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Original Paper

Quality of Life after Radiation Therapy of Cerebral Low-grade Gliomas of the Adult: Results of a Randomised Phase III Trial on Dose Response (EORTC Trial 22844)

G.M. Kiebert,[1] D. Curran,[2] N.K. Aaronson,[3] M. Bolla,[4] J. Menten,[5] E.H.J.M. Rutten,[6] E. Nordman,[7] M.E. Silvestre,[8] M. Pierart,[2] A.B.M.F. Karim[9] on behalf of the EORTC Radiotherapy Co-operative Group

[1]MEDTAP International, 27 Gilbert Street, London W1Y 1RL U.K.; [2]EORTC Data Centre, Brussels, Belgium; [3]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [4]Centre Hospitalier Regional Universitaire, Grenoble, France; [5]University Hospital Gasthuisberg, Leuven, Belgium; [6]University Hospital St Radboud, Nijmegen, The Netherlands; [7]Turku University Central Hospital, Turku, Finland; [8]Hospital Santa Maria, Lisbon, Portugal; and [9]Free University Hospital, Amsterdam, The Netherlands

In 1985, the EORTC Radiotherapy Co-operative Group launched a randomised phase III study comparing high-dose (59.4 Gy in 6.5 weeks) versus low-dose (45 Gy in 5 weeks) radiotherapy with conventional techniques in patients diagnosed with low-grade cerebral glioma. The primary endpoint of the study was survival. No difference in survival was observed between the two treatment strategies. A quality of life (QoL) questionnaire consisting of 47 items assessing a range of physical, psychological, social, and symptom domains was included in the trial to measure the impact of treatment over time. Patients who received high-dose radiotherapy tended to report lower levels of functioning and more symptom burden following completion of radiotherapy. These group differences were statistically significant for fatigue/malaise and insomnia immediately after radiotherapy and in leisure time and emotional functioning at 7–15 months after randomisation. These findings suggest that for conventional radiotherapy for low-grade cerebral glioma, a schedule of 45 Gy in 5 weeks not only saves valuable resources, but also spares patients a prolonged treatment at no loss of clinical efficacy.

Key words: low-grade gliomas, radiotherapy, quality of life
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INTRODUCTION

To date, the optimal treatment strategy for low-grade gliomas remains controversial [1–3]. Operative resection and/or external beam radiotherapy, interstitial radiosurgery, radiosurgery and stereotactic radiotherapy have all been reported in the literature as potentially valuable treatment modalities for specific subgroups of patients (see [4]) for an overview). Almost all reports in the literature are based on retrospective, cross-sectional studies in heterogeneous cohorts of patients. Although a few are prospective studies, longitudinal data with sufficient long-term follow-up from randomised clinical trials are not found in the literature with the exception of a recent EORTC study [4]. Another limitation is that most studies focus only on duration of survival or time to progression as relevant outcome parameters. In recent years it has been recognised that cancer and its treatment have a major impact on people's lives. Oncological treatments can cause considerable short-term and long-term side-effects and cure is seldom guaranteed. Therefore, expected gains and losses have to be balanced against each other when deciding on the optimal treatment. It is for this reason that quality of life (QoL) research has become an important issue in oncology. However, of the recent reports concerning the management of low-grade gliomas, only very few studies have addressed this issue [5–8]. In these studies the definition and assessment of

Correspondence to G.M. Kiebert.
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QoL vary substantially. For instance, Scerrati and colleagues [5] and Kreth and associates [6] define QoL as the performance status of the patient and use the well-known Karnofsky scale as the instrument to measure this. Lunsford and colleagues [7] define satisfactory QoL as 'prolonged normal functioning and employment status' and also employ the Karnofsky scale. Van Kampen and associates [8] equate QoL with clinical (primarily neurological) symptoms. Although it is mentioned in this latter study that a subjective questionnaire was administered to the patients, no description of the instrument is provided nor are any data presented. As far as could be determined, all presented data involved clinicians' ratings.

The approaches in these studies do not meet the principle criteria agreed upon by many QoL researchers, i.e. that QoL is a multidimensional, dynamic, and subjective construct. Translated into methodological terms, this implies that QoL questionnaires should measure a minimal, basic set of health-related QoL domains (physical, psychological, social well-being and functional abilities) as well as specific disease- and/or treatment-related symptoms that may occur, the measurement should be repeated over time, and it should preferably be based on patients' own subjective ratings.

