Diffuse brainstem glioma in children: critical review of clinical trials

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Diffuse intrinsic brainstem gliomas constitute 15–20% of all CNS tumours in children, and are the main cause of death in children with brain tumours. Many clinical trials have been done over the past three decades, but survival has remained static. More than 90% of children die within 2 years of diagnosis, and conventional fractionated radiation remains the standard treatment. However, median survival differs substantially between clinical trials, suggesting a survival benefit with some strategies. We appraised the consistency between protocols in terms of eligibility criteria, definition and assessment of response and progression, statistical design, and endpoints. Study designs varied substantially, which could explain the differences in outcome, and no treatment has shown a benefit over conventional radiotherapy. However, consistency between protocols (eg, eligibility criteria and outcome measures) is important to measure the progress in management of diffuse pontine gliomas.

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Introduction

Brain tumours (figure 1) account for 20% of all neoplasms in children, and are the largest group of solid tumours that develop in childhood.[1] These tumours are both anatomically and histologically diverse. One of the most complex groups is the glioma family: these tumours can arise anywhere in the CNS; they have various histological characteristics, which sometimes differ within the tumour; and can metastasise if they are histologically benign or malignant. Gliomas that are located in the brainstem are a specific entity: 15–20% of these tumours are low-grade astrocytomas that have characteristic clinical features, growth patterns of low-grade glial tumours, and generally follow an indolent course.[2] Most of the remaining 80% of tumours are diffuse and involve the pons (figure 2). Because the consensus is that biopsies should not be done to diagnose diffuse brainstem gliomas, cancer registries, which are based mostly on pathology reports, might not record their incidence accurately. However, between 20 and 30 diffuse pontine gliomas are thought to develop in children every year in the UK[2] and between 100 and 150 a year in the USA.[3] Despite collaborative efforts to improve treatments, survival has remained static over the past 20 years, and diffuse pontine gliomas are now the main cause of death by brain tumour in children. Substantial advances have been made in the definition of this entity, which is based on a combination of clinical signs and symptoms and MRI findings. A tissue biopsy sample is not needed for diagnosis, and most children are treated within days of the diagnostic MRI scan. There have been many protocols for study of diffuse pontine gliomas over the past three decades, but by contrast with most experiences in paediatric oncology and haematology, no improvement in survival has been seen in cooperative studies.

Radiation remains the standard treatment for diffuse pontine gliomas, and so far chemotherapy has not shown any benefit. However, few studies have been done to assess the role of chemotherapy, and most prospective studies have investigated alternative radiation options, such as hyperfractionation, rather than combinations of chemotherapy.

Studies[2] have concluded that standard conventional radiotherapy is as efficient as alternative radiation techniques; thus, in 2005, the standard treatment of this tumour is conventional focal radiotherapy. Overall, outlook is poor and nearly all children eventually die: most studies showed a median survival time of shorter than 1 year.

One of the main issues that has already been addressed in other brain tumours associated with a poor outcome, such as adult glioblastomas, is the ability to detect a benefit from a new strategy. Theoretically, randomised studies are the method of choice to test a new hypothesis. However, when the standard treatment group provides no chance of success, the rational to have a randomised design with a standard treatment group is questionable, and practically very difficult, especially in paediatric oncology. The best method for clinical study of these patients remains to be defined. This review will

