PREFACE

The changing face of brain tumours

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As a junior doctor on a neurosurgical team I remember reviewing together with the consultant neurosurgeon a patient with a glioblastoma. Afterwards he said to me:

it's a dreadful disease, it doesn't respond to any chemotherapy, resection never cures it and I'm not sure radiotherapy makes all that much difference, basically it's a death sentence and I'm not sure that the treatment doesn't do more harm than good.

I have been disproportionately fascinated by glial cell tumours ever since, there is a sort of dark glamour and a tremendous challenge about a disease that seems as inevitably fatal as walking into the path of a freight train. Having said that, fascination would soon wear thin if we really had no hope that the prognosis of this miserable disease would improve.

So, was my nihilistic mentor accurate in his assessment? In fact he wasn't at all far out. Although resection and radiotherapy carry a real survival benefit it averages only a small number of months and both treatments are associated with significant potential morbidity. The failure of conventional chemotherapeutic agents in glioblastoma is attested by a long and depressing history of clinical trials showing little or no benefit, even from agents with significant survival benefit in other aggressive tumour types. In 2002, a meta-analysis of 12 randomised trials of chemotherapy plus radiotherapy, compared with radiotherapy alone, showed a 5% increase in survival at 2 years from 15% to 20% despite a preponderance of tumours with prognostically favourable features [1].

So what has changed in the quarter century since I was an impressionable junior doctor on a neurosurgical ward? Well most clinicians would agree that the major change has been the identification of a survival benefit associated with the use of concomitant and adjuvant temozolamide identified by Roger Stupp's group in 2005

which is now standard therapy worldwide [2]. Finally we had a chemotherapy agent with some effect on glioblastoma, albeit an increased 2 year survival to only 26%. At the present time, median overall survival is 15 months with a 2 year survival of 26% but failure to recur after treatment is exceptional [2].

So why do I remain so dedicated to glioma research after 25 years that has seen the identification of only 1 additional effective therapeutic manoeuvre and a median survival increase of only 2.5 months? Some of my detractors might argue that this represents blind uninformed optimism, or even incipient dementia, but I would take issue with them. I believe that our current understanding of the biology and genetics of glial cell tumours combined with our ability to identify molecular targeted therapies put us on the edge of a golden age in the development of effective therapeutic approaches for glioblastoma. I also believe that the effective testing and implementation of new therapies will become increasingly dependent on imaging techniques that we currently use only sparingly, or which many radiologists regard as methods for research not for clinical practice.

25 years ago we knew that glial tumours developed from glial cells because they are the only actively dividing cells in the brain. They produced tumours that were composed predominantly of astrocytes, oligodendroglial cell lines or a mixture. Their behaviour could be best predicted by a simple classification based on histological grading, which, in adults, identified three grades of astrocytoma or mixed astrocytoma/oligoastrocytoma and two grades of oligodendroglioma.

In fact, we now know that division can occur in both neural stem cells and glial progenitor cells that exist in multiple regions of the adult brain, including the sub-ventricular zone (SVZ), the dentate gyrus, hippocampus and subcortical white matter [3–6]. Neural stem cells and glial progenitor cells can migrate and there is increasing evidence that neoplastic transformation of these cells is the origin of glial cell tumours [3].

One of the most important advances in our understanding of glioma is the recognition of significant biological heterogeneity across tumours with identical histology and grading. Putting it simply, our current clinical classification systems are grossly inadequate, or

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as a colleague eloquently put it: "a glioma just isn't a glioma any more and to make it worse, an oligo isn't an oligo and, I suspect an astro isn't an astro!" It is important to recognise the frustration underlying that comment. The rationale behind tumour classification and grading schemes is to provide the best possible framework to support treatment selection and clinical trials of new agents. In glial cell tumours it is now clear that our current classification and grading systems are outmoded and, at best, suboptimal [7, 8].

Even within individual tumours there is significant biological heterogeneity with areas of hypoperfusion, hypoxaemia and an ongoing process of active angiogenesis [9, 10]. These regional intratumoural variations affect radiotherapy response, drug delivery and the effectiveness of individual therapeutic agents, particularly of novel biologically targeted small molecules such as anti-angiogenics.

We have long recognised that approximately 10% of glioblastomas (secondary glioblastoma) develop from lower grade tumours through a process of dedifferentiation. The majority apparently arise *de novo* (primary glioblastomas) with a short clinical history, usually in older patients [11]. Although these are classified and graded identically they demonstrate major differences in tumour biology and genetics. Secondary glioblastoma show *IDH1* or *IDH2* mutations in over 70%, *TP53* mutations in 65% of cases, overexpression of platelet-derived growth factor receptor (PDGFR) and other specific mutational changes. Primary glioblastomas are characterised (40% of cases) by upregulation of epidermal growth factor receptor (EGFR) and genetic alterations that disrupt cell cycle control but rarely demonstrate *TP53* mutation [8, 11–13].