Two studies from a single institute were found in the recent literature that focused specifically on the evaluation of QoL in patients treated with radiation for low-grade glioma using a more comprehensive approach [9, 10]. In these studies, different cohorts of patients were tested on neurological status, neuropsychological, cognitive functioning, and affective state using standardised techniques. In a structured interview patients were evaluated regarding socio-economic status, physical complaints, problems with daily activities, social functioning and perceived social support, overall health perception and well-being and treatment experiences and outlook. The results showed that, compared with a control group of patients with non-Hodgkin's lymphoma or chronic lymphatic leukaemia, the patients with low-grade glioma had significantly more cognitive disturbances and suffered more frequently from fatigue and depressed mood. There was no difference between the two groups of low-grade gliomas, i.e. those who received or did not receive radiotherapy. It was thus concluded that radiotherapy did not cause these disturbances and had no negative impact on the QoL of these patients. However, the small number of patients included in this study may not have been sufficient to detect significant differences. Although not using a longitudinal design, these two studies did assess QoL in a relatively comprehensive manner *and* from the perspective of the patient. The measures used encompassed the basic health-related domains as well as a number of disease-specific problems. However, in many clinical research settings, particularly if they are multicentre in nature, it is not feasible to carry out extensive patient interviews to evaluate neuropsychological functioning. Many institutions do not have the required infrastructure, tools, or specialists to conduct such a comprehensive evaluation. Therefore, in large, multicentre studies a compromise between what is desirable and what is feasible is often necessary. A more feasible alternative is to employ standardised self-report questionnaires containing a core instrument supplemented with disease- and treatment-specific questions, administered in a longitudinal design. Such an approach is currently being used by the European Organisation for Research and Treatment of Cancer (EORTC).

In 1985, the EORTC Radiotherapy Co-operative Group launched a randomised phase III study comparing a high-dose (59.4 Gy in 6.5 weeks) versus low-dose (45 Gy in 5 weeks) of radiotherapy with conventional techniques in patients diagnosed with low-grade cerebral glioma. The primary endpoints of the study were dose response in terms of overall and progression-free survival. The detailed biomedical results of this study have recently been published [4]. The results showed no significant difference between the two doses of radiotherapy in terms of overall survival or progression-free survival after a median follow-up period of 74 months. Prognostic factor analysis indicated that T-classification, neurological status and surgery (amount of tumour removed) were the most important variables both in univariate and multivariate analysis of both overall and progression-free survival.

In this multinational trial, patients' symptoms experience and QoL were also evaluated, based on ratings provided by both the patient and the physician. The present paper reports on the results of these aspects of the study.

PATIENTS AND METHODS

From April 1985 until September 1991, 379 patients diagnosed with low-grade cerebral glioma were randomised, after informed consent was obtained, to receive either high-dose (59.4 Gy) or low-dose (45 Gy) radiotherapy with conventional techniques. QoL was a secondary, non-mandatory endpoint in this study. If the institution and the patient agreed, QoL data were collected by means of a self-administered questionnaire. The schedule of assessment was before and after radiotherapy, at 3, 6, and 12 months after radiotherapy and annually thereafter.

Patients' questionnaire

Since at the start of the study no well-validated, standardised QoL questionnaire was available for this population of patients, a questionnaire was constructed to meet the requirements of this study protocol. The questionnaire designed for this study was primarily adapted from a variety of sources including the Sickness Impact Profile (SIP) [11], the Rand Corporation Health Insurance Study battery of questionnaires, the Center for Epidemiological Studies Depression Scale, and from previous questionnaires employed within the EORTC. A preliminary version of the questionnaire was pretested on a sample of patients at the Free University Hospital in Amsterdam, The Netherlands [12]. The final questionnaire consisted of 47 items assessing a range of physical, psychological, social and symptom domains (see Appendix). The hypothesised scale structure of the questionnaire is presented in Table 1.

Clinicians' rating of patients' neurological signs and symptoms

Clinicians were asked to evaluate at regular intervals a number of key domains and symptoms pertaining to patients' QoL. These elements were: performance status (WHO scale); neurological signs and symptoms, including headache, epilepsy, mental disturbances, sensory deficits, aphasia and cranial nerve abnormalities. Signs and symptoms were rated using a four-point Likert type scale with categories 1 = absent, 2 = mild, 3 = moderate, 4 = severe. Data were collected prior to the start of radiotherapy, at 3, 6, 12, 18, 24 months after radiotherapy and annually thereafter and documented on the clinical case report forms. The collection of these

Table 1. *Patient's questionnaire: construction of scales*

Scale	Items	Source
Physical functioning	1–8	Rand HIS-Physical capacities scale
Leisure time	9–11	EORTC questions
Memory and concentration	12–17	Adapted from the SIP
Social interaction	18–22	Adapted from the SIP
Work	23–26	Adapted from the SIP
Paralysis	27	EORTC questions
Epilepsy	28	EORTC questions
Headaches	29	EORTC questions
Fatigue/malaise	30–34	EORTC questions
Insomnia	35	EORTC questions
Sexual functioning	36–37	EORTC questions
Emotional functioning	38–44	Adapted from the CES-D
Overall well-being/satisfaction	45–47	EORTC questions

clinician-generated data was mandatory for all patients and at all timepoints mentioned above.

