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Original Paper

Multivariate Analysis of Prognostic Factors in 106 Patients with Malignant Glioma

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The aim of this study was to evaluate the outcome and prognostic factors influencing survival in 106 patients with supratentorial malignant gliomas treated with radiotherapy. The study group included 84 patients treated by surgery and post-operative radiotherapy and 22 patients treated by postbiopsy irradiation. Radiotherapy was delivered to the tumour area with a 2 cm margin, the aimed curative dose was 60 Gy in 6–7 weeks. The 60-month overall survival (Kaplan–Meier) was 20%. Following a univariate analysis, younger age ($P < 0.001$), longer duration of symptoms ($P = 0.009$), good performance status after radiotherapy ($P < 0.001$), other than grade 4 histology ($P < 0.001$) and higher radiation dose ($P < 0.001$) were associated with better overall survival rates. Multivariate analysis found that age, symptom duration, histology, extent of symptoms and radiation dose were independent prognostic factors influencing survival. In conclusion, conventional radiotherapy of supratentorial malignant gliomas results in survival that is comparable to results from clinical experiments with different fractionation schedules and radiation with chemotherapy or radiosensitisers. To improve the results, new approaches are needed, especially for patients with the poorest prognosis after standard treatment.

Key words: malignant glioma, radiotherapy, prognostic factors, survival

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INTRODUCTION

MALIGNANCIES OF the central nervous system comprise less than 1.5% of all malignant disease with a slightly higher prevalence in males [1]. There is evidence of an increase in the age-standardised incidence and mortality of brain cancer during recent decades and thus the incidence of malignant gliomas has increased in Finland (Table 1). The incidence peak occurs between 50 and 70 years of age. High-grade gliomas comprise more than 40% of central nervous system malignancies [3]. Most high-grade gliomas have diffuse growth [4] and aggressive behaviour, so continuing to be a major clinical problem.

The major goal of therapy in the treatment of malignant gliomas is local tumour control. External radiotherapy has an important role as an adjuvant treatment to surgery. A dose–response relationship with survival up to 60 Gy has been observed [3]. Higher doses are, however, associated with increased frequency of brain tissue necrosis, and survival is not improved [5, 6]. Despite higher doses, local failure is the most common pattern of recurrence. Samples from the tumour taken after 70–80 Gy have shown viable tumour tissue in high-grade malignant gliomas [7].

The aim of this study was to evaluate the outcome and prognostic factors influencing survival in adult patients with malignant gliomas.

PATIENTS AND METHODS

Between 1988 and 1994, 106 adult patients with malignant glioma were treated with radiotherapy at the Department of Radiotherapy and Oncology in Turku University Hospital.

From each patient's clinical record we recorded the date of histological and radiological diagnosis, symptoms, patient age at diagnosis, tumour type, extent of resection, performance status prior to and after radiation therapy, response to treatment and treatment of recurrences, and the date and

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Table 1. *The number of brain tumours diagnosed in Finland from* 1968 *to* 1992, *by histology and sex. Percentage change between* 1968 *and* 1972 *and* 1988 *and* 1992. *Included are tumours with confirmed histological diagnosis only* [2]

Histology	1968–1972 M/F	1978–1982 M/F	1988–1992 M/F	% change
Medulloblastoma	25/10	18/10	21/9	− 16/ − 10
Ependymoma	37/18	20/20	23/22	− 38/ + 22
Other glioma	335/281	504/452	643/577	+ 91/ + 106
Angiogenic tumours	28/21	20/15	32/45	+ 61/ + 114
Meningeoma	103/279	217/518	167/535	+ 62/ + 92
Craniopharyngeoma	10/15	18/18	19/14	+ 90/ − 7

M, male; F, Female.

cause of death. Symptoms were graded according to Färkkilä [8]; local symptoms included cerebral nerve palsies, motor or sensory disturbances and coordination disturbances. General symptoms comprised epileptic seizures, headache, vertigo, vomiting, personality changes, and both included local and systemic symptoms. Performance status was estimated according to the Zubrod scale [9].

