

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

YR Lawrence^{*,1,2}, M Wang³, AP Dicker¹, D Andrews⁴, WJ Curran Jr⁵, JM Michalski⁶, L Souhami⁷, W-KA Yung⁸ and M Mehta⁹

¹Department of Radiation Oncology, Thomas Jefferson University, Kimmel Cancer Center, Bodine Cancer Center, 111 S. 11th Street, Philadelphia, PA 19107, USA; ²Department of Radiation Oncology, Sheba Medical Center, Tel HaShomer, 52621, Israel; ³Department of Statistics, Radiation Therapy Oncology Group, 1818 Market Street, Suite 1600, Philadelphia, PA 19103-3604, USA; ⁴Department of Neurological Surgery, Thomas Jefferson University, 111 S. 11th Street, Philadelphia, PA 19107, USA; ⁵Department of Radiation Oncology, Emory University School of Medicine, 1365 Clifton Road, Atlanta, GA 30322, USA; ⁶Department of Radiation Oncology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8224, St Louis, MO 63110, USA; ⁷Department of Radiation Oncology, McGill University, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada; ⁸Department of Neuro-Oncology, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; ⁹Department of Radiation Oncology, Northwestern University Feinberg School of Medicine, 251 East Huron Street, Chicago, IL 60611, USA

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 \geq 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 analysed using a stepwise logistic regression model. The association between the occurrence of acute NT and survival was analysed as an independent variable.

RESULTS: There were 2610 analysable patients (86% glioblastoma, 10% anaplastic astrocytoma). All received a systemic agent during radiation (83% 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.

British Journal of Cancer (2011) **104**, 1365–1371. doi:10.1038/bjc.2011.123 www.bjcancer.com

Published online 12 April 2011

© 2011 Cancer Research UK

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

*Correspondence: Dr YR Lawrence;

E-mail: yaacov.lawrence@sheba.health.gov.il

Received 17 November 2010; revised 14 March 2011; accepted 15 March 2011; published online 12 April 2011

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

Table 1 Clinical trial data analysed

Study	Phase	Study question	BID RT	Concurrent systemic agent	Number of analysable subjects	BED	Acute neurological toxicity	Late neurological toxicity	Overall toxicity	Survival	Ref.
8302	I/II	Hyperfractionated RT, dose escalation	Y	BCNU	756	73.6–114.2	86	9	Acceptable	HC	(Curran <i>et al</i> , 1992)
8409	I/II	Role of AZQ	N	AZQ	54	74–95	11	0	NR	HC	(1998)
9006	III (R)	Conventional vs hyperfractionated RT	Y/N	BCNU	693	100–100.8	28	15	NR	HC	(Scott <i>et al</i> , 1998a)
9305	III (R)	Radiosurgical boost	N	BCNU	187	100, >120	6	4	Acceptable	HC	(Souhami <i>et al</i> , 2004)
9411	II	Dose escalation for small tumours	Y	BCNU	105	98.1–108	5	3	Acceptable	HC	(Coughlin <i>et al</i> , 2000)
9417	II	Role of tirapazamine	N	Tirapazamine	122	100	3	1	More toxicities at higher dose	HC	(Del Rowe <i>et al</i> , 2000)
9513	II	Role of topotecan	N	Topotecan	84	100	4	3	Significant haematological toxicity	HC	(Fisher <i>et al</i> , 2002)
9602	II	Role of paclitaxel	N	Paclitaxel	61	100	1	4	Acceptable	HC	(Langer <i>et al</i> , 2001)
9710	II	Role of beta-interferon	N	Beta-interferon	55	100	1	2	Acceptable	HC	(Colman <i>et al</i> , 2006)
9803	I/II	Conventional fractionation, dose escalation	N	BCNU	203	110–140	10	13	Acceptable	HC	(Tsien <i>et al</i> , 2009)
9806	II	Role of thalidomide	N	Thalidomide	125	100	19	12	Acceptable	Slightly better than HC	(Yung <i>et al</i> , 2001)
0013	II	Intra-tumoral bleomycin	N	Bleomycin	14	100	1	4	— ^a	— ^a	— ^a
0021	II	Role of tamoxifen	N	Tamoxifen	75	100	2	4	Acceptable	HC	(Robins <i>et al</i> , 2006)
0023	II	Role of stereotactic RT boost	N	BCNU	76	172	5	9	Acceptable	HC	(Cardinale <i>et al</i> , 2006)