Statistical considerations

The reliability (i.e. internal consistency) of the multi-item scales of baseline data was assessed using Cronbach's alpha coefficient. As recommended by Nunally and Bernstein [13], alpha coefficients ≥ 0.70 were considered the minimal standards of reliability for the scales. Scale scores were calculated by averaging items within scales and transforming average scores linearly to a 0–100 scale, with higher scores representing a higher level of functioning or a lower level of symptoms. In the presence of missing items within a scale, provided at least half the items were completed, the scale score was calculated using the completed items which were present for that respondent [14, 15]. A two-sided Wilcoxon rank sum test was used to compare QoL scores in the two treatment arms. The analysis was performed on all patients according to the 'intention-to-treat' principle. Finally, descriptive statistics were used to examine clinicians' ratings of neurological signs and symptoms and to compare clinicians' ratings with those of their patients.

RESULTS

Patient accrual and follow-up

Of the 27 institutions that participated in the clinical trial, 14 contributed to the QoL part of the study. In total, 180 patients (47% of the total patient sample) completed at least one QoL questionnaire. The quantity and schedule of completion of questionnaires varied considerably from patient to patient, but compliance was similar in both study arms. To include as many patients as possible in the analysis, it was decided to concentrate on the first three assessments of QoL (see Table 2). Compliance with further follow-up was so poor that analysis of these latter data was considered to be inappropriate. Baseline scores were analysed for descriptive purposes only and were not used to compare pretreatment QoL scores with post-treatment QoL scores due to the limited sample size.

Table 2. *Compliance with completion of quality of life questionnaires*

	Patients			
Assessment	Dead	Lost to follow-up	Known to be alive	Forms received *n* (%)
Baseline before radiotherapy	0	0	345	82 (22)
After radiotherapy until 6 months after randomisation	9	9	327	113 (35)
7–15 months	26	17	302	109 (36)
19–30 months	57	28	260	79 (30)
36–60 months	124	78	143	61 (43)

A few patients completed more than one questionnaire within the same time period. For these patients, the questionnaire that was completed first during that time period was included in the analysis.

Patient characteristics

The characteristics of all patients at randomisation are presented in Table 3. Patient characteristics of those who completed a QoL questionnaire at baseline and those who did not were compared and no statistically significant differences were observed.

Since QoL was assessed in a subset of patients whose composition changed over time, the distribution of patient characteristics in these two subsets is also provided. A QoL questionnaire was completed by 113 patients immediately after radiotherapy. Patient characteristics of this group at entry were compared with the characteristics of patients at entry who did not complete a questionnaire. No obvious or statistically significant differences were observed. Between 7 and 15 months after randomisation a QoL questionnaire was completed by 109 patients. The characteristics of these patients at entry were compared with those who did not complete a questionnaire and again no obvious or statistically significant differences were observed.

Reliability of the QoL instrument

Table 4 presents Cronbach's alpha coefficient for all of the multi-item scales. The social functioning scale was the only multi-item scale which failed to meet the minimal standards of reliability (Cronbach's alpha coefficient ≥ 0.70). Interscale correlations ranged from 0.11 to 0.62 (median = 0.42) indicating that, although related, the scales were assessing distinct QoL components.

Patients' self-reported QoL

The results pertaining to the patients' self-reported QoL at baseline, following radiotherapy, and at 7–15 months post-randomisation are presented in Figure 1. Baseline results (Figure 1a) are the medians and their 5–95 percentile range of all 82 patients who completed a questionnaire prior to the start of radiotherapy. A ceiling effect was indicated for the scales assessing physical functioning and leisure time, with the medians located at the maximum scale level, indicating the highest level of functioning assessed. The lowest median scores were found for fatigue/malaise and overall well-being.

At postradiotherapy (Figure 1b), the patients who had received the higher radiation dose tended to report lower levels of functioning and more symptom burden than those who had received the lower dose. These group differences were statistically significant for fatigue/malaise and insomnia only (the latter based on a single item measure not included in the figure (81% in the low-dose group indicated having no trouble sleeping versus 64% in the high-dose group ($P = 0.05$)). At the 7–15 months postrandomisation follow-up

