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Early toxicity predicts long-term survival in high-grade glioma

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BACKGROUND: Patients with high-grade gliomas are treated with surgery followed by chemoradiation. The risk factors and implications of neurological side effects are not known.

METHODS: Acute and late grade 3 neurological toxicities (NTs) were analysed among 2761 patients from 14 RTOG trials accrued from 1983 to 2003. The association between acute and late toxicity was assessed using a stepwise logistic regression model. The association between the occurrence of acute NT and survival was assessed as an independent variable.

RESULTS: There were 2610 analysable patients (86% glioblastoma, 10% anaplastic astrocytoma). All received a systemic agent during radiation (85% chemotherapy, 17% biological agents). Median radiation dose was 60 Gy. There were 182 acute and 83 late NT events. On univariate analysis, older age, poor performance status, aggressive surgery, pre-existing neurological dysfunction, poor mental status and twice-daily radiation were associated with increased acute NT. In a stepwise logistic regression model the occurrence of acute NT was significantly associated with late NT (OR = 2.40, 95% CI = 1.2–4.8; P = 0.014). The occurrence of acute NT predicted poorer overall survival, independent of recursive partitioning analysis class (median 7.8 vs 11.8 months).

INTERPRETATION: Acute NT is significantly associated with both late NT and overall survival.


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Keywords: glioblastoma; toxicity; normal tissue effects; radiation therapy

Second to meningioma, high-grade gliomas (WHO grade 3, 4) are the most frequent type of primary brain tumours in adults. Treatment consists of maximal safe resection followed by partial brain radiation. Following the introduction of concomitant and adjuvant temozolomide, long-term survival for grade 4 gliomas (glioblastoma, GBM) has improved, with almost 10% of subjects now living 5 years (Stupp et al, 2009). The long-term toxicity of treatment is, therefore, of increasing importance.

Patients with high-grade glioma undergoing chemoradiation experience various side effects, including dermatological, endocrine, systemic and neurological events. Dermatological side effects such as radiation dermatitis and alopecia occur early and are generally transient, although alopecia may take several months to reverse. These rarely interfere with functional independence, but may contribute significantly to a reduction in quality of life because of a diminution in self-worth. Endocrine side effects are usually delayed by several months to years, are gradual in onset and often subtle, in terms of clinical presentation, and hence are underdiagnosed; they are more frequent in children than adults (Cross and Glantz, 2003). Systemic side effects such as myelosuppression and diarrhoea are generally attributable to chemotherapy.

Neurological side effects occur both early and late. Acute effects (within 90 days of the commencement of therapy) are often transient and include fatigue, headache, nausea, motor/sensory disturbances, raised intracranial pressure, cranial nerve palsies, visual disturbances, seizures and subtle changes in short-term memory. Late side effects (more than 90 days after the commencement of therapy) include many of the same symptoms, with the addition of cognitive decline (Taphoorn and Klein, 2004), cerebellar dysfunction and the consequences of white matter atrophy such as normal pressure hydrocephalus; these are rarely reversible.

It is often impossible to determine whether such neurological symptoms are side effects of radiation therapy (RT), surgery, chemotherapy, medications (e.g., anti-epileptics), an effect of the tumour itself or a combination of the above. The pathophysiology of radiation-induced neurological damage is complex and imperfectly understood; it is thought to involve (1) an increase in permeability of the blood–brain barrier, (2) death of oligodendroglial precursor cells leading to demyelination, (3) subtle changes in neuronal activity and vascular damage leading to frank radiation necrosis and (4) loss of radio-sensitive
stem cell compartments, which under the inflammatory stress, induced by radiation, preferentially undergo gliogenic maturation, as opposed to participating in neurogenesis (Mizumatsu et al., 2003; Soussain et al., 2009).

A recent review across a wide range of tumour types suggested that risk factors for radiation-induced neurological toxicity (NT) include both treatment variables (radiation dose, fraction size, conformality index, volume treated, overall treatment time, chemotherapy use) and patient variables (older age, diabetes mellitus) (Lawrence et al., 2010). We are not aware of any large studies that have specifically examined the NT of radiation treatment in subjects with high-grade gliomas, with a view to identifying risk factors and associations between acute and late toxicity, and eventual survival.

**Purpose**

By performing a retrospective analysis of RTOG high-grade glioma studies we sought to answer the following questions:

1. What is the incidence of acute and late NT following RT for high-grade glioma?
2. What are the risk factors for acute and late NT following RT for high-grade glioma?
3. Is there an association between acute and late NT?
4. What are the long-term implications of acute NT?

