Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

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Summary

Background Most patients with glioblastoma are older than 60 years, but treatment guidelines are based on trials in patients aged only up to 70 years. We did a randomised trial to assess the optimum palliative treatment in patients aged 60 years and older with glioblastoma.

Methods Patients with newly diagnosed glioblastoma were recruited from Austria, Denmark, France, Norway, Sweden, Switzerland, and Turkey. They were assigned by a computer-generated randomisation schedule, stratified by centre, to receive temozolomide (200 mg/m² on days 1–5 of every 28 days for up to six cycles), hypofractionated radiotherapy (34·0 Gy administered in 3·4 Gy fractions over 2 weeks), or standard radiotherapy (60·0 Gy administered in 2·0 Gy fractions over 6 weeks). Patients and study staff were aware of treatment assignment. The primary endpoint was overall survival. Analyses were done by intention to treat. This trial is registered, number ISRCTN81470623.

Findings 342 patients were enrolled, of whom 291 were randomised across three treatment groups (temozolomide n=93, hypofractionated radiotherapy n=98, standard radiotherapy n=100) and 51 of whom were randomised across only two groups (temozolomide n=26, hypofractionated radiotherapy n=25). In the three-group randomisation, in comparison with standard radiotherapy, median overall survival was significantly longer with temozolomide (8·3 months [95% CI 7·1–9·5; n=93] *vs* 6·0 months [95% CI 5·1–6·8; n=100], hazard ratio [HR] 0·70; 95% CI 0·52–0·93, p=0·01), but not with hypofractionated radiotherapy (7·5 months [6·5–8·6; n=98], HR 0·85 [0·64–1·12], p=0·24). For all patients who received temozolomide or hypofractionated radiotherapy (n=242) overall survival was similar (8·4 months [7·3–9·4; n=119] *vs* 7·4 months [6·4–8·4; n=123]; HR 0·82, 95% CI 0·63–1·06; p=0·12). For age older than 70 years, survival was better with temozolomide and with hypofractionated radiotherapy than with standard radiotherapy (HR for temozolomide *vs* standard radiotherapy 0·35 [0·21–0·56], p<0·0001; HR for hypofractionated *vs* standard radiotherapy 0·59 [95% CI 0·37–0·93], p=0·02). Patients treated with temozolomide who had tumour *MGMT* promoter methylation had significantly longer survival than those without *MGMT* promoter methylation (9·7 months [95% CI 8·0–11·4] *vs* 6·8 months [5·9–7·7]; HR 0·56 [95% CI 0·34–0·93], p=0·02), but no difference was noted between those with methylated and unmethylated *MGMT* promoter treated with radiotherapy (HR 0·97 [95% CI 0·69–1·38]; p=0·81). As expected, the most common grade 3–4 adverse events in the temozolomide group were neutropenia (n=12) and thrombocytopenia (n=18). Grade 3–5 infections in all randomisation groups were reported in 18 patients. Two patients had fatal infections (one in the temozolomide group and one in the standard radiotherapy group) and one in the temozolomide group with grade 2 thrombocytopenia died from complications after surgery for a gastrointestinal bleed.

Interpretation Standard radiotherapy was associated with poor outcomes, especially in patients older than 70 years. Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma. *MGMT* promoter methylation status might be a useful predictive marker for benefit from temozolomide.

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Introduction

Glioblastoma is the most frequent primary brain tumour and is mainly seen in people older than 60 years. Median survival is less than 1 year.[1,2] Chemoradiotherapy with temozolomide became the standard of care in 2004, but its introduction was based on a pivotal study in which patients were aged 70 years or younger; increasing age was found to be a negative prognostic factor.[3,4] Elderly and frail patients might, therefore, not be viewed as candidates for combined therapy, and extensive treatment might not be seen as justifiable owing to the short survival.[5–10]

Alternatives to the standard 6 weeks of radiotherapy that are associated with similar or improved survival and quality of life would be beneficial. Outpatient treatment or short treatment times could also lessen demands on medical resources and reduce the risk of treatment being withheld. Chemotherapy with temozolomide, an oral alkylating agent, has been efficacious as a treatment for glioma with low risk of

toxic effects[11–13] and hypofractionated radiotherapy has been advocated.[14,15] In contrast to radiotherapy, temozolomide chemotherapy can be administered from local hospitals and can be started quickly after diagnosis.