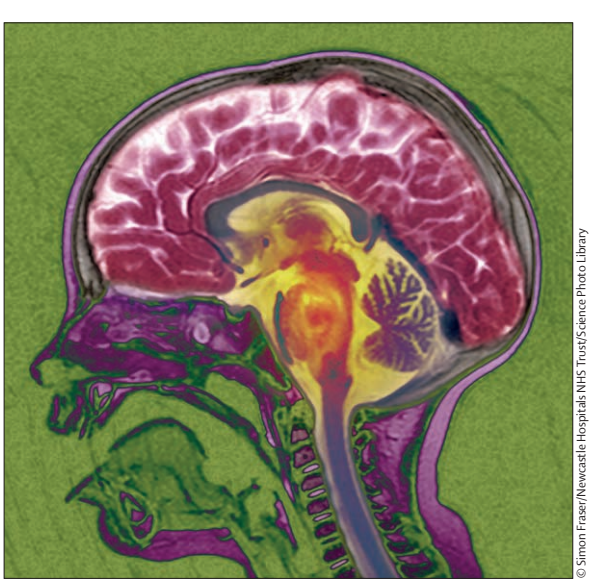

Figure 1: **Gliomas are main cause of death from brain tumours in children**

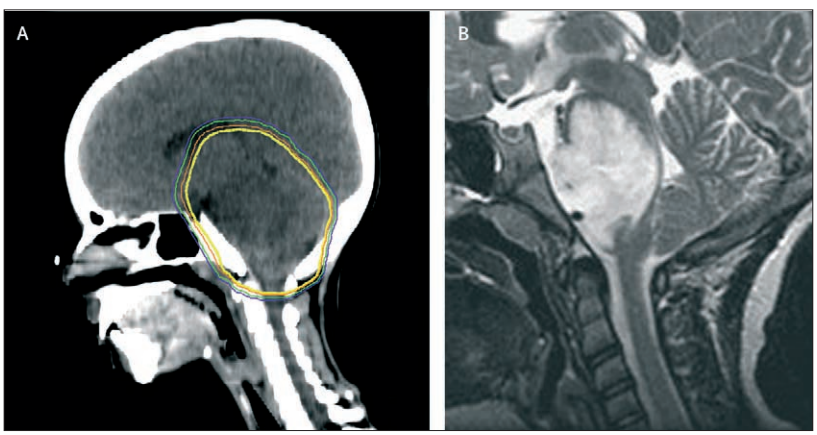

Figure 2: **Diffuse pontine gliomas**
(A) Sagittal MRI scan. (B) Radiation planning of diffuse pontine glioma.

assess the methods and results of reported clinical studies in children with diffuse pontine gliomas.

Study characteristics

29 studies[4–32] have reported on 973 patients between 1984 and 2005. In some studies[33–37] the information was too limited to be used for this review, either because data for children were not clearly identifiable in a mixed series of children and adults or because details of patients' characteristics and information on outcome were insufficient. 22 studies were done in the USA (six from the Paediatric Oncology Group,[7,9,11,12,21,30] eight from the Children's Cancer group,[4,6,13,14,15,18,26,28] and eight from non-group publications),[5,8,17,19,20,27,29,31] three in France,[22,25,32] one in Brazil,[23] one by the UK group The UK Children's Cancer Study group,[16] one by the German group German Society of Paediatric Oncology and Haematology,[24] and one single-institution Japanese study.[10] The mean number of patients per study was 33·5 (range 6–130). Most studies were done over a short time, and 18 were completed within 3 years. Estimates on yearly accrual were available in 26 studies and showed significant differences between studies done by cooperative groups (median accrual 17·3 patients per year; range 3·2–50·8) and those done by institutions (3·0; 1·1–10·3). The median age varied from 5 years[6] to 9·5 years.[8] However, in 21 of 28 series for which this information was available, the median age was between 6 and 8 years. Some studies included infants: the youngest patient was 6 months old.[10] Nine reports[4,5,8,10,13–15,23,28] included children younger than 3 years.

Assessment of eligibility

Table 1[4–32] shows the study design and eligibility criteria. A maximum duration of symptoms was necessary for enrolment in 12 studies and 12 protocols required symptoms to be specific neurological manifestations[7,9,11,12,16,17,21–23,27,30,32] (cranial nerve deficit or long tract signs or ataxia or a combination of any two). Information on the duration of symptoms was provided in 13 studies[7,9,11,12–14,16,17,19,22,23,27,32] and at least seven studies[7,9,13,14,19,23] enrolled patients with a clinical history of longer than 6 months. A clinical history of shorter than 6 months was required in 12 series, and two studies required a clinical history of shorter than 3 months. 16 studies did not report any information on the duration of clinical history.[4–6,8,10,15,18,20,21,22–26,28–31] In six series, all patients had fewer than 6 months' clinical history.[11,12,16,17,22,23] Seven series accepted patients with longer clinical history, up to 36 months in one study.[7,9,13,14,19,23]

When the information was available, the imaging modality required was MRI in 15 studies, CT in two, and CT or clinical characteristics in one. The non-MRI studies were done before MRI was available in the mid 1980s. 13 studies did not specify the required extent of pontine involvement; six studies required at least 50% involvement, eight studies required at least 66% involvement, and one study required involvement of at least 75%. No study had specific criteria in terms of enhancement, tumour density, or encasement of the basilar artery. However, some protocols included histological requirements for tumours of the brain stem with a large exophytic component. As expected, the inclusion of the MRI scan as a prerequisite for eligibility changed over time: ten of 11 studies published since 2000 used MRI, compared with none of five published in the 1980s and five of 13 published in the 1990s. Centralised review of the radiology images was done in 13 of 20 cooperative studies.[7,9,11–14,16,21,23–26,32] The outcome of the review was documented in seven studies, and 291 (95%) of the 305 reviewed CT or MRI scans were in agreement with the radiological definition of a diffuse pontine lesion. Furthermore, all studies allowed inclusion of biopsy-proven high-grade glioma. 249 (26%) patients underwent a biopsy, and 229 samples were diagnostic. 76 samples were labelled low-grade glioma, either by the institution or on central review; however, these patients were not excluded from the study on this histological criterion, most commonly because their clinical or radiological characteristics agreed with the diagnosis of diffuse pontine glioma.