Table 3. Patient characteristics

	All patients at entry		Patients with quality of life forms immediately after radiotherapy		Patients with quality of life forms 7–15 months after radiotherapy	
	Low-dose ($n=174$) n (%)	High-dose ($n=171$) n (%)	Low-dose ($n=57$) n (%)	High-dose ($n=56$) n (%)	Low-dose ($n=52$) n (%)	High-dose ($n=57$) n (%)
Gender						
Male	107 (61)	90 (53)	33 (58)	28 (50)	33 (63)	28 (49)
Female	67 (39)	81 (47)	24 (42)	28 (50)	19 (37)	29 (51)
Age (years)						
< 35	60 (34)	59 (35)	22 (39)	18 (32)	20 (38)	16 (28)
35–44	60 (34)	51 (30)	17 (30)	18 (32)	15 (29)	20 (35)
≥ 45	54 (31)	61 (36)	18 (32)	20 (36)	17 (33)	21 (37)
Employment						
Full-time	63 (36)	81 (47)	20 (35)	30 (54)	18 (35)	28 (49)
Other	109 (63)	88 (51)	36 (63)	25 (45)	33 (63)	27 (47)
Unknown	2 (1)	2 (1)	1 (2)	1 (2)	1 (2)	2 (4)
Type of surgery						
< 50% tumour excised	77 (44)	82 (48)	23 (40)	30 (54)	23 (44)	29 (51)
≥ 50% tumour excised	97 (56)	89 (52)	34 (60)	26 (46)	29 (56)	28 (49)
Histopathology						
Astrocytoma	123 (71)	117 (68)	37 (65)	35 (63)	31 (60)	35 (61)
Oligodendroglioma	35 (20)	38 (22)	15 (26)	17 (30)	15 (29)	18 (32)
Mixed	16 (9)	16 (9)	5 (9)	4 (7)	6 (12)	4 (7)
Grade of tumour						
0 or 1	15 (9)	16 (9)	6 (11)	6 (11)	7 (13)	8 (14)
> 1	159 (91)	155 (91)	51 (89)	50 (89)	45 (87)	49 (86)
Neurological status						
1	99 (57)	100 (58)	32 (56)	32 (57)	31 (60)	37 (65)
2–4	75 (43)	71 (42)	25 (44)	24 (43)	21 (40)	20 (35)
WHO performance status						
0	56 (32)	44 (26)	19 (33)	16 (29)	16 (31)	17 (30)
1–3	118 (68)	127 (74)	38 (67)	40 (71)	36 (69)	40 (70)

(Figure 1c) a similar pattern of results favouring the lower dose radiotherapy arm was observed. Statistically significant group differences favouring the low-dose radiotherapy arm were found for leisure time activity and emotional functioning.

No statistically significant changes from baseline (pre-treatment) to post-treatment scores on any of the QoL composed functioning scales were observed.

Clinicians' ratings of patients' neurological signs and symptoms

Data were analysed in two different ways. First we compared clinicians' ratings of neurological signs and symptoms in patients in the two treatment arms immediately after radiotherapy and at 7–15 months after randomisation. No significant differences in impairment were observed between the two treatment arms at either point in time (data not shown). Second, we compared the frequency distribution of the lowest scores, which indicates in this case maximum impairment, of neurological signs and symptoms per patient at any given point in time as rated by the clinician. Since this method takes all available data into account, 'worst' score analysis is more conservative than a comparison at the two fixed points in time. The results are presented in Table 5. No significant differences in impairment were observed between the two treatment arms.

Table 4. Internal consistency of the quality of life scales based on baseline scores

Scale	Number of items	Number of patients	Cronbach's alpha
Physical functioning	8	78	0.77
Leisure time	3	81	0.75
Memory and concentration	6	81	0.84
Social interaction	5	78	0.54
Work	4	14	0.76
Fatigue/malaise	5	79	0.83
Sexual functioning	2	69	0.77
Emotional functioning	7	70	0.70
Overall well-being/satisfaction	3	79	0.76

Comparison of patients' and clinicians' ratings

Ratings were available from both clinicians and patients on two variables, headache and epileptic seizures. Table 6 presents the results of a comparison of the clinicians' and patients' ratings. Assuming that the response categories 'not at all', 'a bit', 'quite a bit', and 'very much' correspond to 'absent', 'mild', 'moderate', and 'severe', respectively, perfect agreement would show all ratings to be on the diagonal (bold in the table). This was the case in 60/104 (58%) of the ratings for headache. In 42/104 (40%) cases clinicians underreported the degree of headaches in patients and in 2 (2%) cases the patients reported absence of headache whereas the clinicians reported mild headaches. Similar results were found for the presence of epileptic seizures. In 79/105 (75%) cases clinicians and patients agreed; in 21/105 (20%) cases clinicians

underreported the degree of seizures, and in 4 cases (4%) the patients reported fewer epileptic seizures than the clinicians.

DISCUSSION

The principal objective of EORTC trial 22844 was to investigate whether high-dose radiotherapy leads to a significantly better overall or progression-free survival than low-dose radiotherapy in patients with low-grade glioma. To date (an update of the clinical data will be reported after 7 years of follow-up), this multicentre randomised controlled trial showed no clinical benefit in terms of overall survival and progression-free survival of high-dose radiotherapy (59.4 Gy) as compared with low-dose (45 Gy) using conventional techniques for treating low-grade cerebral glioma in adults.