To define an evidence-based treatment recommendation for patients aged 60 years or older with glioblastoma, the Nordic Clinical Brain Tumour Study Group (NCBTSG) did a randomised trial to compare survival, health-related quality of life, and safety with single-agent temozolomide chemotherapy, hypofractionated radiotherapy, or standard radiotherapy.

Methods

Patients

Between Feb 2, 2000, and June 18, 2009, we recruited patients from 28 centres treating patients with brain tumours (mainly oncology departments) in Austria, Denmark, France, Norway, Sweden, Switzerland, and Turkey, to which patients were referred after neurosurgery. Patients with newly diagnosed, histologically confirmed glioblastoma (WHO grade IV astrocytoma) and aged 60 years or older were eligible. To resemble the characteristics of patients seen in clinics, patients with WHO performance scores 0–2 (even if neurological deficits gave them a performance score of 3) could be included. Patients were required to have adequate haematological (neutrophil count $1{\cdot}5\times10^9$/L or higher, platelets 100×10^9/L or higher, and haemoglobin 100 g/L or higher), renal (creatinine concentrations in serum less than 1·5 times the upper limit of normal), and liver (bilirubin concentrations in serum less than 1·5 times the upper limit of normal and aspartate aminotransferase and alanine aminotransferase no more than three times the upper limit of normal) functions, and were expected by the doctor to tolerate all treatment options. After Oct 15, 2004, patients younger than 65 years who were deemed fit to receive combined treatment were excluded, owing to positive results of the European Organisation for Research and Treatment of Cancer (EORTC) trial on concurrent and adjuvant temozolomide and radiotherapy for glioblastoma.[3] The age cutoff of 65 years was based on subgroup analyses in that trial, which showed an increase in median survival for patients younger than 65 years who received combined treatment, whereas no such benefit was seen for older patients (Stupp R, personal communication). Exclusion criteria were other primary cancers, except radically treated squamous-cell or basal-cell carcinoma of the skin or other curatively treated malignancy without relapse at least 2 years after diagnosis, WHO performance score 3–4 (except a score of 3 owing to

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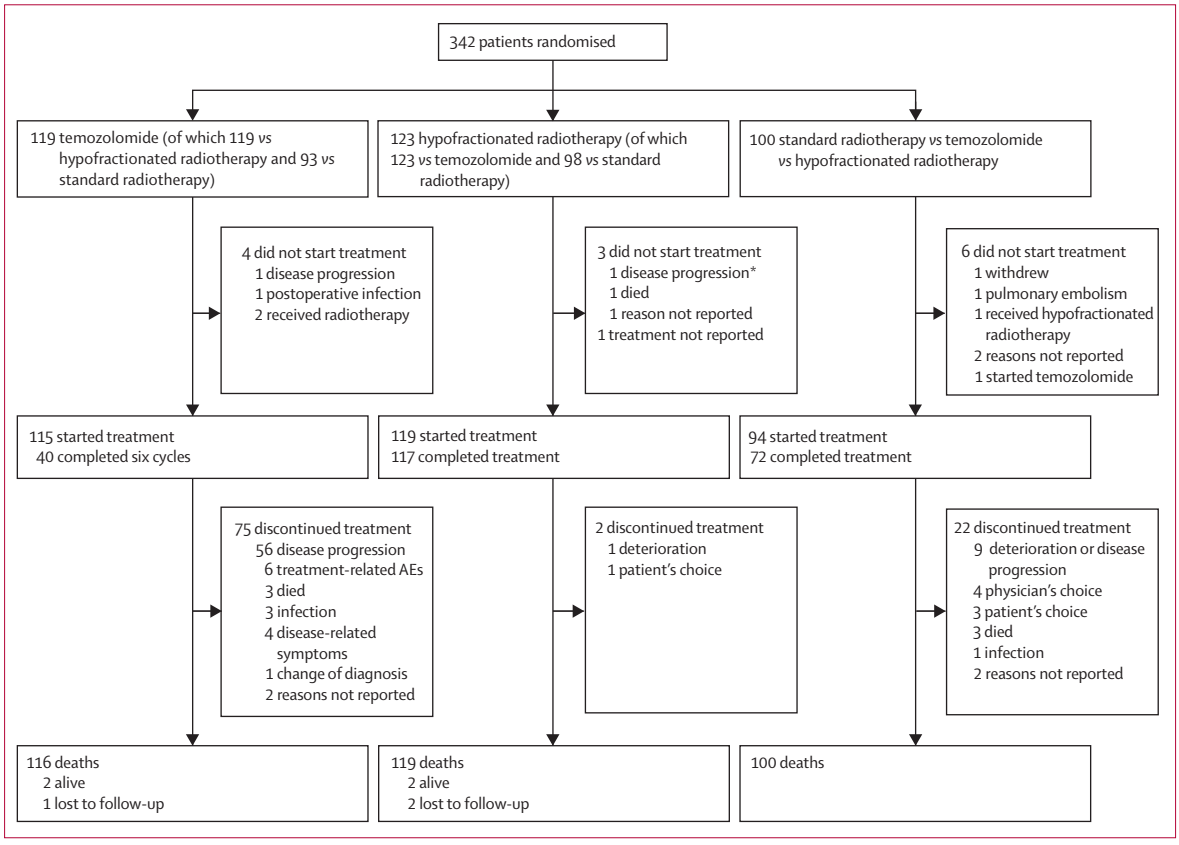

