Effect of radiotherapy and other treatmentrelated factors on mid to longterm cognitive sequelae in lowgrade gliomas: a comparative study

Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study

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Summary

Background Because survival benefits of treatment with radiotherapy are questionable and such treatment can cause substantial damage to the brain over time, the optimum management strategy for low-grade gliomas remains controversial. We aimed to identify the specific effects of radiotherapy on objective and self-reported cognitive function, and on cognitive deterioration over time, in patients with low-grade gliomas treated with early radiotherapy.

Methods 195 patients with low-grade glioma (of whom 104 had received radiotherapy 1–22 years previously) were compared with 100 low-grade haematological patients and 195 healthy controls. Our analyses aimed to differentiate between the effects of the tumour (eg, disease duration, lateralisation) and treatment effects (neurosurgery, radiotherapy, antiepileptic drugs) on cognitive function and on relative risk of cognitive disability.

Findings Low-grade glioma patients had lower ability in all cognitive domains than did low-grade haematological patients, and did even less well by comparison with healthy controls. Use of radiotherapy was associated with poorer cognitive function; however, cognitive disability in the memory domain was found only in radiotherapy patients who received fraction doses exceeding 2 Gy. Antiepileptic drug use was strongly associated with disability in attentional and executive function.

Interpretation Our findings suggest that the tumour itself has the most deleterious effect on cognitive function and that radiotherapy mainly results in additional long-term cognitive disability when high fraction doses are used. Additionally, the effects of other medical factors, especially antiepileptic drug use, on cognitive function in glioma patients deserve attention.

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Introduction

Among adult cancer patients, patients with gliomas (ie, primary brain tumours arising from glial tissue) form a minority. Compared with lung and breast cancer, which have rates of about 60 per 100 000 in the Netherlands, the rate of gliomas is tenfold lower, with about 1000 new patients every year.[1] Nevertheless, these cancers have a serious effect on the health-care system in general, and especially on patients and their families. Not only do glioma patients have to cope with the diagnosis of incurable disease, they and their families are usually also confronted with the patient's decrease in cognitive and emotional function as a result of cerebral disease.

Although the median survival of adult glioma patients with low-grade tumours is much longer than that of those with high-grade tumours, nearly all will die of their disease. In these patients, early treatment does not prolong survival,[2] and no randomised prospective studies have been done to assess the effects of neurosurgery. Moreover, retrospective data on the role of neurosurgery in extended survival (as opposed to a policy of observation) are controversial.[3]

What is the role of early radiotherapy in these patients? Low-grade gliomas can be moderately responsive to radiotherapy,[4] but the survival benefits of adjuvant radiotherapy after neurosurgery are debatable. Results of some retrospective studies suggest that early radiotherapy improves survival;[5] other investigators have reported that it does not,[6] or have shown that older patients might benefit most.[5] Findings of several studies by the European Organisation for the Research and Treatment of Cancer (EORTC) clearly do not recommend early treatment with radiotherapy of patients with low-grade gliomas.[7,8]

Apart from potential favourable survival effects, radiotherapy itself could negatively affect the patient's health-related quality of life through irreversible late-delayed brain damage induced by irradiation, ultimately resulting in cognitive deficits and dementia.[9,10] In long-term survivors of brain metastases from systemic cancer, and in patients with primary lymphoma of the central nervous system, treatment with whole-brain radiotherapy can lead to radiation-induced encephalopathy.[11,12] Partly because of these side-effects, standard treatment of glioma patients is based on focal radiotherapy rather than on whole-brain radiotherapy. Apart from a large radiotherapy treatment volume, high radiotherapy total and fraction dose, concomitant chemotherapy, and old age have been identified as potential risk factors for cognitive deterioration in glioma

patients.[9] The incidence of late-delayed encephalopathy in these patients is steadily increasing, not only because of increased survival but also because of improved detection (neuroimaging and extensive cognitive function testing) and raised awareness among physicians and patients.[9]

With 5-year and 10-year progression-free rates of 50% and 12%, respectively, for supratentorial low-grade astrocytomas, low-grade oligodendrogliomas, and mixed gliomas,[13] and a median better survival of 16·7 years for the latter two groups,[14] patients with low-grade gliomas can survive in a stable state for several years after diagnosis. The long-term cognitive and psychosocial sequelae of the disease and its treatment in these long-term survivors are especially salient. In 1994, we showed serious cognitive deficits in low-grade glioma patients, which, surprisingly, could not be attributed to focal radiotherapy.[15] Here, we present results from a nationwide study with a larger group of such patients and with the use of a more extensive cognitive test battery than in our previous report.