Overall, the differences in the patients' characteristics between protocols is a concern because it precludes appropriate comparisons, particularly when treatment results suggest some improvement in survival. The development of modern imaging techniques has standardised the radiological diagnosis of diffuse pontine glioma.[38] As cooperative studies become standard in clinical research in paediatric neuro-oncology, the need for central radiology review is crucial, even when diagnostic criteria are mostly validated. The consequences of allowing patients with atypical lesions with or without a histological diagnosis of malignant disease to enter studies for diffuse pontine glioma are unknown. In

	n	Imaging	Radiological requirements	Clinical requirements	Ref
Pilot study					
Chemotherapy during conventional radiation at 55·0 Gy	28	Clinical or CT	NA	NA	4
Hyperfractionation at 64·8 Gy	16	CT or MRI	NA	NA	5
Hyperfractionation at 72·0 Gy	22	CT or MRI	NA	NA	8
Chemotherapy during and after conventional radiation at 40–60 Gy	8	CT or MRI	NA	NA	10
Hyperfractionation at 72·0 Gy	53	CT or MRI	Tumour in pons, no percentage of pons infiltration required	NA	13
Hyperfractionation at 72·0 Gy plus interferon	32	MRI	Tumour in 50% of pons	NA	15
Hypofractionation at 48·6–50·4 Gy	28	CT or MRI	NA	Cranial nerve deficit or long tract signs or both	16
Chemotherapy before hyperfractionation at 72·0–78·0 Gy	6	NA	NA	NA	18
Chemotherapy during conventional radiation at 50–59 Gy	6	MRI	Tumour in epicenter of pons	NA	20
Chemotherapy after conventional radiation at 54 Gy	35	CT or MRI	Tumour in 66% of pons	One of three classic brainstem symptoms	22
Conventional radiation at 45–60 Gy plus tamoxifen during and after radiation	27	MRI	Tumour in 50% of pons	Two of three classic brainstem symptoms	23
Chemotherapy during and after conventional radiation at 50–56 Gy	20	MRI	NA	NA	24
Chemotherapy before and during conventional radiation at 45–57 Gy	38	MRI	NA	NA	25
Chemotherapy before and after conventional radiation at 55·8 Gy	33	MRI	Tumour in epicentre of pons	NA	31
Phase I					
Hyperfractionation at 78·0 Gy	66	CT or MRI	Tumour in 50% of pons	NA	14
Etanidazole during hyperfractionation at 66·0 Gy	18	MRI	NA	One of two classic brainstem symptoms	27
Chemotherapy during conventional radiation at 59·4 Gy	17	MRI	Tumour in >50% of pons	NA	28
Chemotherapy during conventional radiation at 59·4 Gy	13	MRI	Tumour in >50% of pons	NA	29
Chemotherapy during conventional radiation at 54 Gy	7	MRI	Tumour in >66% of pons	Two of three classic brainstem symptoms	30
Phase I–II					
Hyperfractionation at 66·0 Gy	34	CT	Tumour in 66% of pons	One of three classic brainstem symptoms	7
Hyperfractionation at 70·2 Gy	57	CT or MRI	Tumour in 66% of pons	Two of three classic brainstem symptoms	9
Hyperfractionation at 75·6 Gy	39	MRI	Tumour in 66% of pons	Two of three classic brainstem symptoms	11
Chemotherapy during hyperfractionation at 70·2 Gy	9	MRI	Tumour in 75% of pons	Two of three classic brainstem symptoms	17
Chemotherapy during hyperfractionation at 72·0 Gy	34	MRI	Tumour in 50% of pons	Cranial nerve deficit	19
Phase II					
Chemotherapy before hyperfractionation at 66·0 Gy	32	CT or MRI	Tumour in 66% of pons	Two of three classic brainstem symptoms	12
Chemotherapy during conventional radiation at 54 Gy	32	MRI	Tumour in >66% of pons	Two of three classic brainstem symptoms	32
Randomised					
Conventional radiation at 50–60 Gy*	33	CT	Tumour in pons or medulla	NA	6
Chemotherapy after conventional radiation at 50–60 Gy*	37	CT	Tumour in pons or medulla	NA	6
Chemotherapy during hyperfractionation at 70·2 Gy†	64	CT or MRI	Tumour in 66% of the pons	Two of three classic brainstem symptoms	21
Chemotherapy plus conventional radiation at 54 Gy†	66	CT or MRI	Tumour in 66% of the pons	Two of three classic brainstem symptoms	21
Chemotherapy before and after hyperfractionation at 66·0 Gy‡	32	MRI	NA	NA	26
Chemotherapy before and after hyperfractionation at 66·0 Gy‡	31	MRI	NA	NA	26

NA=not available. *Prospective trial. †Phase III trial. ‡Phase II trial, study assessed different chemotherapy regimens.

