

# Randomized Trial of Procarbazine, Lomustine, and Vincristine in the Adjuvant Treatment of High-Grade Astrocytoma: A Medical Research Council Trial

By the Medical Research Council Brain Tumour Working Party

**Purpose:** Meta-analyses of the published literature suggest a survival benefit to adjuvant chemotherapy for high-grade astrocytoma, which individual small trials have been unable to demonstrate reliably. The Medical Research Council Brain Tumour Working Party initiated the largest randomized trial of adjuvant chemotherapy for glioma in an attempt to provide a definitive answer.

**Patients and Methods:** After surgery, patients aged  $\leq 70$  years, with World Health Organization grade 3 or 4 astrocytoma, were randomized to radiotherapy alone (RT) or RT plus procarbazine, lomustine, and vincristine (PCV) chemotherapy (RT-PCV) given at 6-week intervals to a maximum of 12 courses (procarbazine 100 mg/m<sup>2</sup> days 1 to 10, lomustine 100 mg/m<sup>2</sup> day 1, and vincristine 1.5 mg/m<sup>2</sup> (max 2 mg) day 1). A neuropathology panel independently reviewed all cases. To reliably detect a 10% increase in 2-year survival (from 15% to 25%), 600 patients were required.

**Results:** Between September 1988 and May 1997, 15 United Kingdom centers randomized 674 patients (RT = 339 patients; RT-PCV = 335 patients). With a median follow-up for survivors of 3 years, 617 patients have died, (RT = 310 patients; RT-PCV = 307 patients). Median survival was 9.5 months for RT and 10 months for RT-PCV (hazard ratio = 0.95; 95% confidence interval, 0.81 to 1.11; log-rank  $P = .50$ ). Tests for interaction revealed no significant differences in treatment effect according to tumor grade, age, performance status, or extent of neurosurgery.

**Conclusion:** This trial shows no benefit to PCV chemotherapy, and current data exclude an increase in median survival of more than 10 weeks and in a 1- or 2-year survival rate of more than 7% to 8%. This suggests that no-chemotherapy control arms remain ethical in randomized trials in high-grade astrocytoma.

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CONVENTIONAL TREATMENT of patients with malignant glioma (grade 3 and 4 cerebral astrocytoma) consists of surgery and radiotherapy (RT). Removal of an intracranial mass by surgical excision relieves increased intracranial pressure and frequently improves neurologic function. However, after surgery alone, the tumor invariably recurs locally, with median survival from initial diagnosis of 3 to 4 months.<sup>1</sup> Postoperative fractionated external-beam RT has been demonstrated to improve survival in randomized studies,<sup>1,2</sup> with a prolongation of median survival to 9 to 12 months. A previous Medical Research Council (MRC) randomized trial demonstrated a dose-response relationship with benefit for higher doses (60 Gy).<sup>3</sup> Nevertheless, despite surgery and RT, the disease recurs largely at the primary site with few long-term survivors.

There have been numerous attempts at improving results with the use of adjuvant chemotherapy. Most individual trials have failed to demonstrate a convincing survival benefit for chemotherapy. However, a meta-analysis<sup>4</sup> of the published literature of eight randomized studies<sup>1,5,6-11</sup> using single-agent nitrosoureas carried out before the launch of the current trial suggested a possible benefit to adjuvant chemotherapy. Later, a further meta-analysis of 16 randomized trials (including the eight studies in the earlier meta-analysis) gave similarly encouraging results.<sup>12</sup> In view of the data available at the initiation of this trial and the need for cautious interpretation of meta-analyses based on pub-

lished data alone,<sup>13</sup> the MRC Brain Tumour Working Party felt that the role of adjuvant chemotherapy in the treatment of high-grade astrocytoma remained uncertain and warranted further investigation.

This trial was designed to look for the smallest difference that might be considered clinically worthwhile, given the necessary trade-off between increased survival and possibly decreased quality of life while on treatment, and as such was considerably larger than all previous trials. The regimen chosen, using procarbazine, lomustine, and vincristine (PCV), could be given as an outpatient treatment and was known to be of limited toxicity.<sup>14-16</sup> Nitrosoureas had shown promise and were considered the most active agents. Procarbazine was demonstrated to show similar benefit to nitrosoureas when used in an adjuvant setting.<sup>17</sup> Vincristine displayed some activity as a single agent against gliomas<sup>18</sup> and had been included in combination chemotherapy protocols with apparent benefit.<sup>19</sup> At the time of initiation of

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For members of the Medical Research Council Brain Tumour Working Party see Appendix.

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the study, the PCV regimen was considered the most effective combination chemotherapy and was subsequently suggested to be of particular value in patients with grade 3 astrocytoma (anaplastic astrocytoma [AA]).<sup>16</sup> Therefore, the primary aim of this major clinical trial was to assess the value of adjuvant PCV chemotherapy on survival in patients with high-grade astrocytoma. A further aim was the evaluation of the prognostic value of *in vitro* chemosensitivity testing, which will be the subject of a separate report.