We aimed to delineate changes in cognitive function and cognitive disability as defined by the WHO International Classification of Functioning, Disability and Health (ICIDH-2).[16] ICIDH-2 components of function and disability can be expressed in two ways. They can be used to indicate non-problematic aspects of health and health-related states, summarised under the umbrella term functioning; or they can indicate problems (eg, impairment, activity limitation, or participation restriction), summarised under the umbrella term disability.

In line with our previous research, we aimed to establish the effect of the tumour (ie, duration of disease, tumour lateralisation) and of treatment (ie, neurosurgery, radiotherapy, antiepileptic drugs) on the mid-to-long-term cognitive function of patients with low-grade glioma. Since we postulated that reductions in cognitive function caused by radiation therapy increase over time, the long-term effect of radiotherapy received special attention. Furthermore, we aimed to find out whether, because the central nervous system is implicated, brain-tumour patients have more extensive cognitive deficits than patients with cancer outside the brain. Cognitive function in patients with non-brain tumours is thought to be compromised by the psychological effect of cancer. Additionally, we tested the hypothesis that especially in brain-tumour patients, there is a dissociation between subjective cognitive complaints and observed cognitive functioning.

With the ICIDH-2 classification in mind, we first defined the extent of restrictions in cognitive function in glioma patients by comparison with patient controls and with healthy controls, and by identification of tumour and treatment characteristics related to cognitive functioning. Subsequently, we investigated which tumour-related and treatment-related characteristics were associated with increased risk of cognitive disability.

Methods

Patients and methods

In this multicentre study, we recruited low-grade glioma patients and patients with low-grade haematological cancers who had (a) no clinical signs of tumour recurrence for at least 1 year after the histological diagnosis and primary treatment, and (b) no radiological signs of recurrence within 3 months before testing. Patients were recruited from neurosurgical centres throughout the Netherlands (listed in the acknowledgments section). Between these centres, therapeutic policies differed as to the use of early radiotherapy for low-grade glioma. Irradiated patients were recruited from centres at which early radiotherapy for low-grade glioma was favoured. The study protocol was approved by the medical ethics committees of the institutions.

Eligibility was checked with the general practitioner and by case-note review. Because study resources were restricted, we aimed to include a maximum of 200 low-grade glioma patients and 100 patients with low-grade haematological cancers stratified geographically (three regions), by disease duration (1·0–3·5 years, 3·6–6·0 years, or 6·1 years or longer) and, for low-grade glioma patients, having received radiotherapy (LGG/RT+) or not (LGG/RT−). We classified low-grade glioma histologically as astrocytomas, oligodendrogliomas, or oligoastrocytomas. Low-grade haematological cancers were restricted to non-Hodgkin lymphomas or chronic lymphatic leukaemia (NHL/CLL) without clinical signs of central nervous system involvement. Patients with NHL/CLL were recruited to compare the cognitive outcome of glioma patients with the psychological effect of having cancer per se on cognitive function.[17]

Tumour recurrence or progression for both low-grade glioma and NHL/CLL patients usually arises after a period of stable disease, and survival rates are similar. Moreover, there are similarities between these tumours with regard to their development and biological behaviour. LGG/RT+ patients were only included if they received radiotherapy as primary treatment within 2 months of histological diagnosis. Patients were excluded if they used corticosteroids, did not have a basic proficiency in the Dutch language, or were unable to communicate adequately.

In addition to glioma and NHL/CLL patients, normative data from a cohort of healthy controls were included in this study. These data were taken from the Maastricht Aging Study[18] which comprised several studies of the biomedical and psychological determinants of cognitive ageing. The core project was a large cross-sectional study of 2000 healthy individuals aged 24–81 years who were followed up for 12 years with regard to health characteristics and neurocognitive status. Healthy controls were individually matched with low-grade glioma patients for age, sex, and educational level, since these sociodemographic characteristics are known to affect cognitive functioning. The latter variable was assessed by a Dutch scoring system that consists of an 8-point scale, ranging from unfinished primary education (level 1) to university education (level 8).

The treating physician invited the patients by letter to participate in the study. Informed consent procedures preceded patients' agreement to participate. Before the day of formal testing, patients completed a postal questionnaire about sociodemographic data, including age, sex, and educational level. During testing we obtained clinical data for functional status, cognitive assessment, and self-reported health-related quality of life; the latter will be the subject of a separate paper. Patients could choose to be tested at home or in the treating hospital.

Clinical data obtained at entry included tumour characteristics (histology, site) and treatment history (neurosurgery, biopsy *vs* resection; radiotherapy target, focal *vs* whole-brain; radiotherapy total dose and fraction dose; boost; and antiepileptic drugs). All clinical data were taken from the case-note reviews.

