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Has the survival of patients with glioblastoma changed over the years?

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Background: Over the last decade, the approach to the management of brain tumours and the understanding of glioblastoma tumour biology has advanced and a number of therapeutic interventions have evolved, some of which have shown statistically significant effects on overall survival (OS) and progression-free survival in glioblastoma. The aim of this study is to compare survival in glioblastoma patients over a 10-year period (1999–2000 and 2009–2010).

Methods: A retrospective cohort study was performed. Identification of all histologically confirmed glioblastoma in a single centre in years 1999, 2000, 2009 and 2010, and production of survival analysis comparing 1999–2000 and 2009–2010 were achieved.

Results: A total of 317 patients were included in the analysis (133 in year 1999–2000, and 184 in year 2009–2010). Cox regression analysis showed that the survival was significantly longer in patients in years 2009–2010 than those in 1999–2000 at $P<0.001$ with HR = 0.56, confidence interval (CI) (0.45–0.71). The 1- and 3-year survival rates were 20.7% and 4.4%, respectively, for patients in 1999–2000, improving to 40.0% and 10.3%, respectively, for patients in 2009–2010. The comparisons between the two groups in survival at 1, 2 and 3 years are all statistically significant at $P<0.001$, respectively. The median OS was 0.36 and 0.74 in 1999–2000 and 2009–2010 groups, respectively.

Conclusions: Over this period, OS from glioblastoma has increased significantly in our unit. We believe this is due to the institution of evidence-based surgical and oncological strategies practised in a multidisciplinary setting.

The prognosis of glioblastoma is one of the most dismal of all cancers and survival is typically reported as less than a year after diagnosis. Over the last decade, the overall approach to the management of glioblastoma has evolved into a formal multidisciplinary structure that involves neurosurgeons, neurologists, neuro-oncologists, neuropathologists, neuroradiologists, palliative care physicians, specialist nurses and therapists. This aims to provide timely, tailored and evidence-based treatment for each patient, as well as awareness of potential for participation in clinical trials. In addition, the understanding of glioblastoma tumour biology and treatment strategies has evolved, with some therapies leading to increased survival. Therapeutic advances and prognostic information is however tempered by the knowledge that glioblastoma is a tumour with considerable molecular, immunohistochemical and genetic heterogeneity, where no 'final common pathway' can yet be exploited for therapeutic purposes (Bonavia *et al*, 2011). The aim of this study is to evaluate overall survival (OS) from glioblastoma in a single centre from 1999–2000 compared with a decade later, 2009–2010. We are not aiming to report the effect of individual patient, tumour or treatment-related factors on survival as we believe any such analysis will require a multicentre approach to sufficiently power the study.

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MATERIALS AND METHODS

We identified all glioblastomas diagnosed at our centre in the years 1999, 2000, 2009 and 2010 from neuropathology central records' database. We then identified the date of death for these individuals from hospital and general practice records. The survival time was calculated from the date of histological diagnosis to the date of death or the date of the last clinic visit for those patients still alive at the time of data collection. We constructed a Kaplan–Meier survival curve for the 1999–2000 cohort and a curve for the 2009–2010 cohort. The reason for choosing this time interval was to allow studying the many changes that had occurred during this time both in terms of delivery of neuro-oncology care and advances in clinical management of patients with glioblastoma (Allahdini *et al*, 2010). The year 2010 was selected as the final year of data collection to maximise the chance of obtaining complete survival data. This study was approved by the King's College Hospital NHS trust audit board.