## PATIENTS AND METHODS

### *Eligibility Criteria*

Adult patients of either sex, up to 70 years of age, with pathologically proven supratentorial astrocytoma grade 3 or 4 (AA and glioblastoma multiforme [GBM]) were eligible, provided their neurologic and mental function was not so seriously impaired as to make RT undesirable. The exact interpretation of this criterion was left to the treating clinician, to reflect their usual practice.

### *Randomization*

Patients giving informed consent were randomized after neurosurgery by a telephone call to the MRC Cancer Trials Office (Cambridge, United Kingdom). Treatment, RT alone or RT followed by chemotherapy (RT-PCV), was allocated using the minimization method, balancing on treatment center and age group (< 45 years, 45-60 years, or > 60 years).

### *Neuropathology Review*

A panel of three neuropathologists was set up to review the eligibility of all patients randomized onto the trial. Each member of the panel reviewed slides independently of the other members and without knowledge of the patient's outcome and graded them according to both the World Health Organization (WHO) classification (grade 3 = AA and grade 4 = GBM)<sup>20</sup> and the Daumas Duport classification.<sup>21</sup> A consensus view of the patient's eligibility and tumor grade was established by taking the majority result of the three panel members.

### *RT*

At the start of the trial, participating centers were asked to choose their standard RT schedule and to adhere to it for all patients randomized, irrespective of their chemotherapy allocation. Initially, the choice was restricted to the two schedules compared in the MRC BR02 trial,<sup>3</sup> namely 45 Gy in 20 fractions, each of 2.25 Gy over 4 weeks, or 60 Gy in 30 fractions, each of 2 Gy over 6 weeks. The choice was permitted because the modest benefit to the higher dose, though statistically significant, was not considered sufficient to warrant the increased treatment time by all the participating centers. For both schedules, RT was to commence within 6 (and preferably 3) weeks of neurosurgery and was delivered using either parallel opposed or three fields. For the 45-Gy schedule and the first 40 Gy of the 60-Gy schedule, RT was given to a volume planned to include all known and potential tumor with a 3- to 5-cm margin. The remaining 20 Gy of the 60-Gy schedule was given to a field that encompassed the defined tumor volume together with an extra 1-cm margin. Later in the study, the range of schedules permissible was extended, allowing the delivery of 60 Gy to one volume without reduction and the use of an accelerated

schedule,<sup>22</sup> to a total dose of 55 Gy, given in 34 twice-daily fractions to a volume defined as the region of enhancement on preoperative computed tomography/magnetic resonance imaging with a 3-cm margin.

### *Chemotherapy*

The first course of chemotherapy commenced 3 to 4 weeks after completion of RT. Each course involved procarbazine at 100 mg/m<sup>2</sup> orally (PO) on days 1 to 10, lomustine at 100 mg/m<sup>2</sup> PO on day 1, and vincristine at 1.5 mg/m<sup>2</sup> (max 2 mg) on day 1, given intravenously (IV), undiluted into a fast-running drip. Treatment was given on an outpatient basis and repeated every 6 weeks to a maximum of 12 courses. Treatment was delayed for 2 weeks if WBC count was less than  $3.0 \times 10^9/L$  or platelet count was less than  $100 \times 10^9/L$ . If, after 2 weeks, the blood count was satisfactory, full-dose treatment was given. If it remained low, treatment was delayed for a further 2 weeks and then reassessed. If, after prolonged delay, blood counts returned to normal, treatment was recommenced with full-dose vincristine and procarbazine and a 50% reduction of lomustine. If blood counts remained unsatisfactory at 12 weeks, lomustine was discontinued.

### *Corticosteroids*

The use of corticosteroids was left to clinical discretion, but it was recommended that patients on corticosteroids during RT should not have the drug withdrawn until at least 6 weeks after completion of RT and that the drug dosage should be completely tailed off gradually over several weeks. When it was not possible to do this, the patient was titrated to the lowest possible dose.

### *Follow-Up*

Patients were seen at least every 3 months in the first year after RT, and then at 3-month intervals for a further 2 years. At each follow-up visit, clinical performance status, neurologic status, and the current corticosteroid dose were recorded. Evidence of clinical progression was also reported, and this was confirmed by computed tomography scan whenever possible. Treatment of progression was left to clinical discretion, but details were reported.

### *Statistical Considerations*

The main end point of the trial was survival, measured from the date of randomization to the date of death from any cause or date last known to be alive. Progression-free survival, in which the event of interest was clinical progression (based on clinical evidence of deterioration with or without radiologic evidence) or death, was a secondary end point. No formal quality-of-life assessments were carried out, but clinical performance status and neurologic status were assessed before and after RT and at each follow-up visit. The trial was designed to detect a 10% increase in survival at 2 years, from approximately 15% to 25% (equivalent to a 4-month increase in median survival), with 90% power at a significance level (two-sided) of 5%. This required approximately 550 patients to be randomized to observe 434 events. Because there was a preplanned subgroup analysis of those eligible on neuropathology review, a minimum target of 600 patients was set, anticipating a 10% ineligibility rate.