Neuropsychological domains and specific tests used in the study

Intelligence	
Dutch adult reading test[22]	Estimates premorbid intellectual functioning on the basis of verbal ability
Perception and psychomotor speed	
Line bisection test[23]	Measures unilateral neglect, which is usually a sequel of massive right hemisphere lesions
Facial recognition test[23]	Detects impairment in the discrimination of faces, a disorder associated with right hemisphere lesions
Judgment of line orientation test[23]	A test of visuospatial judgment, also detects right hemisphere dysfunction
Letter-digit substitution test (LDST)[23]	Measures psychomotor speed that is relatively unaffected by a decline in intellectual ability
Memory	
Visual verbal learning test (VVLT)[23]	Examines several aspects of verbal learning, organisation, and memory
Working memory task (WMT)[23]	Measures the speed of memory processes
Attention and executive function	
Stroop colour-word test (SCWT)[23]	Examines attention, mental speed, and mental control
Categoric word fluency task[23]	Measures the speed and flexibility of verbal thought processes
Concept shifting test (CST)[24]	Measures attention, visual searching, mental-processing speed, and the ability to mentally control simultaneous stimulus patterns

Study measures

We assessed patients' overall degree of physical function with the Karnofsky performance status scale,[19] which is frequently used in clinical oncological research. Scores range from 0 (lowest level) to 100 (highest level).

The ability to do daily activities was assessed with the Barthel activities of daily living index.[20] This index consists of ten items (assessing continence of bowels and bladder, grooming, toilet use, feeding, transfer, mobility, dressing, climbing stairs, and bathing) which are ordered in ascending degree of difficulty. High scores indicate good functional independence.

We rated neurological functioning with the neurological functional status scale developed by Order and colleagues.[21] Originally developed for use with patients with brain metastases, this scale has been used in studies with brain-tumour patients. Scores range from 1 to 4, with high scores for strong neurological function.

Cognition refers to an individual's ability to perceive, store, retrieve, and use sensory and perceptual information from the environment and past experience, and to such mental activities as plans and strategies. Detailed information about the standard tests used to assess cognitive status is shown in the panel. Because of the heterogeneity in the origin and severity of cognitive disturbances in patients with glioma, we assessed a wide range of functions. Since inspection of the performance patterns of individual patients can be very useful, because it could reveal information that is not apparent from analyses of the group means, we calculated a disability score for every patient; cognitive test scores were converted to *z* scores, with the mean scores of the healthy controls as a reference. We defined cognitive disability as a test score of 2 SD below the mean of the healthy controls. To calculate an overall disability score for every patient, we counted the number of tests on which the patient was disabled. The 95th percentile of the healthy controls was used as a cutoff score for cognitive disability.[25] The application of this algorithm to our data showed that a glioma patient was judged to have a cognitive disability if he or she had deviant scores for at least four of the 20 tests. Only tests for which healthy controls could be individually matched with low-grade glioma patients for age, sex, and educational level were used for this analysis.

We assessed self-reported cognitive function with a six-item scale developed for use in the Medical Outcomes Study.[26] This scale assesses day-to-day problems with cognitive function, such as difficulty with reasoning and problem solving, slowed reaction time, forgetfulness, and problems with concentration. Raw scores are converted linearly to a 0–100 scale, with high scores for high levels of self-reported cognitive function.

Statistical analysis

We did analysis of covariance (*F* tests), with correction for differences in age, sex, education, and disease duration, to test for differences between glioma and NHL/CLL patient groups in mean scores for objective cognitive functioning. Additional Student's *t* tests for independent samples were done to determine whether cognitive function of glioma patients differed from that of healthy controls. Because of the exploratory nature of this analysis, no correction for multiple comparisons was applied. We investigated the prevalence of cognitive disability (on the basis of previously described cutoff scores) in glioma versus NHL/CLL, and in irradiated versus non-irradiated glioma patients, with logistic regression analysis, corrected for differences in age, sex, education, and duration of disease. Disease duration for both glioma and NHL/CLL patients was defined as the time between histological diagnosis and formal neuropsychological testing.

To assess the association between objective and self-reported cognitive function in glioma patients, we calculated Pearson's correlations between functional indicators of four major cognitive domains: memory (visual verbal learning test total recall), attention (Stroop colour-word test-III), psychomotor speed (letter-digit substitution test-writing), and graphomotor speed (concept-shifting test motor), and the Medical Outcomes Study scale. For purposes of data reduction, we chose these outcome measures since they correlate well with other tests in the same cognitive domain and thus are judged to be representative for this domain.