Figure 1: **Trial profile**
AEs=adverse events. *Received temozolomide.

neurological defecits), any disorder that was likely to interfere with the study treatment, previous therapy for any brain tumour, except surgery or medical treatment within 3 years for other malignant diseases, and previous radiotherapy to the head that would prevent further irradiation.

The protocol was approved by the ethics committees of all participating institutions and all patients gave written informed consent. Study data were monitored at study centres and collected in a database by an independent company (NS-CRI) in Umeå, Sweden.

Randomisation and masking

Randomisation was done by the Oncology Centre, University Hospital, Linköping, Sweden. The randomisation lists were generated by computer and were only available to the Oncology Centre staff. Each time a new patient was to be randomised, the participating institution sent a randomisation form to the Oncology Centre by fax, which was returned by fax to the investigator with the relevant treatment information.

At the time the study started, common practice included refraining from standard radiotherapy and offering a hypofractionated short course of radiotherapy or withholding antitumour therapy for patients older than 60 years who had a poor outlook. For these reasons, some centres were permitted to randomise patients to only two of the treatment groups (temozolomide or hypofractionated radiotherapy) if this represented their standard of care. Therefore, patients were randomised in a ratio of 1:1:1 in blocks of nine to receive temozolomide, hypofractionated radiotherapy, or standard radiotherapy, or in a ratio of 1:1 in blocks of eight to receive temozolomide or hypofractionated radiotherapy. Investigators and patients were aware of treatment assignment.

Treatment

Temozolomide was administered orally in 200 mg/m² doses on days 1–5 of every 28 days for up to six cycles or until radiological progression, clinical progression, or both, unacceptable adverse effects were seen, or until a physician or patient chose to discontinue treatment.[13] We based the hypofractionated radiotherapy schedule on a previously documented schedule of 30·0 Gy administered in six fractions of 5·0 Gy on 3 days per week over 2 weeks,[11] although we allowed for daily fractionation, which is often preferred. The hypofractionated radiotherapy schedule, therefore, was 34·0 Gy delivered in ten fractions of 3·4 Gy on 5 days per week over 2 weeks. Planning target volumes for both radiotherapy groups were calculated from dedicated CT or MRI scans of the whole brain, with the patient positioned in an immobilisation device and in the treatment position. A multiple-field technique was used to obtain the optimum dose distribution. Standard radiotherapy was 60·0 Gy administered in 30 fractions of 2·0 Gy on weekdays for 6 weeks.