All randomized patients were included in the main analyses, which were carried out according to the intent-to-treat principle. Survival rates

Table 1. Pretreatment Characteristics by Allocated Treatment

	Patients					
	Radiotherapy (n = 339)		Radiotherapy + Chemotherapy (n = 335)		Total (n = 674)	
	No.	%	No.	%	No.	%
Age						
< 45 years	81	24	78	23	159	24
45 to 59 years	172	51	171	51	343	51
≥ 60 years	86	25	86	26	172	26
Sex						
Female	112	33	112	33	224	33
Male	227	67	223	67	450	67
History of fits/seizures						
Absent	217	66	205	63	422	64
Present	113	34	122	37	235	36
Information unavailable	9		8		17	
Tumor location*						
Frontal	127	39	109	34	236	36
Parietal	158	48	179	55	337	52
Temporal	113	35	115	35	228	35
Occipital	39	12	49	15	88	14
Deep	39	12	43	13	82	13
Extent of surgery						
None, aspiration only	1	0.3	4	1	5	1
Stereotactic biopsy	81	25	75	23	156	24
Biopsy	55	17	63	19	118	18
Partial removal	136	42	137	42	273	42
Macroscopic removal	52	16	48	15	100	15
Information unavailable	14		8		22	
Performance status before radiotherapy						
0	82	25	78	24	160	25
1	163	50	160	49	323	49
2	71	22	67	21	138	21
3	11	3	18	6	29	4
4	2	1	1	0.3	3	0.5
Information unavailable	10		11		21	
Neurologic status before radiotherapy						
0	107	33	99	31	206	32
1	134	41	141	44	275	42
2	79	24	73	23	152	23
3	8	2	11	3	19	3
Information unavailable	11		11		22	
Consensus tumor grade						
3, AA	60	18	53	16	113	17
4, GBM	226	67	223	67	449	67
3/4, other, eligible	12	4	20	6	32	5
Other, ineligible	29	9	27	8	56	8
Other not assessable	12	4	12	4	24	4

\*Some patients had more than one tumor site.

were estimated using the Kaplan-Meier method and were compared using the log-rank test. Multivariate analyses used Cox's proportional hazards regression model. Hazard ratios (HR) of less than 1 indicate a benefit to RT-PCV.  $\chi^2$  tests for interaction were used to test for consistency of treatment effect across different subgroups of patients defined by pretreatment characteristics; when these characteristics had a natural order, such as age,  $\chi^2$  tests for trend were used. All *P* values stated with tests of significance are two-sided.

## RESULTS

Between December 1988 and May 1997, 674 patients (339 allocated to RT and 335 allocated to RT-PCV) were randomized from 15 United Kingdom centers (Fig 1). Patient characteristics are listed in Table 1 and were well balanced between the treatment groups. Median age was 53

**Table 2. Post-RT Performance and Neurologic Status**

	Patients					
	Radiotherapy (n = 339)		Radiotherapy + Chemotherapy (n = 335)		Total (n = 674)	
	No.	%	No.	%	No.	%
Performance status after radiotherapy						
0	48	16	55	18	103	17
1	156	51	144	47	300	49
2	68	22	64	21	132	22
3	23	8	33	11	56	9
4	11	4	8	3	19	3
Information unavailable	33		31		64	
Neurologic status after radiotherapy						
0	93	30	104	34	197	32
1	116	38	101	33	217	36
2	73	24	71	23	144	24
3	23	7	24	8	47	8
4	2	1	4	1	6	1
Information unavailable	32		31		63	

years, and two thirds of the patients were male. Fifty-eight percent of patients had partial or macroscopic tumor removal. Slides for review by the neuropathology panel were received for 671 cases (99.6%), and for 650 patients (96% of those randomized), the material sent was sufficient to determine the patient's eligibility. In the remaining 21 cases, at least two members of the panel felt a diagnosis could not be made based on the material available. Of the 650 assessable patients, 594 (91%) were considered eligible on unanimous or majority verdict. Seventy-six percent of these patients had grade 4 tumor (GBM), 19% had grade 3 (AA), and the remaining 5% were of indeterminate grade. Of the 56 patients considered ineligible, 26 had lower grade tumors, nine had oligoastrocytoma or mixed oligoastrocytoma, two had gliosarcoma, one had a meningioma, and 18 had other diagnoses. Thus, 91% of all patients with sufficient material for review had their eligibility confirmed by the panel.

### RT

The majority of centers elected to use the 60-Gy schedule, and this was the intended dose in 501 patients. A further 135 patients came from centers at which the intended dose was 45 Gy, and 38 came from one center using the 55-Gy accelerated RT schedule. Median received dose was 60 Gy, with an interquartile range of 45 Gy to 60 Gy in each arm. RT started within 3 weeks of neurosurgery in 47% of patients and within 6 weeks in 89%. WHO performance status and neurologic status after RT are listed in Table 2.