Table 1: **Study design and eligibility criteria**

typical diffuse pontine glioma, the need for histological confirmation of diagnosis has been studied extensively, and no evidence has been found that analysis of a biopsy sample will change the management or the outcome.[39] However, confusion arises when a protocol includes broad eligibility criteria that could allow a patient with

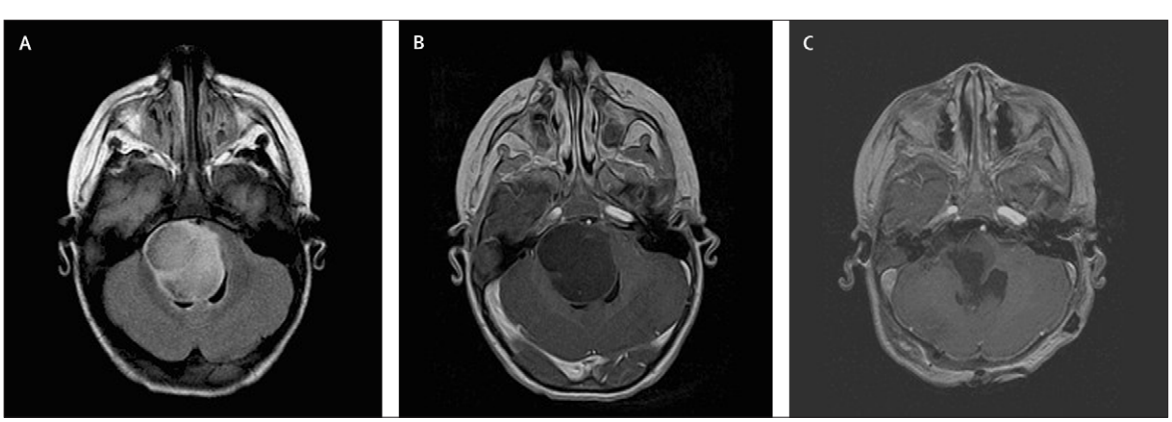

Figure 3: **Atypical pontine glioma**
(A) Pilocytic astrocytoma in 3-year-old child with atypically long (7 month) history of progressive brainstem symptoms. (B) No progression after 6 months' treatment with vincristine and carboplatin. (C) Subtotal resection of tumour after 9 months.

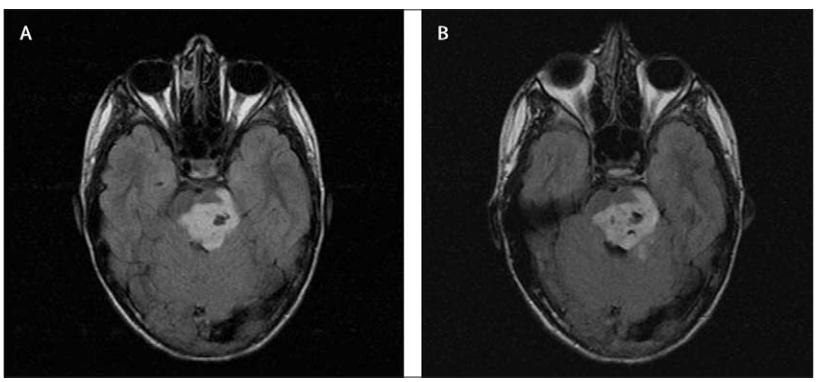

Figure 4: **Atypical pontine lesion**
(A) Pontine tumour in child with 12-month history of chronic headaches and long-term clumsiness. (B) No clinical or radiological progression after 18 months with no treatment.

atypical clinical history or radiology (figures 3 and 4) to be included. Two reviews[40,41] of cooperative experiences suggest that these differences in inclusion criteria could ultimately account for differences in survival. A consensus on a standardised clinicoradiological definition of typical diffuse pontine glioma is needed, and should be used as a prerequisite for enrolment in a study. This definition should take into account the duration and type of symptoms, and the radiological characteristics. Only six of the studies reviewed,[9,11,12,17,21,32] four of which were done by the Pediatric Oncology Group, had comparable eligibility criteria (history <6 months, at least two of three brainstem symptoms, and >66% of the pons is infiltrated with tumour).

Review process

26 series were single-group studies[4,5,7–20,22–25,27–32] and three were randomised studies.[6,21,26] Table 1 shows the design characteristics of these studies. The first randomised study[5] was done before MRI was introduced and had eligibility criteria that would not be accepted today: some patients probably did not have typical diffuse pontine glioma. This was the only randomised study that compared radiotherapy alone with radiotherapy and chemotherapy—the other two studies compared either two different chemotherapy regimens in addition to radiotherapy,[26] or two different radiotherapy techniques with the same chemotherapy regimen.[21]

	Complete response	Partial response	Minor response	Stable disease	Progressive disease	Ref
Cisplatin and cyclophosphamide	0	3	3	20	6	12
Carboplatin	0	0	1	6	12	25
Carboplatin, etoposide, and vincristine	0	2	1	12	12	26
Cisplatin, etoposide, cyclophosphamide, and vincristine	0	1	4	8	9	26
Irinotecan	0	0	0	10	5	31
Total (n=115)	0	6 (5%)	9 (8%)	56 (49%)	44 (38%)	