To identify which tumour-related and treatment-related characteristics were associated with objective and self-reported cognitive functioning, we did a stepwise linear regression analysis with possible confounders (ie, age, sex, and education) entered into the model at the first step. Subsequently, duration of disease, use of radiotherapy, relation between radiotherapy and disease duration (entered as an interaction term), antiepileptic drug use (none *vs* any), tumour lateralisation (left *vs* right), and neurosurgical intervention (biopsy *vs* resection) were entered as independent variables. The separate cognitive test scores, the Medical Outcomes Study scale, and the total number of deviant test scores based on a cutoff of

2 SD below the mean of the healthy controls were entered as the dependent variables. In a subsequent identical analysis restricted to the LGG/RT+ group, we calculated the relative contributions of total radiotherapy dose and fraction dose. The level of significance was set at $p<0·05$.

To identify tumour-related and treatment-related factors that were associated not only with cognitive functioning per se (ie, mean test scores), but also with cognitive disability, we did an additional series of logistic regression analyses. Using individual cognitive disability scores (on the basis of the previously described cutoff of 2 SD below the mean of the healthy controls and subsequent 5th percentile scores, which we assumed would seriously interfere with everyday life functioning), we calculated the relative risk and 95% CI for cognitive disability, corrected for differences in age, sex, and education, for the same variables as those used in the linear regression analysis. Probability for entry was set at 0·05 and probability for removal at 0·10.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Patient groups				
	LGG/RT+ (n=104)	LGG/RT− (n=91)	NHL/CLL (n=100)	p*	p†
Characteristics					
Mean age in years (SD)	42·6 (12·2)	38·7 (11·5)	49·7 (8·0)	0·017	<0·0001
Male sex	62 (59·6%)	58 (63·7%)	51 (51·0%)	0·555	0·083
Level of education‡ (SD)	4·1 (0·2)	4·2 (0·2)	4·2 (20·0)	0·782	0·491
Premorbid intelligence					
Dutch adult reading test‡ (SD)	99·9 (12·2)	100·0 (10·5)	102·4 (11·0)	0·936	0·072
Histological diagnosis				0·896	
Astrocytoma	73 (70·2%)	66 (72·5%)	..		..
Oligodendroglioma	24 (23·1%)	19 (20·9%)	..		..
Oligoastrocytoma	7 (6·7%)	6 (6·6%)	..		..
Low-grade NHL	..	..	71 (71·0%)	..	..
CLL	..	..	29 (29·0%)	..	..
Tumor lateralisation				0·125	..
Left-sided	55 (52·9%)	42 (46·2%)	..		..
Right-sided	43 (41·3%)	48 (52·7%)	..		..
Bilateral	6 (5·8%)	1 (1·1%)	..		..
Neurosurgical intervention				<0·0001	
Biopsy	55 (52·9%)	29 (31·9%)	..		..
Resection	49 (47·1%)	62 (68·1%)	..		..
Radiotherapy					
Focal/+ boost	50 (48·1%)/ 44 (42·3%)	..	..	..	
Whole brain/+ boost	2 (1·9%)/ 8 (7·7%)	..	..	..	..
Total dose Gy (SD)	55·6 (6·1)	..	..	..	..
Fraction dose Gy (SD)	2·0 (0·1)	..	..	..	..
Fraction dose 1·8–2 Gy	86 (82·7%)	..	..	..	..
Fraction dose >2 Gy	18 (17·3%)	..	..	..	..
Epileptic seizures	89 (85·6%)	78 (85·7%)	..	0·933	..
Antiepileptic drug use	74 (71·2%)	65 (71·4%)	..	0·935	..
Years since diagnosis (SD)	6·1 (4·1)	5·1 (2·9)	6·6 (4·0)	0·040	0·042
Functional/ performance status					
Karnofsky‡ (SD)	87·0 (16·3)	89·4 (10·5)	88·9 (11·0)	0·212	0·594
Barthel‡ (SD)	19·5 (2·0)	19·9 (1·0)	19·9 (1·0)	0·027	0·018
Order‡ (SD)	3·8 (1·0)	4·0 (1·0)	3·9 (1·0)	0·010	0·376

Data are number (%) of patients unless otherwise indicated. *Comparisons between LGG/RT+ and LGG/RT− groups, and †between combined glioma patients and NHL/CLL patients. ‡Mean test scores (see text).

Table 1: **Sociodemographic and clinical characteristics of the study patients**

Results

195 adult patients with supratentorial low-grade gliomas were recruited between February, 1997, and January, 2000, of whom 104 (53%) had received radiotherapy 1–22 years previously. Focal radiotherapy, with a margin of 2 cm around the lesion seen by CT or MRI, was mostly used. In several centres, a boost radiation dose, limited to the tumour volume, was given alongside focal radiotherapy. About 10% of patients had whole-brain radiotherapy, with or without boost. The main reason for whole-brain radiotherapy was a large tumour volume that made focal radiation very difficult. Low-grade glioma patients were compared with 100 patients with low-grade NHL/CLL. 44 of the 239 glioma patients (18%) and 38 of the 138 NHL/CLL patients (28%) who met the inclusion criteria declined to participate; the main reasons given were that patients found participation too burdensome, or were reluctant to be confronted with what they believed to be a cured illness. 93% of glioma patients and 96% of NHL/CLL patients were tested at home; the rest were tested in the hospital.