### Chemotherapy

Of 335 patients allocated chemotherapy, 19% are known not to have started chemotherapy, the principal reasons

being the early deterioration of the patient's condition and/or the refusal of the patient or their family (ie, consent withdrawn). The median number of cycles of chemotherapy received by those who started treatment is three (range, one to 12 cycles; interquartile range, two to five cycles). Approximately 50% of patients starting chemotherapy required a delay to at least one cycle, mainly because of hematologic toxicity, but in general, toxicity was moderate, and in particular, no grade 3 or 4 neurotoxicity was reported. The maximum WHO grade over all cycles of chemotherapy received is listed in Table 3.

### Survival

With a median follow-up time for survivors of 3 years (range, 1 to 8 years), 617 deaths have been reported, 310 among those allocated no chemotherapy and 307 among those allocated to chemotherapy. There was no evidence of a survival difference between the two groups (Fig 2; log-rank  $P = .50$ ; HR = 0.95; 95% confidence interval [CI], 0.81 to 1.11). Similar results were seen with respect to progression-free survival, with an HR of 0.93 (95% CI, 0.78 to 1.10),  $P = .46$ , and median progression-free survival times of 6 months in each group. Use of chemotherapy on progression was rare; 20% of patients allocated RT, and 10% of those allocated RT-PCV received chemotherapy on relapse.

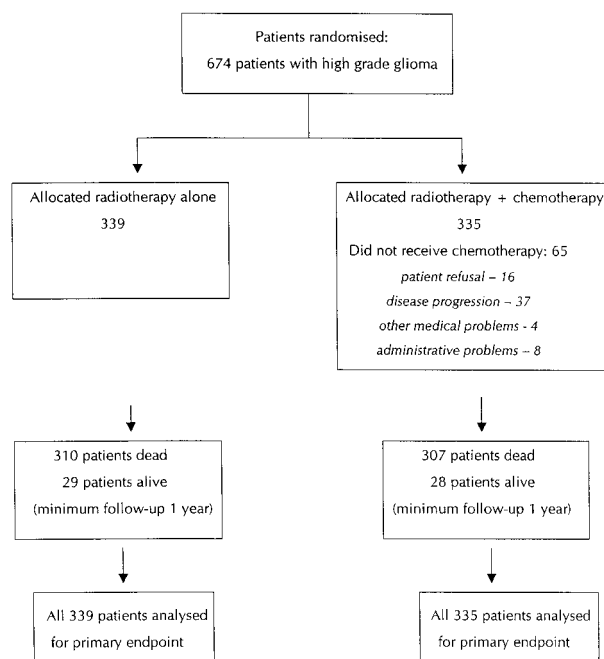
Of those patients with eligibility confirmed by the review panel, 298 were allocated RT (278 of whom have died) and 296 were allocated RT-PCV (279 of whom have died). Again, there was no evidence of a survival difference among these patients (log-rank  $P = .55$ , HR = 0.95; 95% CI, 0.80 to 1.12), with a median survival time of 10 months in each group.

**Table 3. Chemotherapy Toxicity**

Toxicity Grade	Patients	
	No.	%
<b>Hemoglobin</b>		
0	176	76.9
1	38	16.6
2	12	5.2
3	1	0.4
4	2	0.9
<b>WBC</b>		
0	126	55.0
1	52	22.7
2	34	14.8
3	13	5.7
4	4	1.7
<b>Platelets</b>		
0	187	81.7
1	15	6.6
2	12	5.2
3	13	5.7
4	2	.9
<b>Nausea/vomiting</b>		
0	73	33.2
1	46	20.9
2	46	20.9
3	40	18.2
	15	6.8
<b>Neurotoxicity</b>		
0	201	91.4
1	16	7.3
2	3	1.4
3/4	0	
<b>Skin rash</b>		
0	194	88.2
1	10	4.5
2	15	6.8
3/4	1	.5

### Effects in Different Subgroups

Formal tests for interaction between treatment and patient characteristics were carried out for several prerandomization characteristics, namely tumor grade (patients eligible on review only), age, history of fits or seizures, extent of neurosurgery, clinical performance status before RT, and intended RT dose (for all patients randomized). The intention of these analyses was to look for strong evidence that the impact of chemotherapy on survival was not consistent across these patient groups. Figure 3 shows the HR plots corresponding to the analysis of treatment effect by age, performance status before RT, extent of neurosurgery, and tumor grade. There was no evidence of a differential treatment effect across any of these factors. For patients with AA (grade 3), the HR was 0.86 (95% CI, 0.58 to 1.30); whereas for patients with GBM (grade 4), the HR was 0.93 (95% CI, 0.77 to 1.12). Survival curves by treatment and

**Fig 1. Study design.**

grade are shown in Fig 4. The only factor that gave a conventionally significant result in the test for heterogeneity was intended RT schedule ( $\chi^2 = 9.6$  on 2 df;  $P = .008$ ; Fig 5). This suggested that the treatment effect in patients planned for 45 Gy was significantly greater (HR = 0.58; 95% CI, 0.41 to 0.83) than in those planned for 60 Gy (HR = 1.06; 95% CI, 0.88 to 1.27). Although there was a statistically significant benefit to RT-PCV when the intended dose was 45 Gy ( $P = .003$ ), the addition of chemotherapy seems only to have shifted the survival expectation of this group to the levels expected of those receiving 60 Gy (Figs 5 and 6).