Information concerning tumour location and resectability was collected from surgery records and confirmed with pre- and postoperative CT sans with or without MRI. Tumours were considered completely resected when no measurable residual tumour images persisted after surgery and the operative and histological records confirmed the total excision of the lesion (9 patients). A partial resection was considered to be a therapeutic surgical attempt followed by the detection of measurable residual tumour in CT or MRI (75 patients). Stereotactic biopsies were performed in 22 cases. These patients were inoperable because of tumour localisation. All evaluated patients had a histologically confirmed tumour. Histological classification was based on a WHO grading [10]. The category of mixed tumours comprises tumours with features of oligodendroglioma, oligoastrocytoma and gemisticytic astrocytoma.

Postoperative CT scans were used for treatment planning, and verification films were taken through each treatment portal in the simulator. Patients were treated with 4 or 6 MeV protons from linear accelerators starting usually with two opposed fields; occasionally a three field plan was used. The curative dose was prescribed as follows: 45–48 Gy/1.8 Gy/fraction for larger fields and a boost of 10–15 Gy/9–9.5 Gy/week in smaller fields (with a 2 cm margin to the tumour area) to the total dose of 60 Gy. In palliative treatment the fields were not changed and the dose did not exceed 40 Gy/21 fractions. 84 patients were treated with surgery and postoperative radiotherapy, and 22 patients were treated by postbiopsy irradiation.

If symptomatic following surgery or during radiation treatment, the patients were given dexamethasone with a standard dose of 9–12 mg/day. This was tapered towards the end of treatment and usually stopped within 3 weeks after radiotherapy.

The evaluation of treatment response was based on CT scan or MRI taken within 6–12 months after treatment was completed. If no residual tumour was found, the response was estimated as complete response (CR) after surgery and radiotherapy. All patients were followed until death or 30 June 1995.

Treatment of recurrences was individualised. 16 patients received additional treatment after treatment failure, consisting of reoperation in 10 patients, 3 of whom also received chemotherapy, additional irradiation in one patient, and chemotherapy (eight drugs in one) in 6 patients.

The effect of preradiotherapy surgery, histology and tumour localisation were assessed using Fishers's exact test, two tailed. The survival curves were calculated from the date of commencement of radiotherapy until the date of death or last day of follow-up using the Kaplan–Meier product limit method. The log-rank-test was used to test differences and trends in survival between subgroups of patients.

Multivariate Cox analysis was used in a forward stepwise mode to examine the effects of specific variables, radiation dose and volume, extent of surgery and response to treatment on survival.

RESULTS

The 106 adults included 59 men and 47 women with supratentorial malignant glioma. The median age at referral was 49.7 years (range 16.4–77.5). At presentation, 14 patients (13%) had local (cerebral nerve palsies, motor/sensor or coordination disturbances) and 58 patients (55%) generalised symptoms (headache, vertigo, nausea, seizures or psychological changes), and 34 patients (32%) expressed both. The mean duration of symptoms prior to diagnosis was 2 months. It was less than 1 month in 26 patients (25%), 1–3 months in 38 patients (37%) and over 3 months (up to 15 months) in 39 patients (38%). The duration was not known for 3 patients.

Histological diagnosis was based on biopsy in 22 patients (21%), subtotal resection in 75 patients (71%), and total resection in 9 patients (8%). Forty-four were grade 3 tumours (42%), 51 were grade 4 tumours (48%) and 11 were mixed gliomas (10%).

The distribution of patients by age, gender and tumour histology is shown in Table 2. Among patients who were younger than 44 years, grade 3 gliomas were most common, whilst in older patients, grade 4 gliomas were most commonly diagnosed. The difference in distribution of histological type in different age groups was statistically significant ($P < 0.023$).

Table 3 presents the median survival by different clinical and pathological variables. Statistically significant difference in median survival was observed by age, performance status after radiotherapy, distribution of symptoms and their duration, and tumour histology. The difference in survival by gender or tumour multiplicity was not significant. Metastases outside the brain were not observed among our patients.