**MATERIALS AND METHODS**

Patient data was pooled from 14 RTOG high-grade glioma trials that accrued a total of 2761 subjects (Table 1). Eligibility criteria were consistent in all of the studies: histologically confirmed supratentorial malignant glioma; age of at least 18 years; normal hepatic, renal and bone marrow function; and an interval of 6 weeks or less from surgery to initiation of radiotherapy. Ineligibility criteria included previous malignancies (except skin carcinomas), previous chemotherapy, or head and neck irradiation. All the trials combined RT with systemic anti-tumour therapy.

**Definition of acute and late neurological toxicity**

‘Acute toxicity’ is defined as adverse events that occurred within 3 months of commencing therapy; events occurring after this were classified as ’late’. RTOG Acute Morbidity Scoring Criteria and RTOG/EORTC Late Radiation Morbidity Scoring Schema were used for the following studies: 8302, 8409, 9006, 9305, 9411, 9417, 9513, 9602 and 9710. NCI – CTC version 2.0 and RTOG/EORTC Late Radiation Morbidity Scoring Schema were used for the following studies: 9803, 9806, 0013, 0021 and 0023. For the purposes of this report, we only considered NTs of grade 3 or greater, without regard to attribution. Owing to the database’s design we were unable to scrutinise details of the NTs.

The trials analysed used a range of doses and fractionation schemes. The effects of different fractionation schemes on the normal brain were compared by calculating the biological-equivalent dose (BED) (Fowler, 1989) using a normal tissue alpha/beta ratio of 3 (Lee et al., 1998). The RTOG trial 9305 combined fractionated therapy (60 Gy, BED 100) with a single-fraction radiosurgical boost. Although there is no accepted way to convert this into a BED, we considered the BED to be ‘above 120’ for the purposes of statistical analysis.

**Statistical methods**

Frequency distributions of patient survival time (survive ≥ 3 month vs survive < 3 months) for two groups (acute NT vs no
acute NT) were compared using χ²-tests. McNemar’s test was used to test the difference between two correlated proportions – occurrence/no occurrence of acute and late NTs. Logistic regression was used to assess the relationship between acute and late NTs. It was also used to assess the relationship between pretreatment characteristics, treatment options and the occurrence of acute NTs. For the survival end point, the Kaplan–Meier method was used to estimate the rates, and the log-rank test was used to compare them between the two patient groups (acute NT vs no acute NT). The Cox proportional hazards (PH) model was used to estimate the hazard ratio (HR) associated with overall survival while adjusting patient-specific factors. A two-sided test was used at a significance level of 0.05 for all the evaluations.

When the two patient groups (patients with and without acute NT) were compared with regard to overall survival, based on the log-rank test, a statistical difference was found (HR = 1.77; 95% CI = 1.52–2.06; P < 0.0001). The median survival times were 7.8 and 11.8 months, respectively. The Kaplan–Meier curve is presented in Figure 1. Subjects with acute CNS toxicities were more likely to die within 3 months of treatment. Approximately 19% of patients with acute CNS toxicities died within 3 months, whereas 10% of patients without acute CNS toxicities died within 3 months, P < 0.001.

Recursive partitioning analysis (RPA) class (a combination of age, histology, Zubrod performance status, mental status, neurological function, symptom time and previous surgery) has

<table>
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Abbreviations: AA = anaplastic astrocytoma; GBM = glioblastoma; RPA = recursive partitioning analysis; RT = radiation therapy.
Clinical Studies

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was robustly established as a prognostic scale for patients with newly diagnosed high-grade glioma (Curran et al., 1993; Scott et al., 1998b; Mirimanoff et al., 2006). Recursive partitioning analysis class, BID radiation (yes vs no), chemotherapy (yes vs no), BED \( < 120 \) vs \( > 120 \) and the occurrence of acute NT were assessed in a PH Cox model for overall survival (Table 5, Figure 2). Twice-daily radiation and BED were considered non-statistically significant and were not included in the multivariate Cox analysis. In a stepwise multivariate Cox model considering RPA class, chemotherapy and acute CNS toxicities, only RPA class and acute NT remained statistically associated with the overall survival (HR \( = 1.43; \) 95% CI \( = 1.2–1.7; \) \( P < 0.0001 \)) after adjusting for the RPA classes (Table 5).

### DISCUSSION

We performed an analysis of the RTOG database to understand the risk factors and consequences of acute NT in patients with high-grade gliomas undergoing RT.