Table 1 shows the sociodemographic and clinical characteristics of the LGG/RT+, LGG/RT−, and NHL/CLL patient groups. NHL/CLL patients were significantly older than the combined glioma group. LGG/RT+ patients were older than LGG/RT− patients and had more frequently undergone biopsy. Disease duration was longer in LGG/RT+ patients than in those who were LGG/RT−, but the disease duration of the combined LGG/RT+ and LGG/RT− group was shorter than that of the NHL/CLL patients. The near optimum levels of physical (Karnofsky scale) and neurological functioning (Order scale) did not differ significantly between the combined glioma group and NHL/CLL patients, although glioma patients were more limited in their activities of daily living (Barthel index). Although LGG/RT− and LGG/RT+ patients both attained high levels of activities of daily living and neurological functioning, the LGG/RT+ group had significantly lower scores.

Data for cognitive function in glioma patients, NHL/CLL patients, and healthy controls are shown in table 2. After we corrected for differences in age, sex, education, and disease duration, glioma patients scored less well on tests of perception and psychomotor speed, memory tests, and tests measuring attention and executive function than did NHL/CLL patients. Reductions in cognitive function were even more pronounced when glioma patients were compared with healthy matched controls. Univariate F tests for LGG/RT+ patients versus LGG/RT− patients showed that irradiated patients scored poorly on one of seven tests in the domain of perception and psychomotor speed, on one of eight memory tests, and on one of 11 tests of attention and executive function (data not shown).

The glioma patients had much lower levels of self-reported cognitive functioning as assessed by the Medical Outcomes Study scales than did the healthy controls: 47·80 versus 82·40, respectively. For the glioma group as a whole, objectively assessed memory, attention, psychomotor speed, and grapho-motor speed correlated moderately with self-reported cognitive functioning ($r=-0·23$, 0·30, −0·34, and 0·31, respectively).

The proportion of patients with cognitive disability (as defined in the methods) was significantly higher in the glioma group as a whole than in the NHL/CLL patients (66 [34%] *vs* 22 [22%], respectively; p=0·035, corrected

	Glioma patients (n=195)	NHL/CLL patients (n=100)	p*	Healthy controls (n=195)	p†
Perception and psychomotor speed					
Line bisection-HD (cm)‡	0·44 (0·15)	–0·03 (0·21)	0·074	n/a (n/a)	n/a
Line bisection-VD (cm)‡	0·02 (0·16)	–0·80 (0·23)	0·006	n/a (n/a)	n/a
Facial recognition (nc)§	21·55 (0·19)	22·40 (0·27)	0·015	n/a (n/a)	n/a
Line orientation (nc)§	12·71 (0·22)	12·21 (0·32)	0·223	n/a (n/a)	n/a
LDST writing (nc)§	42·55 (0·74)	50·21 (1·06)	<0·0001	54·77 (0·69)	<0·0001
LDST reading (nc)§	49·53 (0·81)	57·70 (1·17)	<0·0001	62·36 (0·72)	<0·0001
LDST motor component (nc)§	6·98 (0·39)	7·43 (0·56)	0·526	7·60 (0·32)	0·463
Memory					
VVLT trial 1 (nc)§	5·20 (0·14)	5·89 (0·21)	0·009	5·25 (0·12)	0·655
VVLT max score (nc)§	10·98 (0·18)	11·93 (0·26)	0·004	12·13 (0·14)	<0·0001
VVLT delta score (nc)§	5·78 (0·16)	6·04 (0·23)	0·338	6·88 (0·14)	<0·0001
VVLT total recall (nc)§	42·11 (0·78)	47·18 (1·12)	<0·0001	46·26 (0·61)	0·003
VVLT delayed recall (nc)§	8·63 (0·23)	10·45 (0·33)	<0·0001	9·96 (0·20)	0·001
VVLT delayed recognition (nc)§	14·10 (0·11)	14·70 (0·15)	0·002	14·46 (0·07)	0·072
WMT slope‡	17·21 (0·66)	13·62 (0·93)	0·003	13·13 (0·44)	<0·0001
WMT intercept‡	31·74 (0·84)	27·39 (1·19)	0·004	22·10 (0·39)	<0·0001
Attention and executive function					
SCWT card I (s)‡	53·39 (1·05)	46·46 (1·51)	<0·0001	43·63 (0·52)	<0·0001
SCWT card II (s)‡	70·71 (1·37)	59·02 (1·97)	<0·0001	55·24 (0·66)	<0·0001
SCWT card III (s)‡	120·22 (3·28)	90·96 (4·70)	<0·0001	85·95 (1·27)	<0·0001
SCWT card IV (s)‡	150·94 (5·99)	108·61 (8·51)	<0·0001	n/a (n/a)	n/a
SCWT interference (%)‡	92·13 (3·79)	77·35 (5·43)	0·033	74·20 (1·87)	0·002
SCWT slowing (s)‡	35·45 (5·18)	17·84 (7·34)	0·061	n/a (n/a)	n/a
Fluency (nc)§	20·60 (0·44)	24·17 (0·63)	<0·0001	24·77 (0·41)	<0·0001
CST A (s)‡	27·15 (1·21)	21·07 (1·75)	0·006	17·69 (0·31)	<0·0001
CST B (s)‡	33·38 (2·10)	23·98 (3·08)	0·015	21·81 (0·44)	<0·0001
CST C (s)‡	43·49 (1·73)	33·94 (2·53)	0·003	27·51 (0·65)	<0·0001
CST motor component (s)‡	7·77 (0·31)	6·48 (0·44)	0·022	4·66 (0·06)	<0·0001
Self-reported cognition§	47·80 (1·61)	52·20 (1·71)	0·552	82·40¶ (1·66)	<0·0001