Abbreviations: AZQ = diaziquone; BCNU = carmustine; BED = biological-equivalent dose; BID = twice daily radiation; HC = historical controls; N = no; NR = not reported; R = randomised; RT = radiation therapy; Y = yes. ^aSmall study, never published.

acute NT) were compared using χ^2 -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 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.

Patients dying within 3 months of RT are by definition not able to develop late NT; they were therefore excluded from analyses of late toxicity.

RESULTS

A total of 2761 patients were accrued; 151 patients (5%) were excluded from the analysis because of being ineligible, no protocol treatment or withdrawal of consent leaving 2610 patients. Baseline characteristics are listed in Table 2.

Median follow-up of all subjects was 11.2 months; median follow-up of the 279 patients censored subjects who were still alive at last follow-up was 57.3 months (this difference in length of follow-up between all subjects (censored and uncensored) and censored subjects reflects the fact that the risk of dying apparently decreases after living up to a certain time). The 265 patients who lived less than 3 months were excluded from analyses of late toxicity. A total of 182 cases (7.0%, crude rate) of acute NT and 83 cases (3.5%, crude rate) of late NT were reported.

Pretreatment characteristics and treatment options were assessed in logistic regression models to predict the occurrence of acute CNS toxicities. Table 3 lists the results, based on the univariate logistic regression analyses. Histology, chemotherapy and BED were considered as non-statistically significant at the significance level of 0.1 and not included in the further multivariate logistic regression analysis. In a stepwise logistic regression model considering the remaining six variables, Zubrod performance status, previous surgery type, neurological function, mental status and twice-daily (BED) radiation were significantly associated with acute NT (Table 3).

Pretreatment characteristics, treatment-related variables and the occurrence of acute NT were assessed in logistic regression models to predict the occurrence of late CNS toxicities. The following variables were considered in the univariate logistic regression analysis: age at diagnosis (<50 vs \geq 50), surgery type (biopsy vs partial/total resection), neurological dysfunction (no dysfunction/minor vs moderate/severe), mental status (normal function vs minor/confusion), once-daily radiation (yes vs no), Zubrod performance status (0 vs 1/2/3), histology (GBM vs anaplastic astrocytoma), chemotherapy (yes vs no), BED (\leq 120 vs $>$ 120) and acute CNS toxicities (yes vs no). Age, Zubrod performance status, type of surgery, neurological function, mental status and histology were considered non-statistically significant at a significance level of 0.1 and not included in further multivariate logistic regression analysis. In a stepwise logistic regression model considering the four remaining variables, once-daily radiation, BED and previous occurrence of acute NT were all statistically associated with late NT (Table 4).

The association between acute and late toxicity amongst subjects who survived at least 3 months was examined by means of McNemar's test. Among the 148 patients experiencing acute NT, 10 (7%) patients experienced late NT; among the 2197 patients not experiencing acute NT, only 73 (3%) patients experienced late NT, $P < 0.0001$, suggesting that acute CNS toxicities are statistically associated with late CNS toxicities.

Table 2 Pretreatment characteristics, (n = 2610)

	N	%
Age		
< 50	907	34
\leq 50	1691	65
Unknown/missing	12	< 1
Zubrod		
0	1294	50
1, 2, 3	1304	50
Unknown/missing	12	< 1
Surgery		
Biopsy	650	25
Partial/total resection	1900	73
Other/unknown/missing	70	2
Neurological dysfunction		
None/minor	1631	62
Moderate/severe	961	36
Unknown/missing	18	1
Mental status		
Normal function	1725	66
Minor, gross confusion	706	27
Unknown/missing	179	7
RPA class		
I, II	183	7
III	410	16
IV	1043	40
V, VI	844	33
Unknown	130	5
Histology		
GBM	2233	86
AA	250	10
Other	127	5
Twice-daily RT		
No	1397	54
Yes	1213	46
Chemotherapy		
No	431	17
Yes	2179	83
Biological drug		
No	2179	83
Yes	431	17
Biological-equivalent dose		
\leq 120	2344	90
$>$ 120	266	10

Abbreviations: AA = anaplastic astrocytoma; GBM = glioblastoma; RPA = recursive partitioning analysis; RT = radiation therapy.