### DISCUSSION

This randomized trial, the largest adjuvant chemotherapy trial for high-grade astrocytoma, gives strong evidence that the PCV schedule tested does not improve survival by a clinically worthwhile amount. The data suggest a 1.7% increase in survival at 2 years, but the 95% confidence limits for the difference (-3.2%, +7.2%) excludes an increase of more than 8%. Similarly, the estimated increase in median survival time is approximately 2 weeks (from 9.5 months in the RT group to 10 months in the RT-PCV group; 95% confidence limits (-4 weeks, +10 weeks), thus an increase in median survival time of more than 10 weeks can be ruled out reliably. The results were consistent across patient groups defined by all the major prognostic factors.

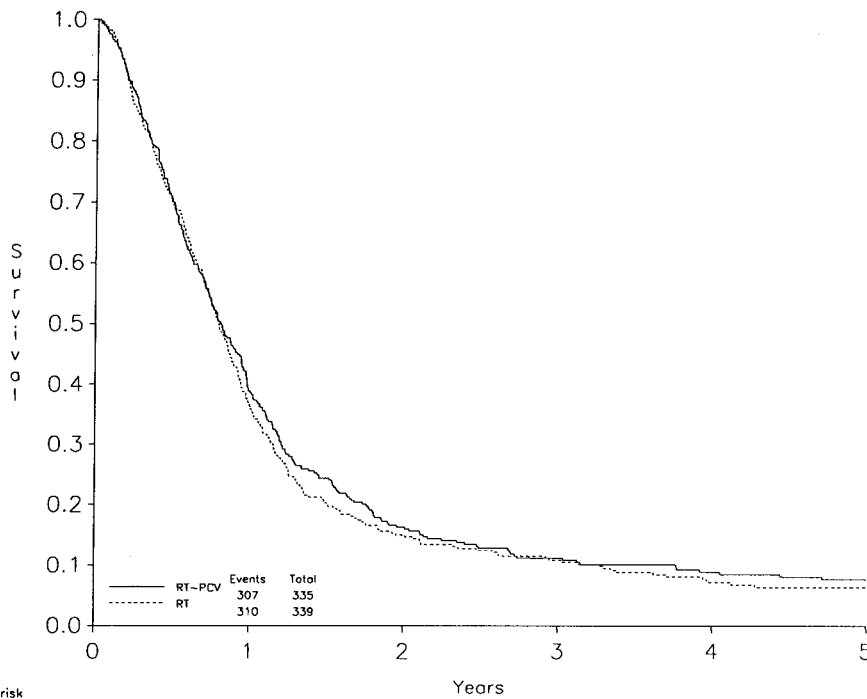


Fig 2. Survival by allocated treatment.

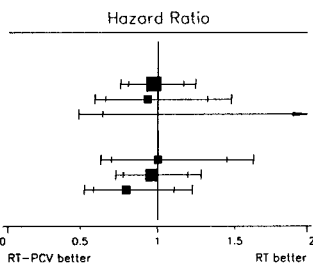
Patients at risk

	0	1	2	3	4	5
RT-PCV	335	129	52	33	22	18
RT	339	119	48	33	17	12

The regimen chosen was that which seemed most promising at the launch of the trial. Since then, support for this choice has come with the publication<sup>23</sup> of the final results of a randomized trial comparing single-agent carmustine (200

mg/m<sup>2</sup> IV every 6 to 8 weeks, starting 2 weeks after RT) with a PCV regimen (lomustine 110 mg/m<sup>2</sup> PO on day 1, procarbazine 60 mg/m<sup>2</sup> PO on days 8 to 21, and vincristine 1.4 mg/m<sup>2</sup> IV on days 8 and 29), which suggested improved

	(no. events/no. entered)		O-E	Variance
	RT-PCV	RT		
<b>PERFORMANCE STATUS</b>				
0 - 1	219/239	224/248	-3.34	105.23
2	64/67	68/71	-2.23	29.82
3 - 4	18/19	12/13	2.11	4.60
<b>AGE GROUP</b>				
< 45	58/78	63/81	0.11	27.87
45 - 60	175/183	172/182	-2.98	78.35
> 60	74/74	75/76	-7.94	34.04

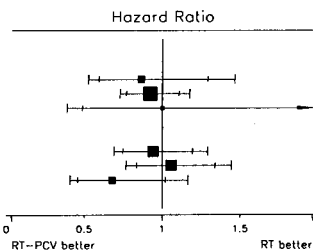


Tests for interaction/trend

Trend p = 0.629

Trend p = 0.335

	(no. events/no. entered)		O-E	Variance
	RT-PCV	RT		
<b>Tumour Grade</b>				
AA	42/53	52/60	-3.38	23.30
GBM	219/223	215/226	-8.86	106.98
AA/GBM	18/20	11/12	0.03	6.78
<b>Extent of surgery</b>				
Biopsy	129/143	126/138	-3.84	63.08
Partial resection	128/137	126/137	3.46	62.91
Complete resection	45/48	48/52	-8.64	21.79