Table 2: **Response to preradiotherapy chemotherapy by 115 evaluable patients.**

Response to treatment

Table 2[12,25,26,31] shows the response to preradiotherapy chemotherapy. The four studies that had data for response accrued 149 patients of whom 115 were evaluable for response. Most non-evaluable patients had discontinued chemotherapy for various reasons, but mainly because of clinical deterioration (28 patients). The number of patients who responded to chemotherapy might therefore be overestimated. Clinical improvement during chemotherapy did not correlate with radiological response, suggesting that radiological assessment is insufficient to assess response to chemotherapy.

Table 3 shows the response rate to radiation reported in 19 studies, in which 700 patients were registered.[5,7,9–17,19–21,23,24,26,29,31] The response was similar between the patients who received hyperfractionation or hypofractionation techniques and those who received conventional radiation (36% *vs* 36% responses [151 of 426 *vs* 54 of 149]). Absent or incomplete data for response in 125 of 700 patients in these 19 studies could affect the results: when these data are taken into account—as response or lack of response—the response can range from 29% to 49%. Clinical response to radiation was diversely reported: only 11 studies provided details on clinical improvement or changes in steroid requirements. However, many patients (43%) still needed steroids after radiotherapy.

Overall, radiotherapy induces neurological improvement, allows reduction or discontinuation of steroids, and is associated with radiological response. The clinical response (85%) seems to be higher than the radiological response (about 50%). No correlation has been shown between clinical and radiological response, and the definition of radiological response is still unclear; in particular, whether radiological assessment should be based on the comparison of T1, T2, or fluid-attenuated inversion recovery, and whether new enhancement or cystic changes should be interpreted as radiation-induced necrosis or evidence of progression. Correlation between radiological response and survival has been assessed in only one study,[11] which did not show a survival benefit for radiological responders.

So far no treatment has shown any benefit over conventional radiation. The use of chemotherapy either before or after radiation has not shown any survival advantage.[42] Concomitant chemotherapy and radiotherapy has been investigated in 12 studies [4,10,17,19,20,21,24,25,28–30,32] and did not seem to confer a survival benefit.

Progression and survival

Most patients had progressive disease and eventually died: only 92 children survived of the 940 patients registered. Several studies included progression-free survival as a primary or a secondary endpoint in their survival analysis (table 4[4–32]). Five studies[7,9,11,12,21] in which progression-free survival was reported did not include a detailed definition

	Complete response	Partial response	Minor response	Stable disease	Progressive disease	n*	Improvement after radiation	Ref
Chemotherapy during conventional radiation at 55·0 Gy	NA	NA	NA	NA	NA	0/28	NA	4
Hyperfractionation at 64·8 Gy	1	2	9	2	1	15/16	15 improved; 14 off steroids	5
Conventional radiation at 50–60 Gy	NA	NA	NA	NA	NA	0/33	NA	6
Chemotherapy after conventional radiation at 50–60 Gy	NA	NA	NA	NA	NA	0/37	NA	6
Hyperfractionation at 66·0 Gy	0	5	0	20	8	33/34	24 improved	7
Hyperfractionation at 72·0 Gy	NA	NA	NA	NA	NA	0/22	NA	8
Hyperfractionation at 70·2 Gy	1	3	0	40	8	52/57	27 off steroids	9
Chemotherapy during and after conventional radiation at 40–60 Gy	2	5	0	1	0	8/8	NA	10
Hyperfractionation at 75·6 Gy	1	5	0	20	3	29/39	10 off steroids; 30 improved	11
Chemotherapy before hyperfractionation at 66·0 Gy	0	4	0	12	4	20/32	NA	12
Hyperfractionation at 72·0 Gy	0	7	21	12	5	45/53	33 off steroids	13
Hyperfractionation at 78·0Gy	1	7	12	24	0	44/66	NA	14
Hyperfractionation at 72·0 Gy plus interferon	2	5	4	15	6	32/32	NA	15
Hypofractionation at 48·6–50·4 Gy	0	14	0	6	6	26/28	13 off steroids	16
Chemotherapy during hyperfractionation at 70·2 Gy	0	2	2	5	0	9/9	3 off steroids	17
Chemotherapy before hyperfractionation at 72·0–78·0 Gy	NA	NA	NA	NA	NA	NA/6	NA	18
Chemotherapy during hyperfractionation at 72·0 Gy	1	14	0	8	6	29/34	NA	19
Chemotherapy during conventional radiation at 50–59 Gy	0	2	1	2	1	6/6	5 improved	20
Chemotherapy during hyperfractionation at 70·2 Gy	1	15	0	23	12	51/64	122 improved†	21
Chemotherapy plus conventional radiation at 54 Gy	1	18	0	25	13	57/66	122 improved†	21
Chemotherapy after conventional radiation at 54 Gy	NA	NA	NA	NA	NA	NA/35	NA	22
Conventional radiation at 45–60 Gy plus tamoxifen	0	8	3	8	3	22/27	NA	23
Chemotherapy during and after conventional radiation at 50–56 Gy	0	3	0	4	5	12/20	NA	24
Chemotherapy before and during conventional radiation at 45–57 Gy	NA	NA	NA	NA	NA	NA/38	NA	25
Chemotherapy before and after hyperfractionation at 66·0 Gy‡	0	4	3	5	11	23/32	NA	26
Chemotherapy before and after hyperfractionation at 66·0 Gy‡	0	3	2	4	9	18/31	NA	26
Etanidazole during hyperfractionation at 66·0 Gy	NA	NA	NA	NA	NA	NA/18	17 improved	27
Chemotherapy during conventional radiation at 59·4 Gy	NA	NA	NA	NA	NA	NA/17	NA	28
Chemotherapy during conventional radiation at 59·4 Gy	0	2	2	7	1	12/13	NA	29
Chemotherapy during conventional radiation at 54 Gy	NA	NA	NA	NA	NA	NA/7	NA	30
Chemotherapy before and after conventional radiation at 55·8 Gy	0	7	0	25	0	32/33	NA	31
Chemotherapy during conventional radiation at 54 Gy	NA	NA	NA	NA	NA	NA/32	16 improved; 20 off steroids	32