RESULTS

There were 500 new referrals to the neuro-oncology multidisciplinary team (MDT) for all brain tumours (excluding skull base and pituitary) in 2009 and 747 new referrals in 2010. An audit of neuro-oncology MDT referrals from 2008 and 2009 demonstrated that just under half of all referrals go on to have diagnostic and therapeutic interventions with the rest deemed palliative at presentation or not requiring treatment. In 1999 and 2000, there was no MDT format and no record of neuro-oncology referrals was therefore kept. The cases then were dealt with by the individual consultant they were referred to with no central register. There were a total of three patients with no data available on survival (two patients in year 1999–2000 and one patient in year 2009–2010). After excluding these three patients, there were a total of 317 patients remaining in the survival analysis (133 in year 1999–2000 and 184 in year 2009–2010, demographics in Table 1). Cox regression analysis (Figure 1) showed that the survival was significantly longer in patients in year 2009–2010 than those in 1999–2000 at $P<0.001$ with hazard ratio (HR) $=0.56$, confidence interval (CI; 0.45–0.71). Of particular interest, the 'longer survival group' was significantly larger in the 2009–2010 cohort compared with the 1999–2000 cohort. Thus 1- and 3-year survival rates were 20.7% and 4.4%, respectively, for patients in 1999–2000, improving to 40.0% and 10.3%, respectively, for patients in 2009–2010. The comparisons between the two groups in survival at 1, 2 and 3 years are all statistically significant at $P<0.001$, respectively. The median OS was 0.36 and 0.74 in 1999–2000 and 2009–2010 groups, respectively. Comparing 1999 with 2000, HR was 1.00 with 95% CI (0.71–1.41) at $P=0.986$. Comparing 2009 with 2010, HR was 0.91 with 95% CI (0.67–1.22) at $P=0.522$. The data therefore suggest a gradual trend towards better survival, rather than a sudden change, over the years. In 2009, 1 patient had carmustine wafers (Gliadel, Archimedes Pharma, UK) and none had a 5-aminolevulinic acid (5-ALA)-assisted resection. In 2010, 7 had carmustine wafers (10% of resections) and 27 (39% of resections) had a 5-ALA-assisted procedures. The Stupp protocol was not practiced in 1999–2000 period. In 2009–2010 cohorts, 48% of patients were treated with the Stupp protocol.

DISCUSSION

The key finding from our study is that OS from glioblastoma has increased significantly between 1999–2000 and 2009–2010.

Table 1. Demographics of glioblastoma cohort diagnosed in 2000 and 2010

	1999–2000 group	2009–2010 group
Total	135	185
Gender	52 (38.5%) female 83 (61.5%) male M : F = 1.6 : 1	69 (36.5%) female 120 (63.5%) male M : F = 1.7 : 1
Mean age	61	59
Tumour location	10 deep seated, 125 lobar	8 deep seated, 177 lobar

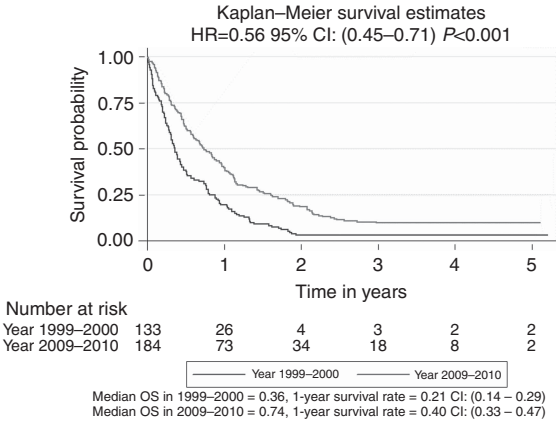

Figure 1. Cox regression analysis of survival in glioblastoma patients diagnosed in 1999–2000 compared with patients diagnosed in 2009–2010.

In particular, the percentage of patients reaching the 'longer survivor' end of the curve has increased most markedly.

The last decade has seen major changes in the management of patients with glioblastoma in the United Kingdom. In our unit in line with many others, we have introduced the use of concomitant temozolamide chemoradiation, intraoperative 5-ALA, carmustine wafers (Gliadel), advanced structural and metabolic imaging and molecular neuropathology. Of equal relevance, the initial assessment, management and follow-up of our patients are now performed in a specialist neuro-oncology MDT environment.

The MDT approach has become central to the practice of neuro-oncology since the 2006 National Institute for Clinical Excellence (NICE) guidance on formal referral of all brain tumour patients to a dedicated neuro-oncology MDT (NICE, 2006). This removes the vast majority of neuro-oncology patients from emergency 'on-call' decision-making processes, allows the case to be managed electively, ensures the patients receive the most appropriate treatment for their tumour, meet national cancer targets, have access to clinical trials and are optimised perioperatively to maximise performance status. The MDT process has reduced hospital stay and costs (Guilfoyle *et al*, 2011) without incurring delay in time to surgery (Rittman *et al*, 2012). In our unit, in addition to the weekly MDT where new referrals and post-treatment patients are discussed, all patients needing treatment are also seen in a specialist MDT clinic involving neurosurgeons, neuroradiologists, neuropathologists, oncologists, neurologists, therapists, specialist nurses and research staff. Involvement in a trial is a factor that is alone associated with improved survival as it is likely to reflect the aggressive approach to glioblastoma taken in that unit (Field *et al*, 2013).