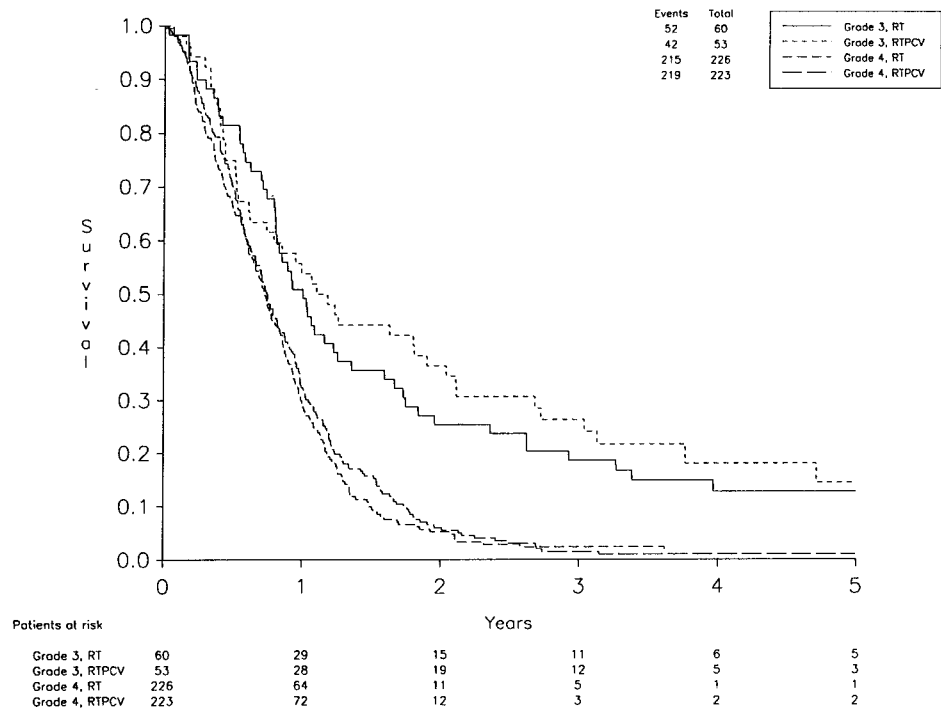


Interaction p = 0.934

Trend p = 0.393

Fig 3. HR plots of treatment effect across prognostic groups. For each subgroup, the central box gives the HR and the horizontal lines indicate the 95% (inner ticks) and 99% CIs. The size of the box is proportional to the amount of information available in each subgroup.

Fig 4. Survival by allocated treatment and tumor grade.



progression-free and overall survival time for patients with PCV in a subgroup of patients with AA (but not GBM) with good performance status.

A potential criticism of this MRC study is the use of a modified PCV regimen where the dose of lomustine was marginally lower (by 10%) and the regimen consisted of only one injection of vincristine given on day 1 rather than days 8 and 21.<sup>23</sup> However, the particular scheduling of vincristine has not been demonstrated to be associated with improved efficacy, and a minor 10% dose modification is also not known to be associated with worse outcome either for this or other chemotherapy regimens used in oncology in a relatively chemoresistant disease.

Although the results of this MRC trial may seem to contrast with much of the current world opinion and recommendations,

they do not directly contradict the results of any of the 14 adequately randomized trials evaluating nitrosourea-based chemotherapy that have been published to date.<sup>1,5,6-10,24-30</sup> Only three of these trials<sup>6,27,30</sup> claimed a statistically significant survival benefit. Two of these trials involved fewer than 100 patients,<sup>6,27</sup> and so, the results were associated with wide Cis. The third trial,<sup>30</sup> which compared RT alone with RT plus dibromodulcitol followed by dibromodulcitol with carmustine, just failed to reach conventional levels of statistical significance when all randomized patients were analyzed.

A number of patients in this trial, which was analyzed by the intent-to-treat principle, failed to receive their allocated chemotherapy, having deteriorated rapidly shortly after RT. It is difficult to compare compliance in other trials because the information is often absent or reported only in a

	(no. events/no. entered)		O-E	Variance
	RT-PCV	RT		
45 Gy	59/66	65/69	-16.32	28.83
55 Gy	19/20	17/18	2.13	8.75
60 Gy	229/249	228/252	5.62	113.28

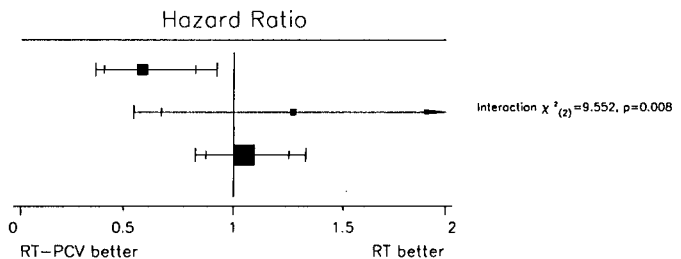


Fig 5. HR plot of treatment effect by chosen RT schedule.