cm=centimetres. nc=number correct. s=seconds. Means (SE) for glioma and NHL/CLL patients represent estimated means based on corrections for age, sex, education, and disease duration. Means and SE for healthy controls are observed scores. See panel for explanation of abbreviations of test variables. n/a=Individually matched data not available. *p values of univariate *t* tests for low-grade glioma patients vs NHL/CLL patients corrected for age, sex, and educational differences. †p values of *t* test comparisons between glioma patients and healthy age-, sex-, and education-matched controls. ‡Lower scores indicate better performance. §Higher scores indicate better performance. ¶Comparison based on historical controls.

Table 2: **Neuropsychological test scores of low-grade glioma patients, NHL/CLL patients, and healthy controls**

for differences in age, sex, education, and disease duration). Although more irradiated glioma patients had deficient test scores than did non-irradiated glioma patients (41 [39%] *vs* 26 [29%], respectively) these differences were not significant (p=0·145). A reanalysis of the data with exclusion of patients who received whole-brain radiotherapy yielded similar results (35 [37%] *vs* 26 [29%], respectively; p=0·168).

Linear regression analysis based on mean test scores showed that the use of radiotherapy was associated with poor scores on one of seven tests in the domain of perception and psychomotor speed, and on two of eight memory tests. Disease duration and objective cognitive functioning were not related in glioma patients, although the interaction between radiotherapy use and disease duration suggested that cognitive functioning in irradiated patients, but not in non-irradiated patients, tends to fall over time. Evidence for this notion was shown by scores of one of seven tests in the domain of perception and psychomotor speed, two of eight memory test scores, and three of 11 tests of attention and executive function (data not shown).

	All glioma patients (n=152)†			Radiotherapy patients only (n=82)†
	Years since diagnosis	Antiepileptics	Tumour lateralisation	fraction dose (Gy)
Perception and psychomotor speed				
LDST reading (nc)	..	..	2·25 (1·01–5·01)‡	..
LDST motor component (nc)	..	6·48 (1·14–36·89)	..	..
Memory				
VVLT max score (nc)	..	..	..	6·23 (1·13–35·36)
Delta score (nc)		..	..	15·83 (2·56–98·00)
Total recall (nc)	..	..	..	6·23 (0·96–40·33)
Delayed recall (nc)	..	..	..	9·80 (1·22–78·72)
Delayed recognition (nc)	..	..	..	6·48 (0·95–44·10)
Attention and executive function				
SCWT card I (s)	..	..	2·54 (1·13–5·69)§	..
SCWT card II (s)	..	..	2·29 (1·10–4·81)§	..
SCWT card III (s)	..	5·79 (2·40–13·95)	5·30 (2·24–12·56)§	..
SCWT interference (%)	..	..	35·34 (4·16–300·01)§	..
Fluency (nc)	1·20 (1·04–1·38)	..	..	..
CST A (s)	1·14 (1·02–1·29)	0·31 (0·10–0·96)	..	..
CST C (s)	..	0·30 (0·09–0·95)	..	..