Table 2. Association between age, gender and histology in patients who received radiotherapy for malignant gliomas

Variable	Age (years) 16–44	45–65	>65
Gender			
Male	19 (18%)	35 (33%)	5 (5%)
Female	17 (16%)	22 (21%)	8 (8%)
			$P = 0.02$
Histology			
Grade III	23 (22%)	19 (18%)	2 (2%)
Grade IV	8 (8%)	33 (31%)	10 (9%)
Mixed	5 (5%)	5 (5%)	
			$P = 0.023$

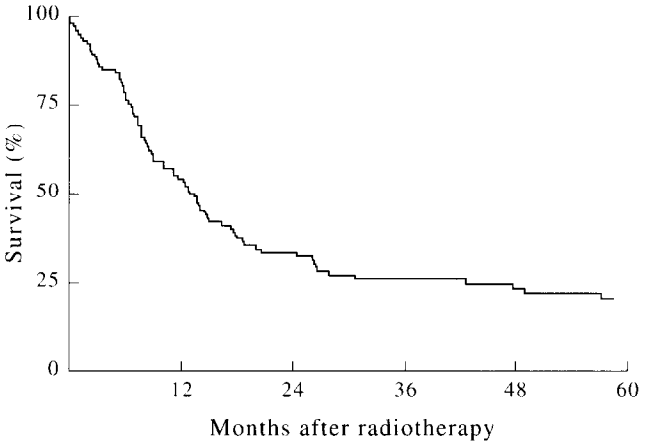

Figure 1. Overall survival of 106 patients treated with conventional external radiotherapy for brain tumours.

The overall 60-month survival (Kaplan–Meier) was 20% (Figure 1). The influence of age at diagnosis on survival is presented in Figure 2. The overall 60-month survival was 40% in the youngest group and 12% in 45–65 years' old patients. None of the older patients survived over 28 months. The difference between groups was statistically significant ($P < 0.001$). Figure 3 shows survival by histology. The three histological groups had significantly different outcomes ($P < 0.001$) with the poorest outcome for grade 4 tumours. Survival of patients with generalised symptoms was better than survival of patients with local symptoms or local and systemic symptoms at presentation (Figure 4, $P = 0.02$).

When survival was calculated by the duration of symptoms, it was observed that symptoms of over 3 months dur-

Table 3. Association of clinical and pathological features with median survival in 106 patients treated with radiotherapy with or without surgery for supratentorial malignant glioma

Feature	No. of patients	Median survival (months)	*P*-value
Gender			
Male	59	13.2	
Female	47	12.7	0.54
Age (years)			
< 44	36	30.0	< 0.001
45–65	57	8.6	
>65	13	6.6	
Performance status post RT			
$Z = 0–1$	52	14.4	
$Z = 2–3$	34	8.9	
$Z = 4$	5	1.3	< 0.001
Symptoms			
Local	14	9.3	
Systemic	58	17.1	
Both	34	8.7	0.02
Duration of symptoms			
< 1 month	26	7.4	
1–3 months	38	10.0	
>3 months	39	26.1	0.009
Histology			
Grade III	44	24.0	
Grade IV	51	7.7	
Mixed	11	100.9	0.001
Single tumour	98	32.1	
Multiple	8	12.5	0.41

RT, radiotherapy.

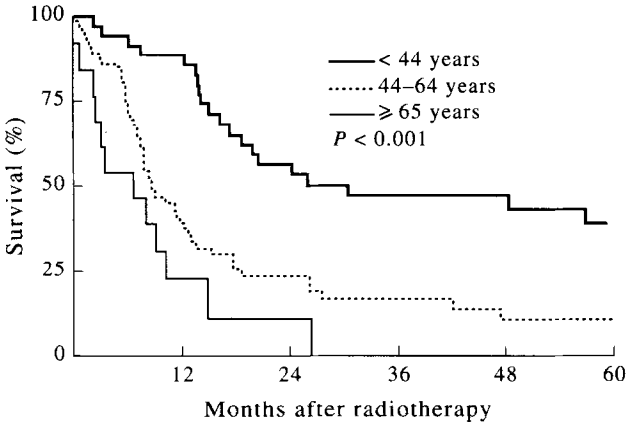

Figure 2. Survival by age.