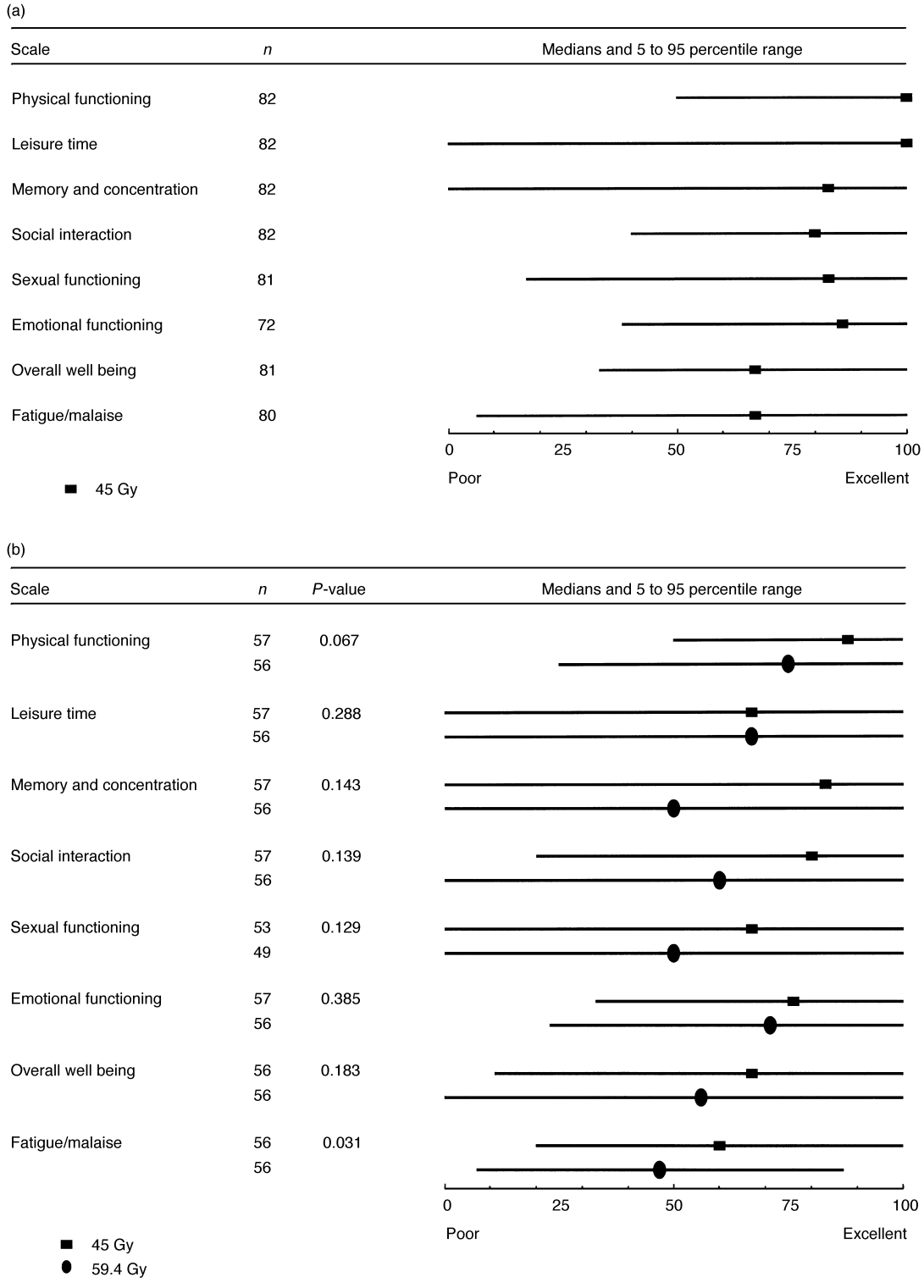

Figure 1. (a) Baseline quality of life scores. (b) Quality of life scores immediately after radiotherapy. (c) Quality of life scores 7–15 months after randomisation (see overleaf).