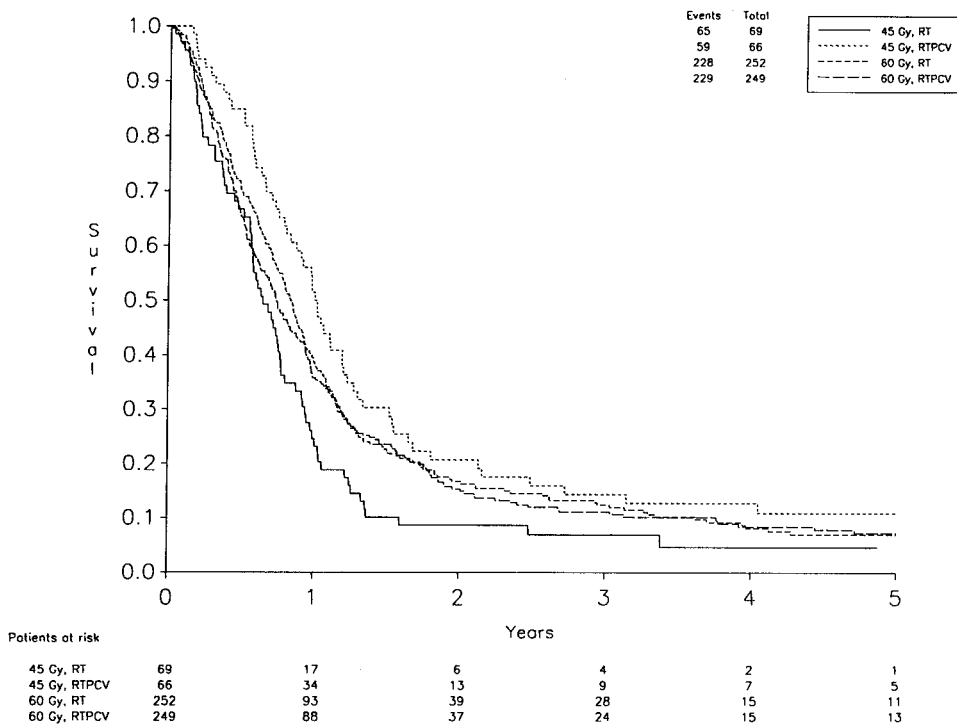


Fig 6. Survival by allocated treatment and chosen RT schedule.

subgroup of patients (sometimes referred to as the valid study group) defined by the fact that they had received at least one cycle.<sup>1-5</sup> Within these constraints, the median number of cycles received seems comparable with other trials, and that the number of cycles was not higher is determined largely by the median survival time and by the median time to progression (6 months). In addition, the trial continued beyond the minimum planned sample size to compensate for the dropout rate (ie, patients allocated chemotherapy who fail to receive any) when this seemed to be somewhat higher than had been anticipated from previous trials. With 617 deaths already observed, the trial has greater than 88% power to detect an overall absolute benefit of 8%, which is the effective difference if 20% of patients allocated chemotherapy fail to receive it (and thus gain no benefit), and the true benefit is 10%. Although it is natural to question what the results might have been had a higher proportion of patients been able to start chemotherapy, there is no completely unbiased way of addressing this question retrospectively. We addressed the question indirectly through the tests for interaction between treatment and age and performance status. Despite the much better overall prognosis in younger patients and patients with good performance status, and hence the smaller proportion deteriorating rapidly shortly after RT, there was no good evidence that the impact of chemotherapy was greater in these

subgroups. In particular, the subgroup of patients with WHO performance status 0 or 1 after the end of RT was studied. This included 206 patients allocated RT and 199 allocated RT-PCV, 92% of whom started chemotherapy and among whom the median number of cycles received was four. Again comparing survival by allocated treatment in this group, the HR was only marginally less at 0.89 (95% CI, 0.72 to 1.09), corresponding to a 1.5-month increase in median survival time (from 12 to 13.5 months) and excluding an increase of more than 5 months through the use of chemotherapy. In terms of 2-year survival, this equates to a 3% absolute increase, with 95% confidence limits ranging from a 2.5% reduction to a 10% increase.

Although the estimated treatment effects among AA and GBM patients were similar, the smaller number of AA patients means the associated CI is wider and, thus, that moderate survival improvements cannot be ruled out. The median survival time for AA patients allocated RT was 13 months, and the 2-year survival rate 37%. The HR of 0.86 corresponds to an 8-week increase in median survival or a 5.5% increase in 2-year survival through the use of chemotherapy, although the 95% CI can only exclude increases of more than 9 months in median survival time and 19% in the 2-year survival rate. For GBM (median survival = 9 months; 2-year survival rate = 8%), the HR suggests a 2-week increase in median survival time and a 1% increase

in the 2-year survival rate, whereas the CI excludes a 3-month increase in median survival time and a 7% increase in the 2-year survival rate.