The identification of temozolomide as an effective concomitant and adjuvant therapy for glioblastoma was quickly followed by the realisation that response differed between patients with apparently identical tumours. Temozolomide acts by methylation and alkylation of DNA, O⁶-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that is silenced by methylation of the gene promoter in 50% of glioblastomas [14] and in oligodendrogliomas with 1p/19q loss [15]. The resulting reduction in DNA repair contributes to chemosensitivity, and these patients have longer survival times when treated with concurrent temozolomide and radiotherapy [15].

The growing evidence that glial tumours of similar classification and grade demonstrate broad genetic and biological variability that is directly related to therapeutic mechanisms has led to increasing recognition that specific biological and genetic features need to be incorporated in assessment and management of glial cell tumours and assessment of 1p19q status in oligodendrogliomas is now routine [16]. Interestingly MGMT status is still not routinely used in clinical management, largely for financial and logistical reasons, but it has been employed in recent drug trials as a method to "enrich" the test population and to identify patients unlikely to derive direct benefit from the use of temozolomide [17].

There is also increasing understanding that gliomas vary considerably in their invasive behaviour [18]. Glial cell tumours are commonly called diffuse gliomas because they show a propensity to infiltrate the surrounding brain.

These invasive cells show low proliferative activity and are relatively refractory to conventional therapy contributing to treatment resistance [19]. Furthermore, the degree of invasion in individual tumours is very variable. Post-mortem studies have shown that a quarter of glioblastomas have limited invasion, with malignant cells seen no more than 1 cm from the edge of the tumour mass [20, 21] whereas 8% show disseminated spread throughout the brain, commonly involving the contralateral hemisphere [22]. It is clear that the use of focal therapies in disseminated tumours is unlikely to be successful, raising the question of whether glioblastoma should be considered as a diffuse disease requiring systemic therapy [23].

The increase in our understanding of the molecular biology and genetics of glial cell tumours is occurring at a time when multiple, biologically targeted small molecular therapies are proving increasingly effective in a range of tumour types. In glioblastoma, targeting angiogenesis by VEGF inhibition using an anti-VEGF antibody, bevacizumab, shows clear survival benefit. However, it has increasingly become clear that much of the survival benefit results from beneficial changes in the hydrodynamics of the brain due to reduction in interstitial oedema [24]. In addition, the use of anti-angiogenic strategies, while showing survival benefit, leads to breakthrough mechanisms that change the characteristics and behaviour of the tumour as it recurs [25]. Despite this, there are clear benefits and potential in the addition of small molecular targeting agents into standard therapeutic regimens for glioblastoma. A large number of potential agents, including anti-angiogenic agents (bevacizumab, enzastaurin), inhibitors of EGFR tyrosine kinase (gefitinib and erlotinib), mammalian target of rapamycin (temsirolimus, everolimus) and integrin inhibitors (cilengitide) are currently in clinical trial. Cilengitide is a potent inhibitor of α_v integrins, which are heavily expressed in glioblastoma and are involved in both the angiogenic process and in cellular migration and invasion [26]. Early phase clinical trials showed a modest survival benefit in Phase I and II studies of patients with recurrent glioblastoma [27, 28]. However, once again, as with bevacizumab, our understanding of the mechanism of action of the drug continues to develop as clinical trials progress and it has been suggested the beneficial clinical effects derived from cilengitide *in vivo* may arise from altered perfusion, which promotes temozolomide delivery to glioma cells [29].

It is becoming increasingly clear that the introduction of targeted small molecular therapies for use in high-grade glioma will require a different approach to the conventional mono-agent clinical trial. It seems likely that [30]:

tailored therapies for tumors harboring specific signaling defects will become more efficient and successful in the management of glioblastoma.

Furthermore, as multi-agent trials develop, based on improved phenotyping of individual tumours, advanced imaging techniques capable of producing quantitative biomarkers which can identify variations in tumour biology will become an essential component both of clinical trials and eventually of clinical management.

This special issue of the *British Journal of Radiology* presents an exhaustive overview of the current state of clinical management of gliomas and the role of imaging. Equally importantly it describes the major leaps in our understanding of glioma biology that have occurred in the past 25 years. It also reviews the roles of imaging modalities in studying and quantifying the major biological processes that affect glioma survival and treatment. Namely genetic variation, proliferation, apoptosis, invasion, hypoxia and angiogenesis.

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