Only significant relations between neuropsychological parameters and tumour or treatment characteristics are listed. *Adjusted for age, sex, and education. †Due to the listwise exclusion of missing values and exclusion of patients with midline gliomas, the number of patients in the regression analyses differs from that in the univariate analyses summarised in table 2. Because of the exploratory nature of the study, the randomly missing values were not substituted by the overall mean, subgroup means, or a regression estimate. ‡Patients with a tumour in the right hemisphere had more deficits in perceptual functioning. §Patients with a tumour in the left hemisphere had more deficits in attentional functioning. See panel for definitions of test names.

Table 3: **Relative risk* (95% CI) of cognitive deficits according to tumour and treatment characteristics**

Radiotherapy was not associated with reduced levels of self-reported cognitive function, whereas longer disease duration was. In the LGG/RT+ group, an increased total radiotherapy dose was associated with a diminished working memory capacity, whereas a high fraction dose interfered with long-term memory storage and retrieval, as shown by deficient scores on five of eight memory tests. Additionally, patients who received large fraction doses did poorly in two of 11 tests in the domain of attention and executive functioning. Only ten patients received whole-brain radiotherapy with or without boost, therefore we could not assess the differential effect of whole-brain versus focal radiotherapy.

Patients on antiepileptics did poorly in two of seven tests in the domain of perception and psychomotor speed and in four of 11 tests of attention and executive function. Use of these drugs was also associated with reduced self-reported cognitive function. Right hemisphere lesions were associated with reduced ability in one of seven tests in the domain of perception and psychomotor speed, whereas left hemisphere lesions were associated with deficient scores in five of 11 tests of attention and executive function. Patients with a tumour in the left hemisphere had a higher total number of deviant test scores than those with right-hemisphere tumours. Biopsy, as opposed to resection, was negatively associated with memory function as shown by diminished ability in four of eight memory tests.

Logistic regression based on the conservative cognitive criteria (described in the methods) showed that the use of radiotherapy per se was not associated with cognitive disability. Increased disease duration was associated with a slightly increased risk of disability in attention and executive function (table 3). Although the linear regression analyses showed that radiotherapy—alone or in combination with lengthened duration of disease—was associated with reduced cognitive function, high total radiotherapy doses were not related to increased risk of disability in any cognitive domains. However, high fraction doses were associated with disability in nearly all memory-related outcome measures, ranging from a six-fold raised risk for the maximum amount of information stored in long-term memory to an almost 16-fold increased risk in learning capacity (Delta score). Data from post-hoc analyses with correction for differences in age, sex, education, and disease duration showed that cognitive disability was mainly present in patients who received fraction doses exceeding 2 Gy. These 18 patients (who had fraction doses of 2·1–3·0 Gy) constituted 17% of all irradiated patients, and were significantly older than patients who received fraction doses equal to or lower than 2 Gy (mean 47·5 *vs* 41·5 years; p=0·028). They did not, however, differ significantly in tumour localisation or in disease duration.

Antiepileptics were associated with a six-fold increased risk of disability in psychomotor speed underlying perceptual tasks, and in the domain of attention and executive function. Right hemisphere lesions were associated with a two-fold increase in risk of disability in the domain of perception and psychomotor speed, whereas patients with left hemisphere lesions had a two-fold to 35-fold raised risk of disability in attentional function. The type of neurosurgical intervention was not associated with an increased risk of cognitive disability.

Discussion

We have shown that both irradiated and non-irradiated low-grade glioma patients have significantly poorer cognitive functioning than do NHL/CLL patients and, moreover, that these deficiencies are not restricted to a single cognitive domain. Disturbances of cognitive function in glioma patients are even more pronounced when compared with matched healthy controls.

These results are in accord with our previous work, which showed that the tumour itself, rather than irradiation, adversely affects neurobehavioural function in patients with low-grade glioma.[15] However, we have now additionally shown several differences in mean cognitive function scores between low-grade glioma patients who received radiotherapy and those who did not. These differences might, in part, be attributable to the larger sample size (195 *vs* 40 patients), the more extensive cognitive test battery, and the recruitment of patients with a longer disease duration (mean 5·5 *vs* 3·5 years) than in our former study. Our study was not a randomised trial. Thus, selection bias could have influenced the results. However, we believe that because patients were recruited from several hospitals with different therapeutic policies, the risk of such a selection bias was small.