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 3 Univariate and multivariate analyses/logistic regression for acute neurological toxicities ($n = 2610$)

Variable	Comparison	Univariate analysis		Multivariate analysis ^b	
		OR (95% CI) ^a	P-value	OR (95% CI) ^a	P-value
Age	<50	—			
	≥50	1.59 (1.1, 2.2)	0.008	—	—
Zubrod	0	—			
	1, 2, 3	2.72 (1.9, 3.8)	<0.0001	1.77 (1.1, 2.7)	0.010
Surgery	Partial/total resection	—		—	
	Biopsy	1.63 (1.2, 2.2)	0.0029	1.43 (1.0, 2.0)	0.038
Neurological dysfunction	None/minor	—		—	
	Moderate/severe	2.91 (2.1, 4.0)	<0.0001	1.80 (1.2, 2.7)	0.0054
Mental status	Normal function	—		—	
	Minor/gross confusion	2.48 (1.8, 3.4)	<0.0001	1.69 (1.2, 2.4)	0.0025
Twice-daily RT	No	—		—	
	Yes	1.79 (1.32, 2.43)	0.0002	1.67 (1.2, 2.3)	0.0025
Histology	AA	—		—	
	GBM	0.95 (0.6, 1.6)	0.84	—	—
Chemotherapy	No	—		—	
	Yes	0.79 (0.5, 1.2)	0.22	—	—
Biological-equivalent dose	≤120	—		—	
	>120	0.84 (0.5, 1.4)	0.52	—	—

Abbreviations: AA = anaplastic astrocytoma; BED = biological-equivalent dose; CI = confidence interval; GBM = glioblastoma; OR = odds ratio; RT = radiation therapy. ^aOdds ratio: the odds ratio of 1 indicates no difference between the two subgroups. ^bMultivariate model derived from stepwise selection. Variable(s) not included in final model: age (dropped out during the stepwise selection process). Variable(s) dropped from modelling as not significant with reference variables: histology, chemotherapy, BED (not significant during the univariate setting).

been 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

Table 4 Univariate and multivariate analyses/logistic regression for late neurological toxicities

Variable	Comparison	Univariate analysis		Multivariate analysis ^b	
		OR (95% CI) ^a	P-value	OR (95% CI) ^a	P-value
Age	<50	—	—	—	—
	≥50	0.95 (0.6, 1.5)	0.81	—	—
Zubrod	0	—	—	—	—
	1, 2, 3	0.93 (0.6, 1.4)	0.75	—	—
Surgery	Partial/total resection	—	—	—	—
	Biopsy	1.09 (0.7, 1.8)	0.73	—	—
Neurological dysfunction	None/minor	—	—	—	—
	Moderate/severe	0.76 (0.5, 1.2)	0.26	—	—
Mental status	Normal function	—	—	—	—
	Minor/gross confusion	0.86 (0.5, 1.5)	0.62	—	—
Twice-daily RT	No	—	—	—	—
	Yes	0.37 (0.2, 0.6)	0.0001	0.42 (0.2, 0.7)	0.002
Histology	AA	—	—	—	—
	GBM	1.76 (0.7, 4.4)	0.23	—	—
Chemotherapy	No	—	—	—	—
	Yes	0.64 (0.4, 1.1)	0.09	—	—
BED	≤120	—	—	—	—
	>120	2.83 (1.7, 4.8)	<0.0001	1.98 (1.1, 3.4)	0.016
Acute CNS	No	—	—	—	—
	Yes	2.11 (1.1, 4.2)	0.03	2.40 (1.2, 4.8)	0.014

Abbreviations: AA = anaplastic astrocytoma; BED = biological-equivalent dose; CI = confidence interval; CNS = central nervous system; GBM = glioblastoma; OR = odds ratio; RT = radiation therapy. ^aOdds ratio: The odds ratio of 1 indicates no difference between the two subgroups, less than 1 indicates a protective effect. ^bMultivariate model derived from stepwise selection. Variable(s) not included in final model: chemotherapy (dropped out during the stepwise selection process). Variable(s) dropped from modelling as not significant with reference variables: age, Zubrod performance status, surgery, neurologic function, mental status, histology (not significant during the univariate setting).