NA=not available. *Number evaluable/total number of patients. †Of all 130 patients in study. ‡Study assessed different chemotherapy regimens.

Table 3: **Response to radiotherapy**

of progression. In the other 12 publications in which progression-free survival data are available, progression was defined either clinically as the time from study entry to the time of clinical progression (one study[6]), radiologically as an increase of 25% or more in the size of the tumour on imaging, (six studies[17,19,20,24,26,31]), or as a clinicoradiological entity (five studies[4,5,13–15]). The median time to progression ranged from 5 months to 8·8 months, without a clear trend toward improvement over time, and overall survival ranged from 7 months to 16 months, suggesting that survival differed between treatment strategies. When only studies for which clinical and radiological eligibility criteria were specified and respected are considered,[11,12,17,21,22,30,32] the median overall survival ranges from 8 months to 11 months. The two studies[10,28] with the longest median overall survival either did not provide information on clinicoradiological requirements for eligibility or included some patients with duration of symptoms of up to 12 months; patients who did not complete the planned protocol were excluded from survival analysis. 23 publications[4–9,11–18,21–26,29,31,32] included survival curves with Kaplan-Meier estimates. 1-year survival ranged from 25% to 53%, and 2-year survival from 5% to 23%.

Although large differences in median survival time were seen between series, suggesting that treatment options differed between studies, the statistical design of single-group studies was not homogeneous and did not allow valid conclusions in terms of survival. This difference was related to the choice of the variable (progression-free survival or overall survival) and the absence of a statistical endpoint in many studies. The choice of progression-free survival as the study endpoint is questionable because no clear consensus has been made on the definition of progression. Standard radiological criteria, which define progression as a 25% increase in the product of the largest perpendicular diameters have not been validated in diffuse pontine glioma. In particular, the clinico-radiological correlation between progressive symptoms and interval increase in tumour size has not been established (figure 5). Prospective descriptive studies, which focus on changes in clinical symptoms, correlations with radiological changes, and possibly PET studies, are urgently needed to ascertain whether early clinical and radiographic progression are related to radiation swelling or actual tumour growth. Overall, large variations could exist between studies that use either clinical or radiological or a clinicoradiological definition for progression—