Monitoring and follow-up

Baseline assessments consisted of physical and neurological examinations, full blood counts, chemistry tests, and administration of the EORTC quality-of-life questionnaire 30 (EORTC QLQ-30), version 3, with the brain cancer module 20.[16] Patients were reassessed

	Temozolomide (n=93)			Hypofractionated radiotherapy (n=98)			Standard radiotherapy (n=100)		
	All	60–70 years (n=51)	>70 years (n=42)	All	60–70 years (n=58)	>70 years (n=40)	All	60–70 years (n=59)	>70 years (n=41)
Sex									
Male	55 (59%)	32 (63%)	23 (55%)	50 (51%)	28 (48%)	22 (55%)	68 (68%)	39 (66%)	29 (71%)
Female	38 (41%)	19 (37%)	19 (45%)	48 (49%)	30 (52%)	18 (45%)	32 (32%)	20 (34%)	12 (29%)
WHO performance score									
0–1	73 (78%)	40 (78%)	33 (79%)	78 (80%)	48 (83%)	30 (75%)	72 (72%)	42 (71%)	30 (73%)
2–3*	20 (22%)	11 (22%)	9 (21%)	20 (20%)	10 (17%)	10 (25%)	28 (28%)	17 (29%)	11 (27%)
Surgery type									
Biopsy	24 (26%)	10 (20%)	14 (33%)	26 (27%)	13 (22%)	13 (33%)	27 (27%)	12 (20%)	15 (37%)
Resection (partial or complete)	69 (74%)	41 (80%)	28 (67%)	72 (73%)	45 (78%)	27 (67%)	73 (73%)	47 (80%)	26 (63%)
Taking steroids at baseline									
Yes	47 (51%)	24 (47%)	23 (55%)	50 (51%)	27 (47%)	23 (57%)	56 (56%)	32 (54%)	24 (59%)
No	32 (34%)	17 (33%)	15 (36%)	37 (38%)	24 (41%)	13 (33%)	30 (30%)	18 (31%)	12 (29%)
Not reported	14 (15%)	10 (20%)	4 (9%)	11 (11%)	7 (12%)	4 (10%)	14 (14%)	9 (15%)	5 (12%)
Median (range) time from surgery† to start of treatment (days)	26 (11–78)	26 (12–78)	27 (11–60)	40 (14–105)	41 (14–73)	38 (20–105)	46 (14–119)	46 (17–96)	46 (14–119)

*Seven were deemed to have a score of 3 because of neurological deficits. †Where no date of surgery was reported it was substituted with date of diagnosis.

Table 1: **Baseline characteristics and times to treatment for patients in the three-group randomisation, by treatment and age groups**