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). Pseudoprogression 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

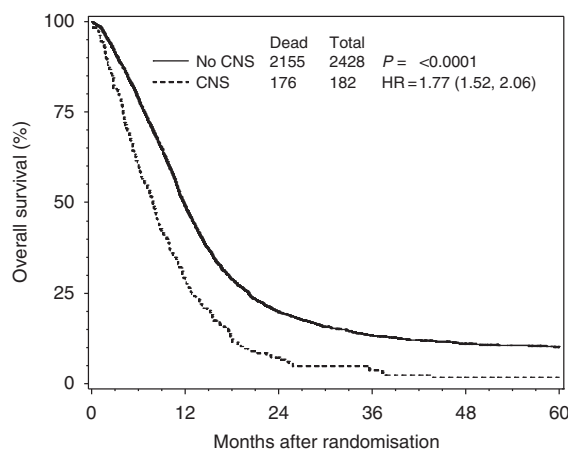


Figure 1 Overall survival, stratified by the presence/absence of acute neurological toxicity.

Table 5 Univariate and multivariate analysis/cox proportional hazards model for overall survival

Variable	Comparison	HR (95% CI)	P-value	HR (95% CI)	P-value
RPA	I, II	—	—	—	—
	III	3.24 (2.6, 4.1)	<0.0001	3.27 (2.6, 4.1)	<0.0001
	IV	5.41 (4.4, 6.7)	<0.0001	5.41 (4.4, 6.7)	<0.0001
Twice-daily RT	V, VI	10.10 (8.1, 12.6)	<0.0001	9.92 (7.9, 12.4)	<0.0001
	No	—	—	—	—
Chemotherapy	Yes	0.93 (0.9, 1.0)	0.09	—	—
	No	—	—	—	—
BED	Yes	0.78 (0.7, 0.9)	<0.0001	—	—
	No	—	—	—	—
Acute CNS	≤120	—	—	—	—
	>120	0.99 (0.9, 1.1)	0.86	—	—
Acute CNS	No	—	—	—	—
	Yes	1.77 (1.5, 2.1)	<0.0001	1.43 (1.2, 1.7)	<0.0001

Abbreviations: BED = biological-equivalent dose; CI = confidence interval; CNS = central nervous system; HR = hazards ratio; RPA = recursive partitioning analysis; RT = radiation therapy. Multivariate model derived from stepwise selection. Variable(s) not included in final model: twice-daily RT and chemotherapy (dropped out during the stepwise selection process). Variable dropped from modelling as not significant with reference variables: BED (not significant during the univariate setting).

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 pseudoprogression with a good prognosis are (1) pseudoprogression 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 pseudoprogression are asymptomatic. Hence, whereas pseudoprogression 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.

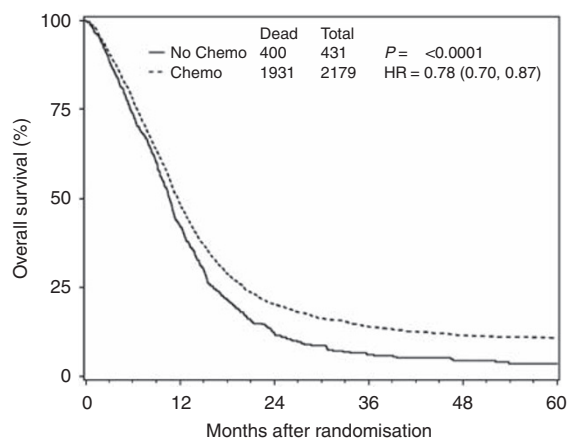


Figure 2 Overall survival stratified by the use of chemotherapy. Of note, 93% of subjects who received chemotherapy received BCNU. All patients who did not receive chemotherapy did receive a systemic agent (temozolomide, diaziquone, tamoxifen, thalidomide or β -interferon).