In the recent times, there has also been a change in terms of surgical management philosophy for patients with glioblastoma, with a move away from limited surgery or a biopsy towards maximal resection where safe and possible. Trials showing that

maximal resection is associated with improved survival are not level 1 evidence as the majority are retrospective. However, the studies that are available, do suggest that maximal resection is associated with improved survival (McGirt *et al*, 2009; Allahdini *et al*, 2010; Sanai *et al*, 2011). Maximal resection is also important as it is cytoreductive and has been shown to facilitate delivery of adjuvant therapy (Ng *et al*, 2007); remove the hypoxic, therapy-resistant tumour core; sensitise cells to chemotherapy by pushing them into the G1 and G2 checkpoints of the cell cycle; obtain large specimen to reduce sampling error for neuropathology; and reduce the need for steroids in patients. Recent American Association of Neurological Surgeons level 2 guidelines recommend that patients with recurrent malignant glioma who have had previous surgical resection are considered for repeat cytoreductive surgery, taking into account performance status, tumour location and size (Ryken *et al*, 2014). We have been routinely practising this in our unit in the recent years.

In patients for whom only a biopsy is possible, surgical and radiological techniques to obtain representative tumour samples are crucial given the intra-tumoural heterogeneity at the cellular, genetic and molecular levels (Bonavia *et al*, 2011). The portions demonstrating contrast enhancement on magnetic resonance imaging (MRI) studies are often chosen for sampling as they are thought to represent the most aggressive part of the tumour, ultimately defining the prognosis (Roberts *et al*, 2011). In tumours with no contrast enhancement, advanced imaging techniques such as perfusion MRI imaging and positron-emission tomography imaging may help choosing a target for biopsy (Pirotte *et al*, 2009; Floeth *et al*, 2011). Newer therapies, especially those used in the clinical trial setting, including vaccines and anti-angiogenic agents may alter MRI findings and enhancement patterns, making correlation with other forms of imaging more useful (Huang *et al*, 2015).

Where possible, in our unit maximal resection is aimed for. Intraoperative image guidance and 5-ALA (Gliolan, Medac, Germany)-assisted surgery facilitates this. 5-Aminolevulinic acid has been shown to maximise surgical resection and prolong progression-free survival by 6 months in patients with malignant glioma (Stummer *et al*, 2006). Aggressive resections with 5-ALA do risk temporary neurological deficit but are overall safe (Stummer *et al*, 2011). In our unit we introduced the use of 5-ALA-assisted surgery in 2010, using the technique in 27 (39%) of resections performed that year. Since, the use has increased further, currently practiced in over 60% of resections. The interim results of an ongoing randomised trial on intraoperative MRI in glioblastoma resection do not show any advantage *vs* conventional neuronavigation although more studies are needed (Kubben *et al*, 2014). Preservation of eloquent white matter tracts by use of intraoperative diffusion tensor imaging has shown some clinical benefits in preventing deficits (Vassal *et al*, 2013).

The delivery of the adjuvant therapy has also changed in the past decade. The European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC–NCIC) trial followed 573 patients with glioblastoma over 5 years after randomisation to temozolamide (an alkylating agent) and radiotherapy or to radiotherapy alone (Stupp *et al*, 2009). The addition of temozolamide generated a significant survival advantage at 2 years and also at 5-year follow-up (Stupp *et al*, 2005, 2009), including in patients up to 70 years (Stupp *et al*, 2009). We use temozolamide and radiotherapy on all patients who fit the Stupp criteria, even if 90% tumour resection was not possible. In 2009–2010 period, 48% of our patients received the Stupp protocol treatment. The effectiveness of temozolamide is more pronounced in patients who demonstrate silencing of the O6-methylguanin-DNA-methyltransferase (MGMT) repair gene via promoter region methylation (Hegi *et al*, 2005; Malmström *et al*, 2012). Dose-dense temozolamide has shown no OS benefit in newly diagnosed glioblastoma (Gilbert *et al*, 2013). Its role in recurrent glioblastoma remains under investigation (Norden *et al*, 2013).