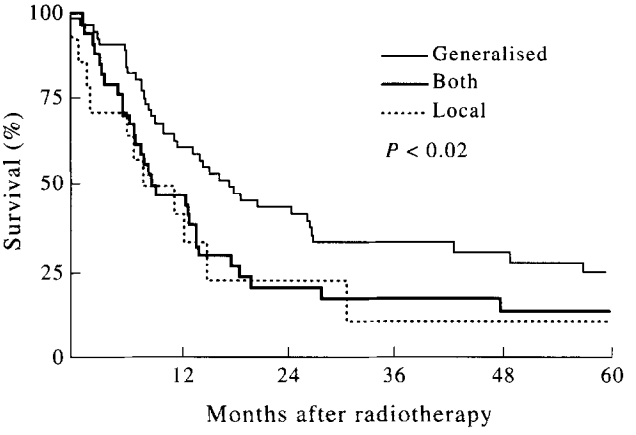

Figure 4. Survival by symptoms categorised as local, systemic, and both (see Patients and Methods for details).

ation were associated with better survival than shorter duration of symptoms (Figure 5, $P = 0.009$).

Univariate analysis found that younger age ($P < 0.001$), other than grade 4 histology ($P < 0.001$), generalised symptoms and longer symptoms duration were associated with prolonged survival (Table 4). In multivariate analysis, radiation dose, age at diagnosis, tumour histology and symptoms duration were independent prognostic factors for survival. Risk of death was almost six times greater for grade 4 histology compared to mixed histology (RR 5.9, 95% CI 0.16–1.04) and almost three times greater for ages over 45 at diagnosis (RR 2.5, 95% CI 1.44–4.27) than under 45 years.

DISCUSSION

Since the 1950s, an increase in the age-standardised incidence of malignant gliomas has been reported by a number of population-based cancer registries around the world in all age groups [1, 11, 12, 14, 15]. Associations of brain tumours with certain medial conditions and with exposures to radiation, viruses, chemicals and nutritional factors have been suggested [13]. Since the late 1960s, reports of parallel increases in brain cancer mortality support the notion of real increases in incidence [16]. The incidence of angiogenic tumours, ependymomas and craniopharyngeomas has not increased as markedly as the incidence of gliomas and meningeomas in Finland (Table 1). The increased incidence in the elderly may partly be explained by increased detection through improved diagnostic facilities, since some tumours are only visible in NMR. However, the overall increase in incidence occurred well before the introduction of CT scanning and rates have continued to rise steadily [12, 16, 17]. MRI has proven to be more reliable than CT in diagnosis of malignant glioma [18] and this was also observed in our series. MRI diagnosed those tumours (10% of all) that had been negative in CT investigation.

To evaluate whether results obtained with conventional radiotherapy alone are comparable to those obtained with investigative schedules, a comparison of our results with others in the literature was made (Table 5), and the results obtained in our study with conventional fractionation and dose are comparable.

Standard treatment for malignant astrocytomas is surgical de-bulking, where possible, and postoperative radiotherapy. Experience with radiation in high-grade brain tumours suggests that there is a dose–response relationship at least up to 60 Gy [26]. Studies have failed to show significant benefit for overall survival from increasing the dose above 60 Gy using higher dose [7], hyperfractionated treatment [5] or accelerated radiotherapy [6]. With dose exceeding 80 Gy, a trend to inferior survival compared to lower doses was observed in a randomised trial, and simultaneously a trend towards increased identifiable toxicity with the increase in dose was noted. In another study, a decrease in survival was observed with doses above 72 Gy [5].