Evaluation of progression	Patients	Survivors	Outcome						
			Median progression-free survival (months)	Median overall survival months (range)	1-year survival	2-year survival	3-year survival	5-year survival	Ref
Clinicoradiological									
	28	12	7·5	10 (NA)	40%	NR	NR	NR	4
	15	3	7	11 (NA)	48%	NR	NR	NR	5
	53	2	5·5	9 (NA)	38%	14%	8%	NR	13
	66	7	8	9·5 (NA)	35%	22%	6%	NR	14
	32	1	5	9 (2·5–>14)	25%	NR	NR	NR	15
Radiological									
	22	7	8·3	12 (NA)	45%	NR	NR	NR	8
	9	1	7·5	10·5 (4–21)	44%	11%	NR	NR	17
	34	5	8	12 (5–104)	NA	NR	NR	NR	19
	6	1	7	7 (5–14)	NA	NR	NR	NR	20
	20	0	5·9	8 (NA)	40%	15%	5%	0%	24
	33	0	8·8	12 (3·9–17·9†)	48%	NR	NR	NR	31
Clinical									
	33	14	7	NA (NA)	NA	NR	17%	17%	6
	37	NA	8	NA (NA)	NA	NR	23%	23%	6
Not defined									
	34	*	6·5	11 (NA)	47%	6%	NR	NR	7
	57	*	6	10 (NA)	40%	23%	NR	NR	9
	8	2	NA	16 (NA)	NA	NR	NR	NR	10
	39	*	7	10 (NA)	39%	7%	NR	NR	11
	32	3	8	9 (NA)	30%	NR	NR	NR	12
	28	NA	NA	8·5 (NA)	32%	11%	NR	NR	16
	6	NA	NA	11 (7–17)	50%	NR	NR	NR	18
	64	NA	5	8 (3–24)	27%	7%	5%	NR	21
	66	NA	6	8·5 (1–23)	30%	7%	4%	NR	21
	35	0	NA	10 (NA)	40%	NR	NR	NR	22
	27	8	NA	10·3 (2·5–30)	37%	NR	NR	NR	23
	38	0	NA	11 (NA)	43%	5%	0%	NR	25
	32	6 (total)	NA	NA (NA)	17%†	6%†	NR	NR	26
	31	NR	NR	NA (NA)	NR	NR	NR	NR	26
	18	NA	NA	8·5 (3–58)	NA	NR	NR	NR	27
	17	NA	NA	15 (NA)	53%	NR	NR	NR	28
	13	1	NA	11 (NA)	45%	NR	NR	NR	29
	7	1	5	11 (7–>60)	NR	NR	NR	NR	30
	32	0	NA	8·3 (NA)	25·5%	NR	NR	NR	32

NA=not available. NR=not reported. *18 of 130 patients from these three trials were alive at last follow-up.[11] †Progression-free survival.

Table 4: **Progression and survival time**

median progression-free survival ranged from 5 months to 8·8 months (table 4). Although not ideal, the use of overall survival is the most reliable variable. The fact that some patients might receive additional treatment at the time of progression does not seem to significantly affect the length of survival, and the median time between progression and death, reported in 19 publications, is very short, ranging from 1 month to 4·5 months.[4–9,11–15,17,19–21,24,31] The absence of clear statistical endpoints in most studies is striking. Many studies conclude that "there is little evidence of efficacy" without a statistical justification for the number of patients accrued to achieve these conclusions or a rational for termination of the trial. Only three single-group studies[22,25,32] included a statistical method with stopping rules. They were done by the same group and the triangular test was used to assess non-comparative phase II clinical trials on the basis of an expected median survival time of 9 months. The 9-month survival time was analysed every five patients. These three studies were terminated when the sequential analyses of 35 patients in the first study, 38 in the second, and 32 in the third led to rejection of the efficacy hypothesis. Only one[23] of the 29 studies reviewed here provides enough information to apply the same model (figure 6). This

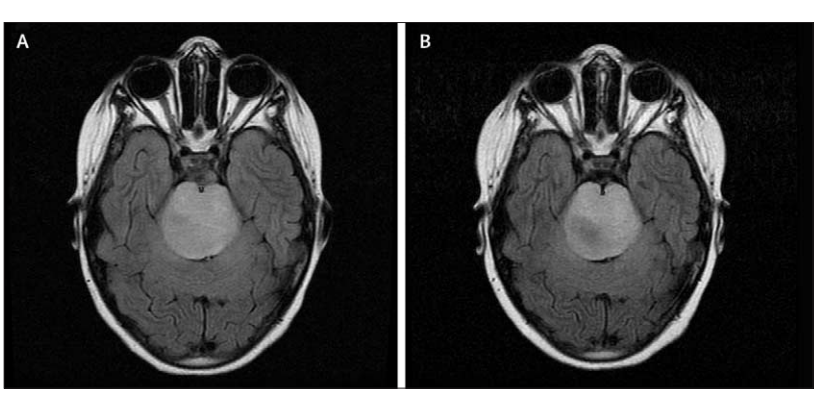

Figure 5: **Diffuse pontine glioma**
(A) Original MRI scan. (B) MRI scan 3 months later. No evidence of radiological progression, although patient showed substantial neurological deterioration.

study[23] concluded that the addition of tamoxifen to conventional radiation was not associated with a survival benefit. These conclusions were based on a median survival time of 10·3 months in this series of 29 patients, and on a 1-year survival of 37 (27·5–46·5%). At the time of the publication, eight patients were alive 220–894 days after diagnosis. The application of the triangular test with the survival data provided in the publication suggests that this trial should have been terminated earlier (when the lower boundary was crossed) or was terminated prematurely at a time the survival in subsequent cohorts of patients was improving. The choice of the best variable for statistical analysis is still a matter of debate, but in the absence of standardised and validated criteria for progression, overall survival seems to provide the most reliable information. Other statistical models can be considered—eg, comparisons with an exponential failure-time model of event-free or overall survival from historical cohorts, which are used in some cooperative studies.[43,44] Again, the choice of the endpoint (overall survival rather than event-free survival) is crucial in the absence of a robust definition of progression.