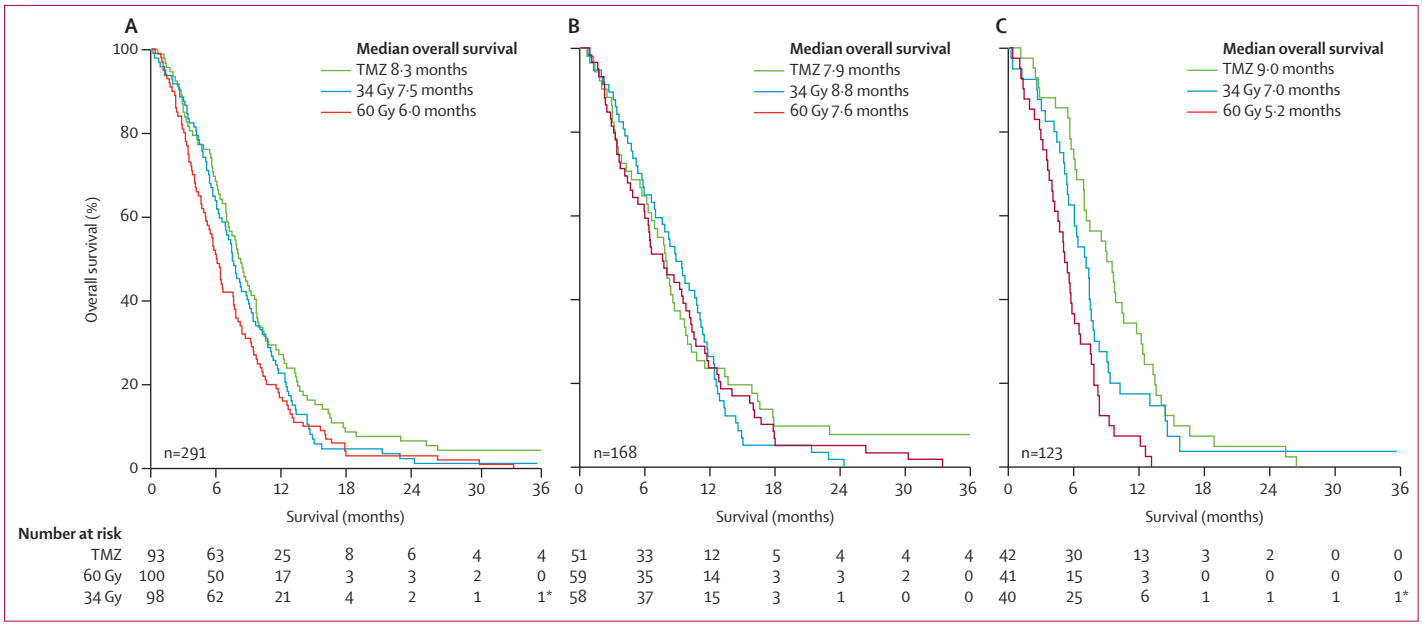

Figure 2: **Kaplan-Meier analysis of overall survival in patients randomised across three treatment groups**
(A) All patients. (B) Patients aged 60–70 years. (C) Patients older than 70 years. TMZ=temozolomide. 34 Gy=hypofractionated radiotherapy. 60 Gy=standard radiotherapy. *Patient censored at 35 months.

6 weeks, 3 months, and 6 months after the start of therapy. For patients treated with temozolomide, full blood counts were repeated on day 21 and within 72 h of day 28 of each cycle. Adverse events were reported according to the WHO grading system,[17] except for nausea and vomiting, for which we used the National Cancer Institute Common Toxicity Criteria version 2.0. Second-line therapy was provided at the discretion of the treating physician.

Pathology review and molecular markers

Central pathology review was done by BL, according to WHO 2007 criteria,[18] at Lausanne University Hospital, Lausanne, Switzerland. Slides were stained with haematoxylin and eosin, and immune histochemistry for glial fibrillary acidic protein, microtubule-associated protein 2, and reticulin silver stains were also used for most cases.

The presence of the IDH1 Arg132His mutation was determined by immunohistochemistry with a mutation-specific antibody[19] (internal clone H14, Dianova, Hamburg, Germany) either on tissue microarray[20,21] or on whole sections.

Promoter methylation status of the O⁶-methylguanine DNA-methyltransferase gene (*MGMT*) was assessed on DNA isolated from paraffin-embedded tumour samples obtained at initial surgery. The test was done by MDxHealth, Liège, Belgium, with quantitative methylation-specific PCR.[22] The copy number of methylated *MGMT* was normalised to the β-actin gene (*ACTB*). A ratio of 2·0 or more, calculated as (methylated *MGMT*/*ACTB*)×1000, was taken to indicate methylation. A minimum of 1250 copies of *ACTB* were required, unless the copy number for methylated *MGMT* was ten or more, which was also scored as methylated *MGMT* promoter.

Statistical analysis

We calculated we would need to recruit 480 patients—160 per treatment group—to be able to detect a 10% survival difference (from 10% to 20%)[14,15] between temozolomide or hypofractionated radiotherapy and standard radiotherapy at 1 year, with 90% power at the 5% significance level, according to the log-rank test. A planned interim analysis in April, 2004, and an additional one in September, 2005, were done to enable exclusion of a treatment group if results were inferior to the two others at a 1% level. The findings resulted in the independent data monitoring board recommending continuation of all treatments after both analyses.

The primary endpoint was overall survival from the date of randomisation, and was estimated by the Kaplan-Meier method with a two-sided log-rank test. Secondary endpoints were health-related quality of life and safety. Analyses were done by intention to treat. Randomisation was stratified by study centre.