An interesting observation was the statistically significant interaction between allocated treatment and chosen RT schedule. Fine et al,<sup>12</sup> in discussing the possible impact of the varying RT doses on their meta-analysis, speculated that the impact of chemotherapy would be greatest in patients who had received optimal RT because these patients had the least tumor burden on commencing chemotherapy. However, our results do not seem to support this premise. In fact, they suggest that chemotherapy may improve survival in patients with lower RT doses, although, by indirect comparison, the implication is that chemotherapy combined with 45-Gy RT produces similar survival to that achieved by 60-Gy RT alone. Among those 501 patients planned for 60 Gy, the estimated difference in survival at 2 years was 3% in favor of RT alone, and benefits to RT-PCV of more than 3.5% could be excluded reliably.

Finally, the results may seem to contradict the results of the two relevant meta-analyses, the first published before this trial was launched<sup>4</sup> and the second 6 years later.<sup>12</sup> However, both meta-analyses included only the published literature and attempted to extract the necessary data from the publications. Many of the trials, having been conducted and published in the 1970s and early 1980s, failed to present intent-to-treat analyses including all randomized patients. The exclusion of what was, in some trials, a substantial number of patients may have introduced bias both in the

individual trials and the meta-analyses. In cases where the analysis focused only on patients who actually started chemotherapy and did not apply comparable selection criteria to the control arm, this is likely to bias the results in favor of chemotherapy. In addition, Fine et al<sup>12</sup> also identified an imbalance in patient characteristics, favoring chemotherapy patients, which could not adequately be accounted for in a summary-based (rather than individual patient-based) analysis. The gold standard method for combining trial results is to carry out a meta-analysis that includes all properly randomized trials, both published and unpublished, and to obtain updated individual patient data on all patients randomized.<sup>31</sup> This allows the most appropriate, sensitive, and unbiased analysis. The MRC Cancer Trials Office Meta-Analysis Group is currently conducting such a meta-analysis.

In conclusion, the results of this large randomized trial have failed to demonstrate a routine place for adjuvant chemotherapy with PCV in the treatment of high-grade astrocytoma. More information on which to base treatment decisions may come from the individual patient data meta analysis currently underway and from the analysis of chemosensitivity testing assays carried out in a subgroup of patients in this trial. Until these results become available, we suggest that no-chemotherapy control arms remain ethical in randomized trials in high-grade astrocytoma and that it is reasonable and appropriate not to offer routine adjuvant chemotherapy to individual patients outside trials.

## APPENDIX

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*Writing Committee:* David Thomas, Michael Brada, and Sally Stenning.

*Clinical Coordinator:* David Thomas.

*Pathology review panel:* Peter Lantos (chair), James Ironside, and Timothy Moss.

*Administrative responsibilities:* David Thomas was chairman of the Medical Research Council (MRC) Brain Tumour Working Party from 1988 to 1995, and Michael Brada was chairman from 1996 to 1999. The trial was coordinated by Jill Whaley at the MRC Clinical Trials Unit, Cancer Division (formerly MRC Cancer Trials Office, Cambridge, United Kingdom); Sally Stenning was the trial statistician.

*The collaborating centers, ordered by number of patients (n) entered, were as follows:* Prof N.M. Bleehen, Addenbrookes Hospital, Cambridge (n = 132); Dr J.T. Roberts, Northern Centre for Cancer Treatment, Newcastle-on-Tyne (n = 119); Dr L.F.N. Senanayake, Royal Free Hospital, London, United Kingdom (n = 79); Dr W.P. Abram, Belvoir Park Hospital, Belfast, Northern Ireland (n = 65); Dr M. Brada, Royal Marsden Hospital, Surrey (n = 38); R. Gullan, Brook Hospital, London (n = 34); Dr D.S. Murrell, Royal Sussex County Hospital, Brighton (n = 31); J. McIntosh, North Staffordshire Royal Infirmary, Stoke on Trent (n = 26); Dr J. Tobias and Dr J.N. Godlee, University College Hospital, London (n = 25 and n = 19); Dr D. Guthrie, Derby Royal Infirmary, Derby (n = 18); R. Bradford, Royal Free Hospital, London (n = 11); D. Campbell, North Staffs Royal Infirmary, Stoke on Trent (n = 11); Dr T. Sarkar, Aberdeen Royal Infirmary, Aberdeen (n = 11); Dr J.V. Watson, Addenbrookes Hospital, Cambridge (n = 11); Dr A. Lamont, Southend General Hospital, Southend (n = 7); Dr J. Stone, Cookridge Hospital, Leeds (n = 7); Dr B. Mantell, Royal London Hospital, London (n = 4); Dr P.N. Plowman, St Bartholomew's Hospital, London (n = 3); Dr H. Hope-Stone and Dr P. Hoskin, Royal London Hospital, London (n = 2 and n = 2); Dr D. Ritchie, Newcastle General Hospital, Newcastle (n = 2); Dr K. Pigott, Royal Free Hospital, London, United Kingdom (n = 2); and Dr R. Hawkins, Dr H. Baillie-Johnson, Dr R. Lindup, Dr F. Adab, Dr D. Hurman, Dr M. Gaze, Dr C. Collis, Dr F. Neave, Dr G. Thomas, and Dr A. Robinson each entered one patient.

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