Future prospects

Several studies on new chemotherapeutic agents, small molecules, or radiosensitisers are ongoing. The European Organisation for Research and Treatment of Cancer randomised study, which compared radiotherapy alone with radiotherapy plus temozolomide in patients newly diagnosed with glioblastoma,[45] showed a significant survival benefit with the addition of chemotherapy and has generated significant enthusiasm. A single-group study using a similar design has been completed by the Children's Oncology Group.[44] The outcome of this study is crucial and we hope that the conclusions will be similar to that of the European Organisation for Research and Treatment of Cancer study in adults. Increased attention is being given to biological correlation with drug development. The precise pattern of genetic abnormalities within the group of diffuse pontine glioma is still poorly documented. A study[46] has suggested that the genetics of these tumours is complex and includes grade-dependent amplification and overexpression of epidermal growth factor receptor (*EGFR*) and grade-independent expression and mutation of *P53*. With the development of targeted therapies, the issue of stereotactic or open biopsies for diffuse brainstem glioma is being readdressed by some cooperative groups to correlate biological findings with drug activity.

However, our review shows that the risks of misinterpretation of outcome data are substantial and that harmony is urgently needed between eligibility criteria and statistical endpoints to allow relevant conclusions and appropriate comparisons.

Conflict of interest

We declare no conflicts of interest.

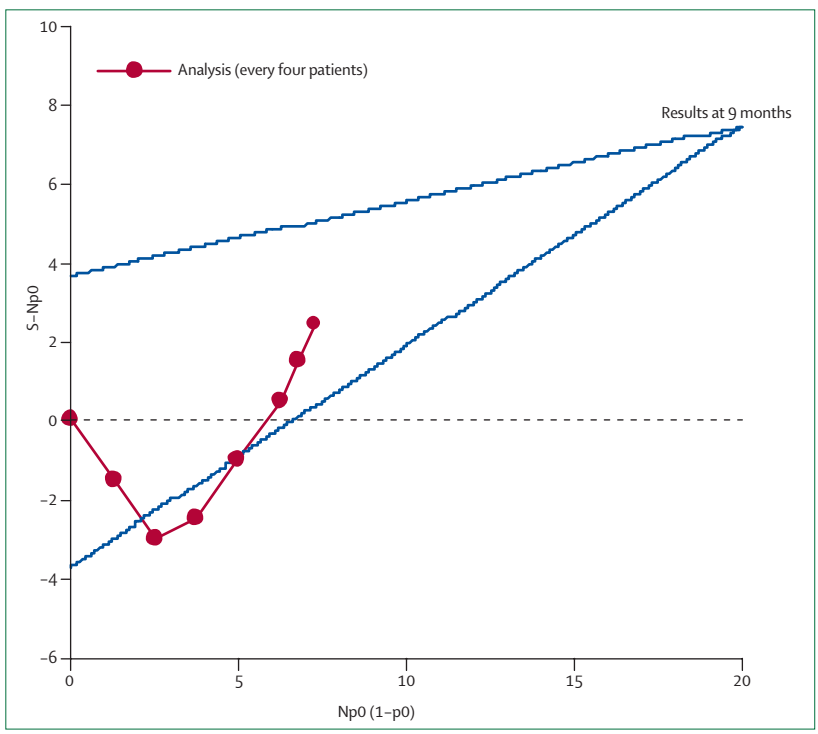

Figure 6: **Triangular test applied to data for 29 patients[23]**

S=number of patients free from event (death only, or death or disease progression). N=number of participants. If red path crosses upper boundary, proposed strategy will provide benefit. If red path crosses lower boundary, proposed strategy will provide no evidence of benefit. In present study, sample path crossed lower boundary after two analyses, suggesting treatment was not effective (rejection of efficacy hypothesis). Subsequently, path crossed lower boundary again and was still inside continuation region at end of trial.

Search strategy and selection criteria

Data for this review were identified by searches of the PubMed database from 1975 to the present. Search terms included: "brainstem" or "brain stem"; "glioma" or "gliomas"; "tumor" or "tumors"; "diffuse"; "pontine"; "radiotherapy"; and "chemotherapy". Reports were also identified from references from relevant articles. The search was limited to the paediatric and young adult populations (1–18 years) reported in English. Only prospective clinical trials with newly diagnosed patients were selected. Letters to editor, case reports, repeat publications, commentaries, and meeting abstracts were excluded. Studies that included a mixed group of patients with brainstem and non-brainstem glioma or paediatric and adult patients were included; however, such studies had to include a specific subanalysis of the population with paediatric brainstem glioma. To improve the quality of the information found by the search, a copy of the trial protocols was obtained, either through the corresponding oncology group website or by contact with the first author of the article.

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