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 to be effective radiosensitizers in this disease (Chang *et al*, 1983; Fine *et al*, 1993; Spiegel *et al*, 2007).

A weakness of this retrospective study is our inability to assess completeness of reporting, and accurate attribution of neurological events. The definition of NT varied between the studies depending on the toxicity scale used; further we do not have descriptions of these events. A possible explanation of our findings associating acute NT with long-term survival is 'misclassification bias', that is, the treating physicians had difficulty distinguishing treatment-related side effects from tumour symptoms, and that what was reported as 'acute toxicity' was in fact early tumour progression. A close reading of our results however, supports the fact that these were indeed true treatment-related side effects: (1) We found that compared with once-daily radiation, BID radiation produced increased acute toxicity, but decreased late toxicity. This is entirely in keeping with classic radiobiology teaching of normal tissue damage. The lack of impact of fractionation scheme on overall survival (Table 5) further supports the supposition that this is related to normal tissue injury and not tumour control. (2) Conversely, histology (GBM vs anaplastic astrocytoma) had no impact on either

REFERENCES

- Artz AS, Pollyea DA, Kocherginsky M, Stock W, Rich E, Odenike O, Zimmerman T, Smith S, Godley L, Thirman M, Daugherty C, Extermann M, Larson R, van Besien K (2006) Performance status and comorbidity predict transplant-related mortality after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 12: 954–964
- Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol* 9: 453–461
- Brian NS, Nicholas JP, Harold OD, Deborah LD, Giuseppina A, Neal JM (1995) Age and sex are independent predictors of 5-fluorouracil toxicity. Analysis of a large scale phase III trial. *Cancer* 75: 11–17
- Cardinale R, Won M, Choucair A, Gillin M, Chakravarti A, Schultz C, Souhami L, Chen A, Pham H, Mehta M (2006) A phase II trial of accelerated radiotherapy using weekly stereotactic conformal boost for supratentorial glioblastoma multiforme: RTOG 0023. *Int J Radiat Oncol Biol Phys* 65: 1422–1428
- Chamberlain MC, Glantz MJ, Chalmers L, Van Horn A, Sloan AE (2007) Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. *J Neurooncol* 82: 81–83
- Chang CH, Horton J, Schoenfeld D, Salazar O, Perez-Tamayo R, Kramer S, Weinstein A, Nelson JS, Tsukada Y (1983) Comparison of postoperative radiotherapy and combined postoperative radiotherapy and

acute or late toxicity, despite the more aggressive nature of GBM. If 'NT' was in fact a measure of 'tumour progression', a correlation would have been expected. (3) This 'misclassification' bias would be expected to especially affect subjects whose tumours progressed very early. Nevertheless, if patients who died within the first 3 months are excluded from the analysis, the survival benefit associated with lack of acute toxicity remains (HR = 1.69; 95% CI = 1.43–2.01; $P < 0.0001$, Supplementary Figure).

A further weakness of our study is the small number of patients encountering toxicity. Although we analysed 2610 subjects, there were only 182 acute toxic events and 83 late toxic events. Confirmatory studies from other large databases, or population-based cohorts are therefore needed to validate our findings.

In conclusion we have elucidated the risk factors for NT amongst patients with high-grade glioma undergoing RT. These should be considered when designing eligibility criteria for clinical trials. The finding that acute NT predicts for both late NT and poor 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.

ACKNOWLEDGEMENTS

This study was supported by a RTOG grant U10 CA21661, CCOP grant U10 CA37422 and ATC grant U24 CA81647 from the National Cancer Institute. This manuscript's contents are solely the responsibility of us and do not necessarily represent the official views of the National Cancer Institute. YR Lawrence is supported by The ASCO Cancer Foundation Young Investigator Award. Any opinions, findings and conclusions expressed in this material are by us and do not necessarily reflect those of the American Society of Clinical Oncology or the ASCO Cancer Foundation. P Dicker is supported by the National Institutes of Health Grant CA10663, Tobacco Research Settlement Fund (State of Pennsylvania) and the Christine Baxter Fund.