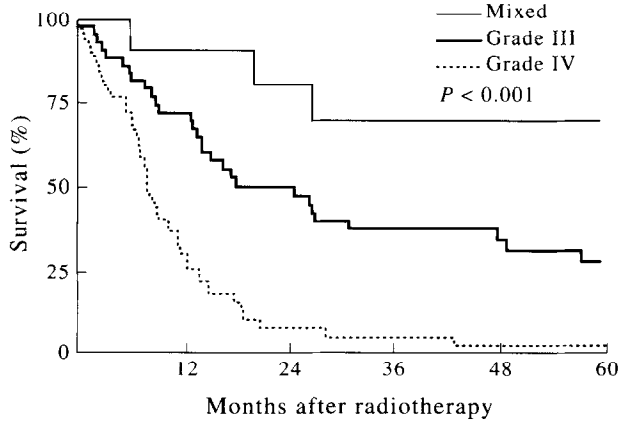

Figure 3. Survival by histology according to grading by WHO.

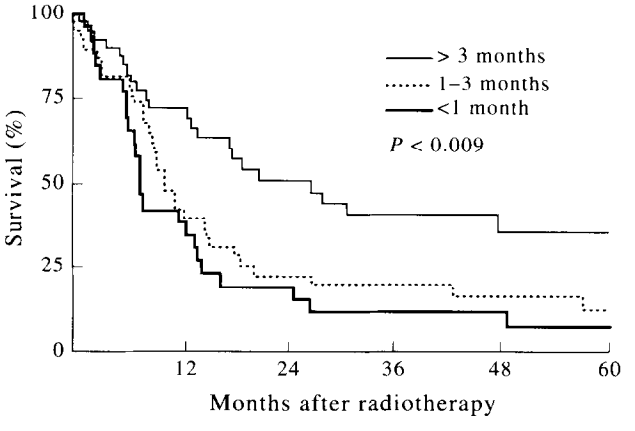

Figure 5. Survival by symptom duration prior to diagnosis.

Table 4. Multivariate and univariate association with survival in 106 patients with malignant gliomas

Variable (Ref. variable)	*P* log rank Multivariate	Univariate
Age ($\leqslant$ 65 years)	0.001	0.001
Sex (male)	NI	0.96
PS (< 4)	0.29	0.001
Histology (not Grade IV)	0.001	0.001
Symptoms (generalised)	NS	0.02
Symptoms duration ($\geqslant$ 1 month)	0.021	0.009
Radiation dose (>40 Gy)	0.001	0.001

NS, not significant; NI, not included; PS, performance status in Zubrod scale. Treatment dose is defined as the radiation dose delivered to the treatment volume.

Despite the higher doses, local failure is the most common pattern of recurrence. Most new combination treatments are significantly more toxic and thus they are offered only to those patients who are young and basically fit. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults [27] showed some benefit of chemotherapy in subgroups of patients, especially those with anaplastic astrocytomas, after combined treatment.

A strong prognostic factor in brain tumours is the age at diagnosis. Patients younger than 50 years have significantly better survival when compared to older patients [8]. Other prognostic factors, especially for high-grade tumours, have also been suggested, including age and performance status, histology, extent of surgery and the length of symptoms. In some subsets of patients, the results of flow cytometry, cytogenetic, and molecular genetic factors may have prognostic value [28].

In our study, the importance of many of these prognostic factors was confirmed in the univariate analysis. The higher the grade, the worse the outcome. Performance status at the end of radiotherapy was significant for the survival of patients. However, performance status estimated prior to radiotherapy in our series was of less prognostic value. The pattern and duration of symptoms was also a significant determinant for outcome. The multitude of symptoms obviously prompted the investigations leading to early diagnosis and treatment. The shorter the length of symptoms was, the worse the outcome for the patients, indicating how the degree of malignancy reflects in clinical symptoms. The length of symptoms as prognostic factors has been previously suggested by Chang and colleagues [29].