We found that both early and late toxicity are comparatively rare (3–7%) – in agreement with published experience (Dinapoli et al., 1993; Stupp et al., 2005; Keime-Guibert et al., 2007). Risk factors for acute NT that remained significant in the multivariate analysis were both patient (functional status, neurological function, mental status) and treatment (biopsy only, BID radiation) related. These findings, though novel in the field of brain tumours, are in keeping with the general oncology literature that frail patients experience more toxicity (Brian et al., 1995; Artz et al., 2006; Kumar Pal et al., 2010). The lack of association between chemotherapy and toxicity differs with the findings of the pivotal EORTC/NCIC phase III trial that established temozolomide and radiation as the standard of care. In that trial, in-field acute grade 3 and 4 toxicities (dermatological, infection and vision and nausea/vomiting) occurred in 7 and 14% of subjects in the control and temozolomide arms, respectively, (Stupp et al., 2005). This difference may reflect the type and extended duration of chemotherapy in the EORTC/NCIC trial. Conversely the rate of late toxicity reported by us (3.5%) is much higher than that reported in each arm of the EORTC/NCIC trial (<1%), it is not clear whether this is due to differences in treatment, population (the EORTC trial excluded older patients) or reporting practices. An important difference is that the statistics from the Stupp trial refer to any non-haematological toxic event, whereas the data presented here are specifically for NT.

Risk factors for late toxicity, significant in multivariate analysis, were once-daily radiation, high total radiation dose and previous acute NT. It is interesting to compare our findings with the recently published QUANTEC meta-analysis of the tolerance of the normal brain to irradiation, which investigated risk factors for late brain toxicity (Lawrence et al., 2010). Many of the studies analysed by the QUANTEC team involved the treatment of non-primary brain tumours (e.g., brain metastases and nasopharyngeal carcinoma). The QUANTEC authors demonstrated a sharp incidence in radiation necrosis when the BED rose above 120. Although the end points are not identical, in the current study we likewise found that a BED above 120, doubled the risk of late toxicity.

The association between acute and late toxicity has not previously been reported, and challenges the classic teaching that acute toxicity is fully reversible. A possible explanation is that these acute toxicities were so severe that healing was not possible; alternatively this may reflect a predisposition to toxicity amongst...
certain patients, possibly related to either tumour location (e.g., close to critical structures) or genetic makeup.

The relationship between acute NT and overall survival was unexpected. Patients who did not experience acute NT were found to have a 4 month longer median survival than those who experienced NT (of at least grade 3). This survival advantage was independent of RPA class. Although we lack a complete explanation, this may demonstrate the importance of normal tissue damage in determining long-term survival. A recent study likewise demonstrated that GBM patients who acquired motor or language deficits post-operatively had poorer overall survival than those who remained neurologically intact (Shinoda et al, 2001).

Our findings are in contrast with the association between pseudo-progression and improved prognosis in high-grade gliomas (Gerstner et al, 2009). Pseudo-progression is generally defined as radiological progression (oedema and sometimes contrast enhancement on MRI) soon after the completion of RT in patients with malignant gliomas, which is followed by spontaneous recovery and stabilisation (Brandsma et al, 2008). Pathologically it is thought to represent a mild form of radiation necrosis. Possible explanations for the difference between our findings and those associating pseudo-progression with a good prognosis are (1) pseudo-progression is especially associated with the use of temozolomide (Chamberlain et al, 2007; Brandsma et al, 2008). None of the patients in our study received this agent; rather the most frequently used systemic agent was BCNU, which appears to be much less potent. (2) Our patients were universally symptomatic, whereas most patients with pseudo-progression are asymptomatic. Hence, whereas pseudo-progression may be a form of intra-tumour necrosis, we suspect that the 'acute toxicity' cases described here represent damage to surrounding normal tissues. A more thorough understanding would require a case-by-case review of imaging, which unfortunately is not possible.
Despite the fact that our study dates from the pre-temozolomide era, we found that the use of chemotherapy was associated with increased survival (Figure 2). Of those who received chemotherapy, 93% received BCNU. As this association was only found on univariate, but not in multivariate analysis, its significance is unclear. Nevertheless, the association is in agreement with previous meta-analyses that have likewise identified methylating agents as significant in moderating survival (Table 5) further supports the supposition that this is related to normal tissue damage. The lack of impact of fractionation scheme on overall survival in patients not receiving temozolomide is provocative and requires validation. This phenomenon appears to be distinct to the ‘pseudoprogression’ seen when temozolomide is combined with RT.

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Conflict of interest

Minesh Mehta has or has had the following roles in the last 2 years (2009–2010); Consultant: Adnexus, Bayer, Merck, Roche and Tomotherapy; Stock options: Colby, Pharmacyclics, Procurctus and Stemina Tomotherapy; Data Safety Monitoring Boards: Apogenix; Board of Directors: Pharmacyclics; Medical Advisory Boards: Colby, Stemina and Procurctus; Speaker: Merck. The other authors, including Dr Lawrence, declare no conflict of interest. Dr Lawrence, Christine Baxter, RTOG, ASCO, AAOS, Magnetic Resonance Society of North America, Photography, Accurate Attribution of Neurological Events, Tumor Progression, and Radiation Induced Toxicity. 

Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)


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