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, Procertus and Stemina Tomotherapy; Data Safety Monitoring Boards: Apogenix; Board of Directors: Pharmacyclics; Medical Advisory Boards: Colby, Stemina and Procertus; Speaker: Merck. The other authors, including Dr Lawrence, declare no conflict of interest. Dr Lawrence had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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

- chemotherapy in the multidisciplinary management of malignant gliomas. A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. *Cancer* 52: 997–1007
- Colman H, Berkey BA, Maor MH, Groves MD, Schultz CJ, Vermeulen S, Nelson DF, Mehta MP, Yung WK (2006) Phase II Radiation Therapy Oncology Group trial of conventional radiation therapy followed by treatment with recombinant interferon-beta for supratentorial glioblastoma: results of RTOG 9710. *Int J Radiat Oncol Biol Phys* 66: 818–824
- Coughlin C, Scott C, Langer C, Coia L, Curran W, Rubin P (2000) Phase II, two-arm RTOG trial (94-11) of bischloroethyl-nitrosourea plus accelerated hyperfractionated radiotherapy (64.0 or 70.4 Gy) based on tumor volume (>20 or ≤ 20 cm², respectively) in the treatment of newly-diagnosed radiosurgery-ineligible glioblastoma multiforme patients. *Int J Radiat Oncol Biol Phys* 48: 1351–1358
- Cross NE, Glantz MJ (2003) Neurologic complications of radiation therapy. *Neurol Clin* 21: 249–277
- Curran Jr WJ, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Krusch RE, Nelson DF (1993) Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 85: 704–710
- Curran Jr WJ, Scott CB, Nelson JS, Weinstein AS, Phillips TL, Murray K, Fischbach AJ, Yakar D, Schwade JG, Powlis WD, Nelson DF (1992) A randomized trial of accelerated hyperfractionated radiation therapy and bis-chloroethyl nitrosourea for malignant glioma. A preliminary report of Radiation Therapy Oncology Group 83-02. *Cancer* 70: 2909–2917
- Del Rowe J, Scott C, Werner-Wasik M, Bahary JP, Curran WJ, Urtasun RC, Fisher B (2000) Single-arm, open-label phase II study of intravenously administered tirapazamine and radiation therapy for glioblastoma multiforme. *J Clin Oncol* 18: 1254–1259
- Dinapoli RP, Brown LD, Arusell RM, Earle JD, O'Fallon JR, Buckner JC, Scheithauer BW, Krook JE, Tschetter LK, Maier JA (1993) Phase III comparative evaluation of PCNU and carmustine combined with radiation therapy for high-grade glioma. *J Clin Oncol* 11: 1316–1321
- Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP (1993) Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 71: 2585–2597
- Fisher B, Won M, Macdonald D, Johnson DW, Roa W (2002) Phase II study of topotecan plus cranial radiation for glioblastoma multiforme: results of Radiation Therapy Oncology Group 9513. *Int J Radiat Oncol Biol Phys* 53: 980–986
- Fowler JF (1989) The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 62: 679–694
- Gerstner E, McNamara M, Norden A, LaFrankie D, Wen P (2009) Effect of adding temozolomide to radiation therapy on the incidence of pseudo-progression. *J Neurooncol* 94: 97–101
- Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, Guillemo J-S, Jadaud E, Colin P, Bondiau P-Y, Menei P, Loiseau H, Bernier V, Honnorat J, Barrie M, Mokhtari K, Mazeran J-J, Bissery A, Delattre J-Y, The Association of French-Speaking N-O (2007) Radiotherapy for glioblastoma in the elderly. *N Engl J Med* 356: 1527–1535
- Kumar Pal S, Katheria V, Hurria A (2010) Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. *CA Cancer J Clin* 60: 120–132