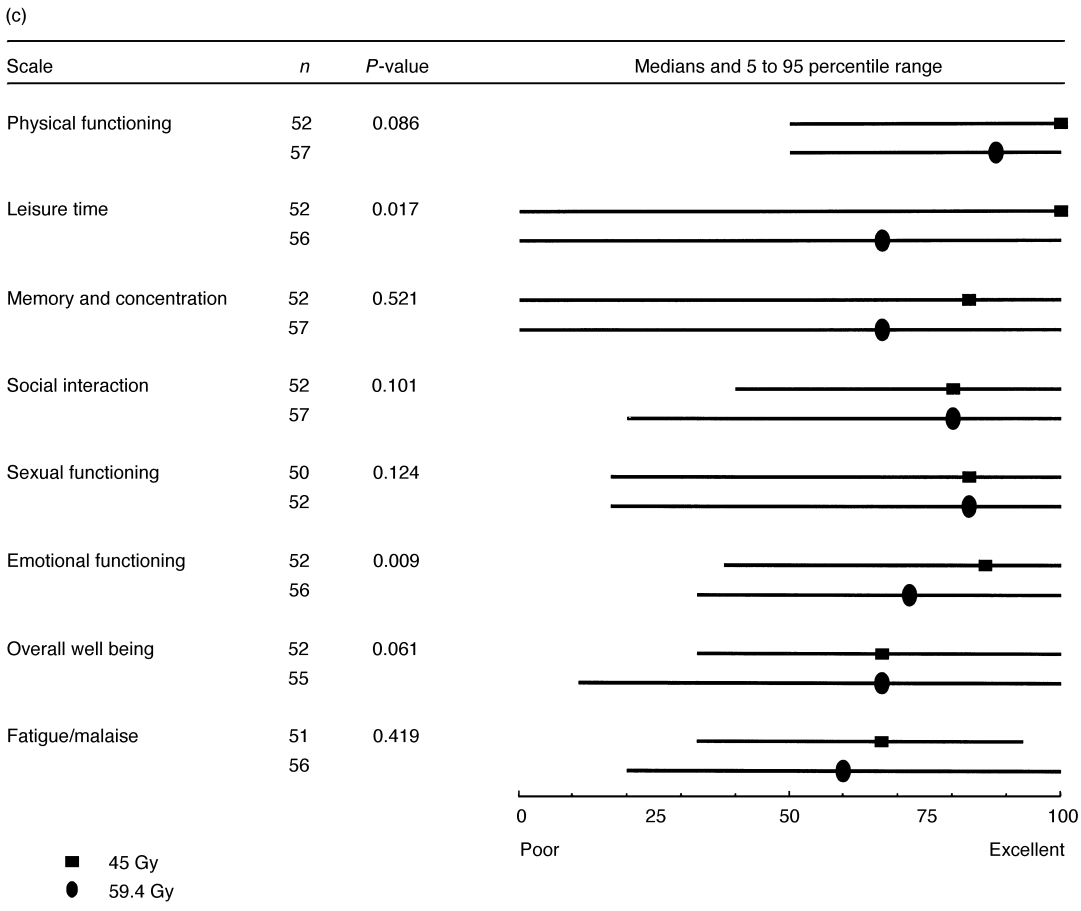

Figure 1. ***continued.***

Table 5. *Frequency distribution of the lowest (i.e. maximum impairment) scores of neurological signs and symptoms per patient at any given point in time as rated by the clinician*

	Absent *n* (%)	Mild *n* (%)	Moderate *n* (%)	Severe *n* (%)	Missing *n* (%)
Headache					
Low-dose ($n=174$)	87 (50)	48 (28)	24 (14)	7 (4)	8 (5)
High-dose ($n=171$)	88 (51)	50 (29)	20 (12)	3 (2)	10 (6)
Epilepsy					
Low-dose ($n=154$)	70 (40)	55 (32)	26 (15)	15 (9)	8 (5)
High-dose ($n=171$)	73 (43)	45 (26)	36 (21)	7 (4)	10 (6)
Mental disturbance					
Low-dose ($n=174$)	83 (48)	55 (32)	22 (13)	7 (4)	7 (4)
High-dose ($n=171$)	81 (47)	41 (24)	28 (16)	11 (6)	10 (6)
Motor disturbance					
Low-dose ($n=174$)	96 (55)	39 (22)	20 (11)	11 (6)	8 (5)
High-dose ($n=171$)	91 (53)	36 (21)	23 (13)	11 (6)	10 (6)
Sensory deficit					
Low-dose ($n=174$)	135 (78)	25 (14)	4 (2)	2 (1)	8 (5)
High-dose ($n=171$)	135 (79)	18 (11)	7 (4)	1 (1)	10 (6)
Aphasia					
Low-dose ($n=174$)	129 (74)	23 (13)	10 (6)	4 (2)	8 (5)
High-dose ($n=171$)	125 (73)	20 (12)	13 (8)	3 (2)	10 (6)
Cranial nerve abnormality					
Low-dose ($n=174$)	142 (82)	19 (11)	4 (2)	1 (1)	8 (5)
High-dose ($n=171$)	138 (81)	14 (8)	9 (5)	0 (0)	10 (6)

A secondary objective was to evaluate the impact of high-dose versus low-dose radiotherapy on the QoL of these patients. In general, the results suggest no major differences in QoL between the two treatment arms. Patients who received high-dose radiotherapy reported significantly more fatigue/malaise and insomnia immediately after radiotherapy, and more impairment in leisure time activities and poorer emotional functioning at 7–15 months postrandomisation. For the

Table 6. *Cross-tabulation of headache and epilepsy as judged by the patient and the clinician*

	Do you have headaches?/ Do you have any epileptic seizures?				
	Not at all	A little	Quite a bit	Very much	Total
Headache					
Absent	**47**	24	7	1	79
Mild	2	**12**	6	2	22
Moderate	0	**0**	0	2	2
Severe	0	0	0	**1**	1
Total	49	36	13	6	104
Epilepsy					
Absent	**65**	9	7	1	82
Mild	2	**11**	4	0	17
Moderate	0	**2**	2	0	4
Severe	0	0	1	**1**	2
Total	67	22	14	2	105

remaining QoL domains, no statistically significant differences between the two treatment arms were found. Based on these findings we thus conclude that conventional radiation therapy for low-grade cerebral glioma using the treatment schedule of 45 Gy in 5 weeks is at least as good as prolonged treatment in terms of clinical efficacy, survival and QoL. In addition, it saves valuable megavoltage space.