Local chemotherapy has been investigated. Intraoperative carmustine wafers (Gliadel) implanted into the tumour bed followed by radiotherapy (*vs* surgery and radiotherapy) have demonstrated a survival benefit in a multicentre trial of 207 patients (Westphal *et al*, 2006). A NICE technology appraisal in 2007 advocated the use of carmustine wafers and adjuvant temozolamide (NICE, 2007), although no comment on combining the two was made. The 2007 NICE technology appraisal recommends that temozolamide is suitable for patients with newly diagnosed glioblastoma, selected by a specialist neuro-oncology MDT, with performance status 0 or 1, over 90% of the tumour resected using neuronavigation and the tumour type verified by intraoperative neuropathology (NICE, 2007). Gliadel has been reported in a Cochrane review of three randomised trials to increase OS but not progression-free survival in glioblastoma (Hart *et al*, 2011). The potential side effects of Gliadel have been a concern in the neuro-oncological community. A phase 3 trial of Gliadel *vs* placebo in 240 patients with high-grade glioma reported a 5% incidence of CSF leak (0.8% with control) and a 9.1% incidence of intracranial hypertension (1.7% in control; Westphal *et al*, 2003). We introduced the use of Gliadel into our unit in 2009 and by 2010, 10% of patients undergoing resection were receiving Gliadel. During our study period, we did not encounter any significant adverse effects from the use of Gliadel such as brain swelling and infection. Of note, we used this drug in accordance with the NICE guidelines, for first operations in patients with more than 90% tumour resected. We stress meticulous dural and wound closure, 5 days of antibiotics and 2 weeks of high-dose dexamethasone. Of particular interest, there were no attributable complications in patients receiving both Gliadel and temozolamide chemotherapy. In line with our experience, a review of 19 retrospective and prospective studies combining carmustine wafers and temozolamide showed an improvement in survival, and no major safety concerns (Gutenberg *et al*, 2013).

In addition to therapeutic interventions, a greater understanding of glioblastoma tumour biology has aided in prognostication. Key markers are isocitrate dehydrogenase (IDH) 1 and 2, 1p19q codeletion, MGMT and epidermal growth factor receptor (EGFR) gene amplification. In our unit over the years, we have introduced analysis of gliomas for IDH1 and 2, 1p19q codeletion, MGMT and EGFR amplification. IDH mutations are found in low-grade glioma and secondary glioblastoma, and are rare in primary glioblastoma (Yan *et al*, 2009). IDH 1 and 2 mutations are associated with better prognosis than wild-type IDH (Sanson *et al*, 2009). MGMT promoter methylation has been shown to predict a favourable response to alkylating agents (Hegi *et al*, 2005; Esteller *et al*, 2000). The 1p19q codeletion in gliomas has been found to be associated with a favourable response to treatment (Wick *et al*, 2009). Amplification of EGFR is associated with increased invasiveness in glioblastoma (Friedman and Bigner, 2005). The interactions between cell-signalling pathways, molecular markers and the effect of therapy on each are myriad, complex and evolving (Weller *et al*, 2012).

Whilst the combined effect of these strategies has been to improve OS, the prognosis still remains dismal for glioblastoma patients. In this study, by definition, all patients included were well enough to at least have had a biopsy to achieve histological diagnosis. Not all, however, would have completed adjuvant therapy. It is of interest to note that perhaps the greatest impact over the years has been on the patients in the more favourable end of the survival curve, predominantly those able to undergo and tolerate their therapy. Thus, the percentage of the patients living beyond 1 and 3 years is now significantly increasing whilst those with the most aggressive tumours continue to have very poor outcomes. Interestingly, similar increase in survival in high-grade glioma has

also been reported in other recent studies, with patients over 60 having significant survival benefit (Asklund *et al*, 2013, 2015).

The challenge in the management of gliomas may reflect molecular heterogeneity and constant evolution of the tumour, making it difficult to discover and therapeutically target a consistently present, reliable final common pathway. Cellular, cytogenetic and molecular heterogeneity is not unique to glioblastoma but is especially pronounced in this tumour type, which may account for its resistance to standard therapies (Inda *et al*, 2010). No single mechanism for tumour heterogeneity has been identified. Possible mechanisms include clonal expansion of single cells, cancer stem cell subpopulations within the tumour and interactions between neighbouring cells (Nishikawa *et al*, 2004). To cope with this inter- and intra-tumour diversity new treatment strategies are needed. Immunotherapy has been considered as one potential avenue to follow given its high degree of specificity and adoptability. In line with this, in our unit we are currently recruiting for a phase 3 trial of dendritic cell immunotherapy vaccine for patients with newly diagnosed glioblastoma (Polyzoidis and Ashkan, 2014). The impact of this therapy on the survival of our patients will be of major interest to report in the future.

In conclusion, within the limitations of a retrospective study, we have demonstrated that OS of patients with glioblastoma in our unit has improved significantly over 10 years. We believe this to be due to advances in glioblastoma diagnostics and therapeutics. Key advances are molecular subtyping, tailored oncological treatments including Stupp regime and carmustine wafers, image-guided surgery and Gliolan-assisted resections. The application of these advances in an MDT setting facilitates organised delivery of care, adherence to national guidelines and access to clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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