cancers precludes a surgical cure, but despite this, cytoreductive surgery remains central to high-quality patient care. In addition to tissue sampling for accurate histopathological diagnosis and molecular genetic characterisation, clinical benefit from decompression of space-occupying lesions and microsurgical cytoreduction has been reported in patients with different grades of glioma. By integrating advanced surgical techniques with molecular genetic characterisation of the disease and targeted radiotherapy and chemotherapy, it is possible to construct a programme of personalised surgical therapy throughout the patient journey. The goal of therapeutic packages tailored to each patient is to optimise patient safety and clinical outcome and must be delivered in a multidisciplinary setting. Here we review the current concepts that underlie surgical subspecialisation in the management of patients with glioma.
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Key words: 5-Aminolevulinic acid; chemotherapy; high-grade glioma; low-grade glioma; radiotherapy; surgery

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search strategy has been defined.

Introduction: the Scale of the Problem

Each year in the UK around 4300 new cases of brain or central nervous system cancer are diagnosed, around 7 per 100 000 population. Although brain tumours account for less than 2% of all primary tumours they are responsible for 7% of the years of life lost from cancer before age 70 years (ONS 2006 Series MB1 No. 34). More people under the age of 40 years die from a brain tumour in the UK than any other form of cancer. Sixty-five per cent more women die from a brain tumour than from cervical cancer (Office of National Statistics, Mortality Statistics: Deaths registered in 2007).

The high rates of mortality make these rare cancers into the third leading cause of cancer-related death among economically active men between 15 and 54 years of age and the fourth leading cause of cancer-related death among economically active women between 15 and 34 years of age [1]. If the burden of disease is considered in terms of the average years of life lost per patient, brain tumours are one of the most lethal cancers, with over 20 years of life lost [2]. The latest survival trends for patients with central nervous system malignancies have remained largely static [3], reflecting the lack of therapeutic options for patients with these cancers.

In optimally managed patients with glioblastoma (GBM) who have a good performance status, a good resection and radical radiotherapy plus concomitant and adjuvant chemotherapy, median survival is about 14 months [4]. In anaplastic gliomas it is about 6–7 years [5] rising to over 14 years in optimally treated 1p19q-deleted anaplastic oligodendrogliomas [6,7]. Improved prognosis for patients with high-grade glial cancers is also strongly associated with mutation of *IDH1* (isocitrate dehydrogenase 1) and promoter methylation of O^6-methylguanine-DNA methyltransferase (MGMT) [8]. However, many patients do not have favourable prognostic factors and/or are not suitable

Author for correspondence: C. Watts, University of Cambridge, Cambridge CB2 0QQ, UK.

E-mail address: cw209@cam.ac.uk (C. Watts).

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for radical therapy. Population-based survival statistics are rare. In one population-based study [9], the median survival for anaplastic astrocytoma was 1.6 years and for GBM just 4.9 months compared with 5.6 years for low-grade astrocytoma, 11.6 years for oligodendrogliomas and long-term survival for surgically resected pilocytic astrocytomas (World Health Organization grade I astrocytomas) (Figure 1).

Rationale for Surgery

The goal of surgery is to obtain a histological diagnosis and, where possible, remove as much of the tumour as possible without damaging the adjacent healthy brain tissue. Achieving a gross macroscopic resection can be complicated by the nature of the tumour (especially if the tumour is invasive or highly vascularised) and by its location in eloquent areas of the brain, such as the motor cortex. Sometimes only partial removal (debulking) of the tumour is possible or safe. Nevertheless, debulking can improve a patient's quality of life by alleviating symptoms, reducing the need for steroids, thereby abrogating associated side-effects and possibly improving the chances for other treatments, such as radiation therapy or chemotherapy, to be effective [10–16]. However, even experienced neurosurgeons have difficulty defining the margins of a GBM during surgery [17]. There is no sharp demarcation between tumour and normal tissue. This can result in unintentional removal of healthy tissue or failure to remove malignant tissue. There is also no objective measure of an operative end point, making the estimation of the extent of resection highly subjective [17]. Even when macroscopically resected, malignant glioma invariably recur because of the infiltrative nature of the disease [18]. Most of these tumour recurrences are local, occurring within 2 cm of the original lesion [19].