The 5-year survival of patients with supratentorial glioma diagnosed from 1953 to 1984 was 29% for men and 34% for women in Finland in the analysis of the Finnish Cancer Registry [11]. In our series, no significant difference was observed between men and women. The survival of patients with mixed tumours was better than of those with other histology. Mixed tumours are histologically between high and low grade gliomas, with less tendency to diffuse, aggressive growth than tumours of higher grade.

High local doses can be administered with stereotactic surgery. It is, however, better suited for well defined lesions than for high-grade gliomas with diffuse growth. Similarly, only a minority of patients with a malignant glioma are eligible for brachytherapy. Florell and coworkers [30] have observed that adjuvant brachytherapy is not suitable for most patients with malignant glial tumours. Longer than expected survival periods following adjuvant brachytherapy are at least in part the result of patient selection.

In an Australian study, no improvement in 5-year survival was observed for any of the age groups or histological types during the time period from 1978 through 1992 [12], although chemotherapy has been added to the treatment of malignant gliomas since that time. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults [27] showed some benefit in some subgroups of patients, particularly in anaplastic astrocytomas, after combined treatment. However, the Radiation Therapy Oncology Group (RTOG) review of results obtained with the combination of conventional radiation with chemotherapy or neutron boost showed that median survival decreases with increasing aggressiveness of treatment and when chemotherapy was included [31]. Patient selection is the strongest factor influencing the outcome of different treatments in malignant gliomas [30]. Therefore, conventional treatment with surgery and adjuvant radio-

Table 5. Median survival of radiotherapy patients reported in high-grade gliomas

Reference	Number of patients	Radiation dose	Median survival (months)
[19]	42	—	4.3
	93	50 and 60 Gy	9.3
[7]	100	63 Gy	13.5
[20]	80	45 Gy + bleomycin	10.8
	35	—	5.2
[21]	73	71 Gy split	12.5
[22]	53	40 Gy + 33 Gy pions	8.5
[23]	70	58 Gy	18.0
[6]	66	48–60 Gy accelr*	8.7
[24]	38	30†	6.0
[25]	84	78 Gy hyperfr‡	12.7
Current study	25	<40 Gy	6.7
	81	40–60 Gy	17.2

* Accelerated radiotherapy. †Hypofractionated. ‡Hyperfractionated radiotherapy.

therapy seems justified in smaller centres such as ours as a standard treatment of malignant gliomas, if participation in clinical trials is not available.