At the same time, we recognise the need to exercise some caution in the interpretation of these results due to methodological and logistical problems encountered in conducting this QoL study. Because QoL assessment was an optional part of the clinical trial, the current results are based on only a subset of the total patient sample. Unfortunately, some of the centres who accrued a large number of patients in this trial decided not to participate in this aspect of the study. Patient participation in the centres who did consent to QoL evaluation was good, but for those enrolled in the study and from whom we received no QoL data, we do not have the information whether this was due to patient refusal or that the patient was not asked to complete these forms. Continuous monitoring of the QoL data was not done. However, before the analysis was performed we asked all institutions to check their files to ensure that all QoL questionnaires had been returned.

Although a comparison of the background and clinical characteristics of those patients who completed any QoL questionnaires with those who did not failed to reveal any statistically significant differences, we cannot entirely rule out the possibility of a selection bias. This, of course, which if present, could limits the generalisability of the results.

A second study limitation concerns the heterogeneity in the timing of the questionnaire administration. Although a fixed assessment schedule was prescribed in the trial protocol, the compliance with the follow-up schedule was far from optimal. Unfortunately, no information was available to aid in the interpretation of missing forms, or of the variability in the timing of the completion of the questionnaires. While we suspect that this was primarily due to administrative error and logistical problems, we cannot rule out the possibility that the missing or delayed forms were due to patient-related problems (e.g. deteriorated health status). In any case, the problems encountered in carrying out this study emphasise the importance of making the QoL component of clinical trials mandatory, and of closely monitoring the compliance with the data collection schedule throughout the course of a trial. The findings of only a moderate degree of agreement between clinicians' and patients' ratings of headache and epileptic seizures are consistent with other studies that have examined the value of proxy ratings in QoL evaluations [16]. In a recent study, Stephens and colleagues [17] reported on the interchangeability of doctors' and patients' ratings of physical symptoms in two large-scale randomised clinical trials in lung cancer where they found 78% complete agreement. In this report, disagreement increased with increasing severity of symptoms, and there was a consistent bias towards underestimation of the severity of problems by the doctors. Taphoorn and associates [10] also found a discrepancy between subjective and objective measures of cognitive functioning in patients with low-grade glioma. It is important to note that, in the case of brain cancer, one cannot necessarily interpret discrepancies between ratings provided by clinicians and their patients as evidence of the inaccuracy or biased nature of clinician-generated information. Deficits in cognitive functioning may, in fact, impair the ability of some patients to provide valid and reliable feedback regarding their functional health and symptom experience [18].

We had, though, expected a higher degree of concordance between clinicians and patients in rating epileptic seizures, in the sense that these symptoms are relatively easy to quantify and less susceptible to ambiguous interpretation. If these findings were to be confirmed in other studies, one might question the common practice of evaluating toxicity and side-effects in phase II studies exclusively on the basis of clinicians' judgements.

1. Recht LD, Lew R, Smith TW. Suspected low-grade glioma: is deferring treatment safe? *Ann Neurol* 1992, **31**, 431–436.
2. Janny P, Cure H, Mohr M, *et al.* Low grade supratentorial astrocytomas. Management and prognostic factors. *Cancer* 1994, **73**, 1937–1945.
3. Levin VA. Controversies in the treatment of low-grade astrocytomas and oligodendrogliomas. *Curr Opin Oncol* 1996, **8**, 175–177.
4. Karim ABMF, Maat B, Hatlevoll R, *et al.* A randomised trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) study 22844. *Int J Radiat Oncol Biol Phys* 1996, **36**, 549–556.
5. Scerrati M, Montemaggi P, Iacoangeli M, Roselli R, Rossi GF. Interstitial brachytherapy for low-grade cerebral gliomas: analysis of results in a series of 36 cases. *Acta Neurochirurgica* 1994, **131**, 97–105.
6. Kreth FW, Faist M, Warnke PC, Rossner R, Volk B, Ostertag CB. Interstitial radiosurgery of low-grade gliomas. *J Neurosurg* 1995, **82**, 418–429.
7. Lunsford LD, Somaza S, Kondziolka D, Flickinger JC. Survival after stereotactic biopsy and irradiation of cerebral non-anaplastic, nonpilocytic astrocytoma. *J Neurosurg* 1995, **82**, 523–529.
8. van Kampen M, Engenhart-Cabillic R, Debus J, Hess T, Schad LR, Wannenmacher MF. Low-grade astrocytoma: treatment with conventionally fractionated stereotactic radiation therapy. *Radiology* 1996, **201**, 275–278.
9. Taphoorn MJB, Klein Schiphorst A, Snoek FJ, *et al.* Cognitive functions and quality of life in patients with low-grade glioma: the impact of radiotherapy. In Karim ABMF, Laws ER, eds. *Glioma Principles and Practice in Neurooncology*. Heidelberg, Springer, 1991.
10. Taphoorn MJB, Heimans JJ, Snoek FJ, *et al.* Assessment of quality of life in patients treated for low-grade glioma: a preliminary report. *J Neurol Neurosurg Psychiat* 1992, **55**, 372–376.
11. Bergner M, Bobbitt BR, Carter WB, Gilson BS. The sickness impact profile: development and final revision of a health status measure. *Med Care* 1981, **19**, 787–805.
12. Karim ABMF. Cure and quality of life after treatment for glioma. In Karim ABMF, Laws ER, eds. *Glioma: principles and practice in neurooncology*. Heidelberg, Springer, 1991.
13. Nunally JC, Bernstein IH. *Psychometric Theory*. New York, McGraw-Hill, 1994.
14. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health survey; manual and interpretation guide*. Boston, The Health Institute, New England Medical Center, 1993.
15. Morris J, Coyle D. Quality of life questionnaires in cancer clinical trials: imputing missing values. *Psycho-Oncology* 1994, **3**, 215–222.
16. Sprangers MAG, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. *J Clin Epidemiol* 1992, **45**, 743–760.
17. Stephens RJ, Hopwood P, Girling DJ, Machin D. Randomised trials with quality of life endpoints: are doctor's ratings of patients' physical symptoms interchangeable with patients' self-ratings?. *Qual Life Res* 1997, **6**, 225–236.
18. Sneeuw KCA, Aaronson NK, Osoba D, *et al.* The use of significant others as proxy raters of the quality of life of patients with brain cancer. *Med Care* 1997, **35**, 490–506.