Our results are in accord with data from preclinical and clinical studies that have shown that, apart from radiotherapy variables such as overall dose and treatment volume, the size of the fraction dose is largely responsible for the development of late neurotoxicity.[11] These findings suggest that radiotherapy given in daily fractions exceeding 2 Gy is harmful for the normal surrounding brain over time, rather than conventional external beam radiotherapy itself. This notion is supported by Corn and colleagues,[27] who reported a strong relation between radiotherapy fraction size and risk of late central nervous system injury, and particularly radiation necrosis. The association between clinical and neuroimaging features of late radiation injury (ie, cerebral atrophy and diffuse white matter disease), which has only partly been elucidated, is the subject of a separate paper.[28]

Although, as expected, patients with a tumour in the dominant hemisphere had more cognitive disability than those with a non-dominant hemisphere tumour, cognitive deficits, if present, were not restricted to specific cognitive domains. This finding is in accord with reports that glioma patients tend to have global cognitive deficits rather than the site-specific deficits seen in stroke patients.[29]

We saw a somewhat stronger relation between objective test results and self-reported cognitive function than that noted in earlier studies of patients with brain tumours and those with systemic cancer.[25,30] Cull and colleagues[17] suggested that cognitive complaints of cancer patients might actually indicate feelings of anxiety, depression, or fatigue. Moreover, a dissociation between objective cognitive test results and self-reported cognitive function holds true especially for patients with brain cancer whose judgment could be severely impaired by the tumour.[30]

The differences in cognitive function noted between glioma patients and NHL/CLL patients are more prominent than those between glioma patients who received radiotherapy and those who did not. This finding suggests that the disease itself often results in poor cognitive function. Because most investigations of cognitive function in long-term survivors of brain tumours do not include pretreatment tests of cognition (which is also true of this study), there is a risk that too much of the cognitive disability will be ascribed to the treatment rather than to the tumour. Patients with haematological cancers also seem to have reduced

cognitive function, as we have shown by the differences between the group of such patients without central nervous system involvement and healthy controls. Obviously, the possibility of tumour recurrence presents a psychological burden with resultant anxiety, depression, or fatigue, which can negatively affect the patient's cognitive function.[17] The long-term cognitive impairment in patients with low-grade gliomas is similar to that seen in patients with mild-to-moderate traumatic brain injury.[31] When cognitive function is compromised because of the tumour or treatment, physical, social, and attitudinal factors will affect the patient's ability to compensate for these cognitive limitations.

Apart from the tumour itself and the relatively minor effect of radiotherapy, other medical treatments seem to affect cognitive function negatively. In our study, the use of antiepileptics was equally frequent among irradiated and non-irradiated glioma patients, and patients on antiepileptics had poorer objectively measured and self-reported cognitive function than did those without such treatment. Since 85% of glioma patients in our study reported seizures, we focused on the use of antiepileptics as a potential source of variation in cognitive function. The issue of whether the association seen between use of antiepileptics and cognitive disability relates to the effect of the medication or to the underlying epilepsy merits further attention.

Patients who had a biopsy had poorer cognitive function than patients who underwent a resection. This unexpected finding was not due to a high frequency of biopsies in patients with dominant hemisphere tumours: 42% of such patients underwent biopsy versus 41% of patients with non-dominant hemisphere tumours. Possibly the explanation for this difference in cognitive deficits is that biopsy was the preferred method for large or deeply located tumours. Perioperative injuries (records of which could not be reliably retrieved from the medical charts) were unlikely to be a major risk factor for cognitive deficits in this group, since if they had been responsible, we would have expected patients who underwent resection to have more serious reductions in cognitive functioning than patients who had a biopsy.

Our results suggest that the tumour is the main cause of cognitive deficits, although low-grade glioma patients treated with early radiotherapy did less well in some cognitive tests than did low-grade glioma patients who had no radiotherapy. The main variable responsible for this difference is the fraction dose size. This observation has implications for the decision to treat low-grade glioma with radiotherapy. Since early radiotherapy in low-grade glioma does not enhance survival, and, moreover, could contribute to cognitive deficits, early radiation should not be applied in patients younger than 40 years who have epilepsy. If radiation is applied, either as an initial treatment or at a later stage, fraction doses should not exceed 2 Gy. Because the cognitive disturbances in low-grade glioma patients are mainly affected by the tumour itself, and, possibly, by antiepileptic drugs, these factors deserve more attention than they have previously received.

Contributors

M Klein, J J Heimans, N K Aaronson, H M van der Ploeg, and M J B Taphoorn designed the study. All these authors contributed to data analysis and to the preparation of the manuscript. M Muller helped with the statistical analyses. M Klein coordinated the day-to-day management of the study. J Grit contributed to the design and logistics of the study, and also obtained data and entered them into a statistical database. T J Postma, J J Mooij, R H Boerman, G N Beute, G J Ossenkoppele, G W van Imhoff, A W Dekker, J Jolles, B J Slotman, and H Struikmans contributed to the selection and inclusion of most of the neurological and haematological patients. All these authors reviewed the manuscript, provided important suggestions for revision, and approved the final version submitted for publication.

Conflict of interest statement

None declared.

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