1. Ahlbom A, Rodvall Y. Brain tumour trends. *Lancet* 1989, **2**, 1272.
2. Cancer Society of Finland, Publication No. 54. *Cancer Incidence in Finland 1992*, Helsinki 1994.
3. Walker M, Green S, Byar D, *et al.* Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Eng J Med* 1980, **303**, 1323–1329.
4. Halperin E, Burger P, Bullard D. The fallacy of localized supratentorial malignant glioma. *Int J Rad Oncol Biol Phys* 1988, **15**, 505–509.
5. Nelson D, Curran W, Scott C, *et al.* Hyperfractionated radiation therapy and bis-chlorethylnitrosourea in the treatment of malignant glioma. *Int J Rad Oncol Biol Phys* 1993, **25**, 193–207.
6. Gonzales D, Menten J, Bosch D, van der Schueren E, Troost D, Hulshof M, Bernier J. Accelerated radiotherapy in glioblastoma multiforme: a dose searching prospective study. *Radiother Oncol* 1994, **32**, 98–105.
7. Salazar O, Rubin P, Feldstein M, Pizzutiello R. High dose radiation therapy in the treatment of malignant gliomas: final report. *Int J Rad Oncol Biol Phys* 1979, **5**, 1733–1740.
8. Färkkilä M. Symptoms, diagnostics and treatment organization in brain tumours. *Finnish Med J* 1994, **32**, 3297–3300.
9. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
10. Zulch K. Histological typing of tumours of the central nervous system. International histological classification of tumours. World Health Organization, Geneva 1979, No. 21.
11. Hakulinen T, Pukkala E, Hakama M, *et al.* Survival of cancer patients in Finland in 1953–1974. *Ann Clin Res* 1981, **13**(s), 13.
12. Shugg D, Allen B, Blizzard L, Dwyer T. Brain cancer incidence, mortality and case survival: observations from two Australian cancer registries. *Int J Cancer* 1994, **59**, 765–770.
13. Giles G, McNeil J, Donnan G, *et al.* Dietary factors and the risk of glioma in adults: results of a case-control study in Melbourne, Australia. *Int J Cancer* 1994, **59**, 357–362.
14. Boyle P, Maisonneuve R, Muir C. Is the increased incidence of primary brain tumours in the elderly real? *J Natl Cancer Inst* 1990, **82**, 1594–1596.
15. Greig N, Ries L, Yancik R, Rapoport S. Increasing annual incidence of primary malignant brain tumours in the elderly. *J Natl Cancer Inst* 1990, **82**, 1621–1624.
16. Davis L, Ahlbom A, Hohl D, Percy C. Is brain cancer mortality increasing in industrial countries? *Am J Ind Med* 1991, **19**, 423–431.
17. Helseth A, Langmark F, Mork S. Neoplasms of the central nervous system in Norway. *Acta Pathol Microbiol Immunol Scand* 1988, **96**, 1066–1074.
18. Seither R, Jose M, Paris K, Lindberg R, Spanos W. Results of irradiation in patients with high grade gliomas evaluated by magnetic resonance imaging. *Am J Clin Oncol* 1995, **18**, 297–299.
19. Walker M, Alexander E, Hunt W, *et al.* Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. *J Neurosurg* 1978, **49**, 333–343.
20. Kristiansen M, Hagen S, Kollevold T, *et al.* Combined modality therapy of astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time. *Cancer* 1981, **47**, 649–652.
21. Marcial-Vega V, Wharam M, Leibel S, Clark A, Zweig R, Order S. Treatment of supratentorial high grade gliomas with split course high fractional dose postoperative radiotherapy. *Int J Rad Oncol Biol Phys* 1986, **16**, 1419–1434.
22. Goodman G, Skarsgard L, Thompson G, Harrison R, Lam G, Lugate C. Pion therapy at TRIUMF. Treatment results for astrocytoma grades 3 and 4; a pilot study. *Radiother Oncol* 1990, **17**, 21–28.
23. Gaspar L, Fisher B, Macdonald D, *et al.* Supratentorial malignant glioma: patterns of recurrence and implications for external beam local treatment. *Int J Rad Oncol Biol Phys* 1992, **24**, 55 57.
24. Thomas R, James N, Guerrero D, Ashley S, Gregor A, Brada M. Hypofractionated radiotherapy as palliative treatment in poor prognosis patients with high grade glioma. *Radiother Oncol* 1994, **33**, 113–116.
25. Prados M, Wara W, Edwards M, *et al.* The treatment of brain stem and thalamic gliomas with 78 Gy of hyperfractionated radiation therapy. *Int J Rad Oncol Biol Phys* 1995, **32**, 85–91.
26. Bleehen N, Stenning S. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. *Br J Cancer* 1991, **64**, 769–774.
27. Fine H, Dear K, Loeffler J, Black P, Canellos G. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993, **71**, 2585–2587.
28. Ganju V, Jenkins R, O'Fallon J, *et al.* Prognostic factors in gliomas. *Cancer* 1994, **74**, 920–927.
29. Chang C, Horton J, Schoenfeld D, *et al.* Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. *Cancer* 1983, **52**, 997–1007.
30. Florell R, MacDonald D, Irish W, *et al.* Selection bias, survival and brachytherapy for glioma. *J Neurosurg* 1992, **76**, 179–183.
31. Laramore G, Martz K, Nelson J, Griffin T, Chang C, Horton J. Radiation Therapy Oncology Group (RTOG) survival data on anaplastic astrocytomas of the brain: does a more agressive form of treatment adversely impact survival? *Int J Rad Oncol Biol Phys* 1989, **17**, 1351–1356.