APPENDIX
QUESTIONNAIRE

We are interested in some things about you and your health. There are no 'right' or 'wrong' answers. Please answer all the questions yourself by circling the number that best applies to you. The information that you provide will remain strictly confidential.

Please fill in today's date: Day____ Month _____ Year ____

		No	Yes
1.	Can you do hard activities at home like scrubbing floors or lifting or moving heavy furniture?	1	2
2.	If you wanted to, could you participate in active sports such as swimming, tennis or rowing a boat?	1	2
3.	If you wanted to, could you run a short distance?	1	2
4.	Can you walk uphill or upstairs?	1	2
5.	Can you do moderate work at home like moving a chair or pushing a vacuum cleaner?	1	2
6.	Can you do light work around the house like dusting or washing dishes?	1	2
7.	Can you walk around inside the house?	1	2
8.	Do you need help with eating, dressing or using the toilet?	1	2
9.	Are you less interested than usual in your hobbies and leisure time activities?	1	2
10.	Are you limited in any way in following your regular hobbies and interests?	1	2
11.	Does your condition keep you from following your regular hobbies and interests?	1	2
12.	Do you finish things that you start?	1	2
13.	Do you have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things?	1	2
14.	Do you forget a lot, for example, things that happened recently, where you put things, appointments?	1	2
15.	Do you have difficulty doing activities involving concentrating and thinking?	1	2
16.	Do you make more mistakes than usual?	1	2
17.	Do you have trouble keeping your attentions on any activity for long?	1	2
18.	Are you going out less to visit people?	1	2
19.	Do you often act irritable toward those around you?	1	2
20.	Are you doing fewer social activities with groups of people?	1	2
21.	Do you talk less with those around you?	1	2
22.	Do you stay alone much of the time?	1	2

ANSWER QUESTIONS 23 TO 26 IF YOU ARE CURRENTLY WORKING AT A JOB. IF YOU ARE NOT CURRENTLY WORKING, PLEASE GO TO QUESTION 27.

		No	Yes
23.	Are you accomplishing as much as usual at work?	1	2
24.	Do you often act irritably toward your work associates?	1	2
25.	Are you working shorter hours?	1	2
26.	Do you work only for short periods of time or take frequent rests?	1	2

CIRCLE THE NUMBER FOR EACH STATEMENT WHICH BEST DESCRIBES HOW OFTEN YOU FELT OR BEHAVED THIS WAY DURING THE PAST WEEK

		Not at all	A little	Quite a bit	Very much
27.	Did you have difficulty with feeling or movement on one side of your body?	1	2	3	4
28.	Did you have any epileptic seizures?	1	2	3	4
29.	Did you have headaches?	1	2	3	4
30.	Did you feel energetic?	1	2	3	4
31.	Did you need to rest?	1	2	3	4
32.	Were you tired?	1	2	3	4
33.	Where you physically well?	1	2	3	4
34.	All in all, did you feel ill?	1	2	3	4
35.	Did you have trouble sleeping?	1	2	3	4
36.	Were you limited in your sexual activity?	1	2	3	4
37.	How satisfied were you with your level of sexual activity?	1	2	3	4
38.	Did you feel sad?	1	2	3	4
39.	Did you feel that you could not shake off the "blues" even with help from your family and friends	1	2	3	4
40.	Did you feel lonely?	1	2	3	4
41.	Did you feel depressed?	1	2	3	4
42.	Did you feel fearful?	1	2	3	4
43.	Were you bothered by things that usually don't bother you?	1	2	3	4
44.	Did you feel that things were going your way?	1	2	3	4
45.	How satisfied were you with your level of daily activity?	1	2	3	4
46.	How satisfied were you with your physical condition?	1	2	3	4
47.	Overall, how satisfied did you feel with your life?	1	2	3	4

PLEASE CHECK THAT YOU HAVE ANSWERED ALL OF THE QUESTIONS