There is now ample evidence that specific molecular changes can be used as biomarkers that provide clinically useful information. Such markers are thus attractive tools for improving unequivocal diagnosis, assessment of prognosis and/or treatment stratification for the individual glioma patient [20].

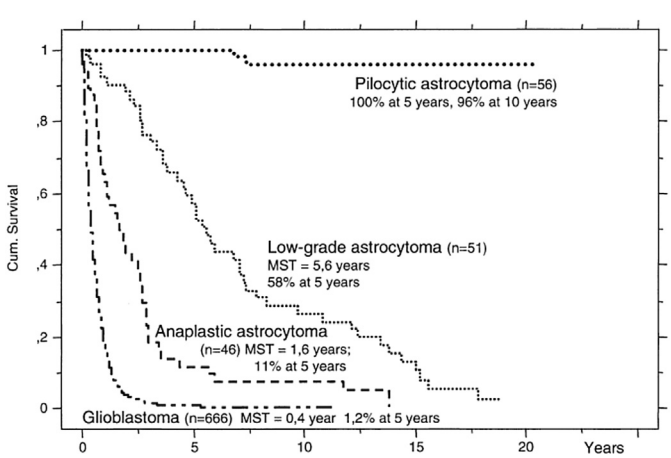

Fig 1. Population-based survival data for patients with astrocytomas. Only those with pilocytic astrocytomas have prolonged survival. Patients with high-grade astrocytomas (anaplastic astrocytoma and glioblastoma) have very poor survival (from [9]).

The vast majority of diffuse low-grade and anaplastic gliomas, as well as secondary GBMs, carry *IDH1* or (much less frequently) *IDH2* mutations. These mutations represent a very early oncogenic event and indicate a more favourable prognosis compared with tumours in the same glioma category lacking these mutations [8,21,22]. Recent data suggest that resection of contrast-enhancing disease in IDH1-mutated high-grade glioma is associated with improved survival that is further enhanced if non-enhancing disease is also removed [23].

Loss of 1p/19q shows a strong association with classical oligodendroglial features on histology [24]. Combined loss of 1p and 19q is exclusively associated with IDH mutation [25] and identifies a favourable prognosis in patients with anaplastic oligodendroglioma undergoing radio- and/or chemotherapy. It is also predictive of response to radiotherapy and procarbazine, lomustine and vincristine (PCV) chemotherapy in this patient group [6,7]. In these studies, complete resection was associated with a better outcome.

MGMT promoter methylation is correlated with the response of GBMs to alkylating chemotherapy [26]. More recent studies, however, indicate that the predictive value of *MGMT* promoter methylation in diffuse gliomas is broader than for alkylating chemotherapy alone and is associated with other, prognostically favourable, molecular features such as 1p/19q co-deletion and *IDH1* mutations [27,28].

In the modern era it is important that neurosurgical oncologists combine clinical practice with an understanding of the clinically relevant biology of glial cancers in order to properly manage and counsel their patients and interpret the results of surgery.

Impact of Gross Total Resection

Cytoreduction and Palliation of Symptoms

Although our understanding of the biological diversity of glioma has increased dramatically [29], diagnosis is still made primarily on morphological criteria by the neuropathologist [30]. Consequently, aggressive cytoreduction rather than radical excision is the primary objective of surgery. This strategy encompasses more than a rapid log kill of tumour cells [31]. Palliation of symptoms related to raised intracerebral pressure and peritumoural oedema has been established in large surgical series, with associated delay in deterioration of neurological function [32–34]. However, in the elderly (>65 years old), a study of 30 patients with radiological high-grade glioma randomised to either biopsy or craniotomy showed improved overall survival in the craniotomy group, but no difference in time to neurological deterioration [35]. This study was too small to draw any definitive statements, but emphasises the need for careful patient selection when considering aggressive

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