- Langer CJ, Ruffer J, Rhodes H, Paulus R, Murray K, Movsas B, Curran W (2001) Phase II radiation therapy oncology group trial of weekly paclitaxel and conventional external beam radiation therapy for supratentorial glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 51: 113–119
- Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE, Dicker AP (2010) Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* 76: S20–S27
- Lee AW, Foo W, Chappell R, Fowler JF, Sze WM, Poon YF, Law SC, Ng SH, O SK, Tung SY, Lau WH, Ho JH (1998) Effect of time, dose, and fractionation on temporal lobe necrosis following radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 40: 35–42
- Mirimanoff RO, Gorlia T, Mason W, Van den Bent MJ, Kortmann RD, Fisher B, Reni M, Brandes AA, Curschmann J, Villa S, Cairncross G, Allgeier A, Lacombe D, Stupp R (2006) Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol* 24: 2563–2569
- Mizumatsu S, Monje ML, Morhardt DR, Rola R, Palmer TD, Fike JR (2003) Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res* 63: 4021–4027
- Robins HI, Won M, Seiferheld WF, Schultz CJ, Choucair AK, Brachman DG, Demas WF, Mehta MP (2006) Phase 2 trial of radiation plus high-dose tamoxifen for glioblastoma multiforme: RTOG protocol BR-0021. *Neuro Oncol* 8: 47–52
- Scott C, Curran JW, Yung W, Scarantino C, Urtasun R, Movsas B, Jones C, Simpson J, Fischbach A, Petito C, Nelson J (1998a) Long term results of RTOG 9006: a randomized trial of hyperfractionated radiotherapy (RT) to 72.0 Gy & carmustine vs standard RT & carmustine for malignant glioma patients with emphasis on anaplastic astrocytoma (AA) patients. (Abstract 1546) *Proc Am Soc Clin Oncol*
- Scott CB, Scarantino C, Urtasun R, Movsas B, Jones CU, Simpson JR, Fischbach AJ, Curran Jr WJ (1998b) Validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: a report using RTOG 90-06. *Int J Radiat Oncol Biol Phys* 40: 51–55
- Shinoda J, Sakai N, Murase S, Yano H, Matsuhisa T, Funakoshi T (2001) Selection of eligible patients with supratentorial glioblastoma multiforme for gross total resection. *J Neurooncol* 52: 161–171
- Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, Schultz CJ, Sause W, Okunieff P, Buckner J, Zamorano L, Mehta MP, Curran Jr WJ (2004) Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys* 60: 853–860
- Soussain C, Ricard D, Fike JR, Mazeran J-J, Psimaras D, Delattre J-Y (2009) CNS complications of radiotherapy and chemotherapy. *Lancet* 374: 1639–1651
- Spiegel BM, Esrailian E, Laine L, Chamberlain MC (2007) Clinical impact of adjuvant chemotherapy in glioblastoma multiforme: a meta-analysis. *CNS Drugs* 21: 775–787
- Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 10: 459–466
- Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987–996
- Tapazoglou E, Lee M, Simpson J, Mohiuddin M, Nelson J, Kinzie J, Al-Sarraf M (1998) Concurrent aziridynyl-benzoquinone (AZQ) chemotherapy and radiotherapy (RT) in patients with malignant gliomas: RTOG Study. *ASCO Annual Meeting*, Los Angeles
- Taphoorn MJB, Klein M (2004) Cognitive deficits in adult patients with brain tumours. *Lancet Neurol* 3: 159–168
- Tsien C, Moughan J, Michalski JM, Gilbert MR, Purdy J, Simpson J, Kresel JJ, Curran WJ, Diaz A, Mehta MP (2009) Phase I three-dimensional conformal radiation dose escalation study in newly diagnosed glioblastoma: Radiation Therapy Oncology Group Trial 98-03. *Int J Radiat Oncol Biol Phys* 73: 699–708
- Yung AW, Seiferheld W, Donahue B, Richards R, Kerlin K, Hug EB, Curran JW, Fine H (2001) A RTOG (Radiation Therapy Oncology Group) Phase II Study of Conventional Radiation Therapy Plus Thalidomide Followed by Thalidomide Post XRT for Supratentorial Glioblastoma. (Abstract 206) *Proc Am Soc Clin Oncol* 20