All statistical analyses were done with SPSS version 18.0. For statistical reasons, comparisons with standard radiotherapy for survival, adverse events, or second-line therapy, were done only in patients who had been initally randomised across all three treatment groups. For the same analyses for temozolomide versus hypofractionated radiotherapy, all patients in these two treatment groups were assessed irrespective of whether they had been intially randomised across three or two groups. We used

Cox's regression analysis to do pairwise comparisons and calculate hazard ratios (HRs) for relative risk of death. Multivariate analysis stratified for randomisation between three or two treatment groups was used to investigate whether age (older than 70 *vs* 60–70 years), type of surgery (biopsy *vs* resection), and WHO performance score (2–3 *vs* 0–1) affected prognosis. We also tested for interactions between treatments and prognostic factors. For comparisons of second-line treatment, we used the χ^2 test. We compared delivered doses in the standard radiotherapy group by age group with Fisher's exact test. To avoid confounding, Kaplan-Meier and log-rank tests for the *MGMT* data were stratified for randomisation to three or two treatment groups. We applied Cox's regression model to test for interaction effects to these data.

See Online for appendix

For health-related quality of life we calculated changes in mean scores from baseline values for each treatment group. To facilitate comparisons for each domain, baseline values were set to a common starting point (zero). The absolute changes in scores were calculated by subtraction of the value for all patients in each treatment group at baseline from the values at 6 weeks and 3 months. The Kruskal-Wallis test and pairwise comparisons with the Mann-Whitney *U* test were done. This trial is registered, number ISRCTN81470623.

	Number of deaths/ patients	Hazard ratio (95% CI)	Log-rank p value	Median (95% CI) survival (months)	1-year (95% CI) survival (%)
Temozolomide or hypofractionated radiotherapy *vs* standard radiotherapy*					
Overall					
Standard radiotherapy	100/100	1·0	..	6·0 (5·1–6·8)	17% (10–24)
Hypofractionated radiotherapy	94/98	0·85 (0·64–1·12)	0·24	7·5 (6·5–8·6)	23% (14–31)
Temozolomide	90/93	0·70 (0·52–0·93)	0·01	8·3 (7·1–9·5)	27% (18–36)
Age 60–70 years					
Standard radiotherapy	59/59	1·0	..	7·6 (5·2–10·1)	24% (13–35)
Hypofractionated radiotherapy	57/58	1·06 (0·73–1·54)	0·77	8·8 (6·9–10·8)	26% (15–38)
Temozolomide	49/51	0·87 (0·59–1·28)	0·48	7·9 (6·5–9·3)	24% (12–35)
Age >70 years					
Standard radiotherapy	41/41	1·0	..	5·2 (4·0–6·3)	7% (0·6–15)
Hypofractionated radiotherapy	37/40	0·59 (0·37–0·93)	0·02	7·0 (5·2–8·8)	18% (6–29)
Temozolomide	41/42	0·35 (0·21–0·56)	<0·0001	9·0 (6·2–11·8)	32% (18–46)
Temozolomide *vs* hypofractionated radiotherapy†					
Overall					
Hypofractionated radiotherapy	119/123	1·0	..	7·4 (6·4–8·4)	20% (13–28)
Temozolomide	116/119	0·82 (0·63–1·06)	0·12	8·4 (7·3–9·4)	25% (17–32)
Age 60–70 years					
Hypofractionated radiotherapy	62/63	1·0	..	8·3 (6·5–10·0)	26% (15–37)
Temozolomide	60/62	0·91 (0·63–1·30)	0·59	7·8 (6·4–9·2)	23% (12–33)
Age >70 years					
Hypofractionated radiotherapy	57/60	1·0	..	6·5 (5·1–7·9)	15% (6–24)
Temozolomide	56/57	0·72 (0·50–1·05)	0·09	9·0 (7·8–10·2)	27% (15–38)
***MGMT* status‡**					
Unmethylated					
Any radiotherapy	67/68	1·0	..	7·0 (5·7–8·3)	26% (16–37)
Temozolomide	43/44	1·16 (0·78–1·72)	0·46	6·8 (5·9–7·7)	16% (5–27)
Methylated					
Any radiotherapy	62/63	1·0	..	8·2 (6·6–9·9)	26% (15–37)
Temozolomide	26/28	0·64 (0·39–1·04)	0·07	9·7 (8·0–11·4)	32% (15–49)
Temozolomide					
Unmethylated	43/44	1·0	..	6·8 (5·9–7·7)	16% (5–27)
Methylated	26/28	0·56 (0·34–0·93)	0·02	9·7 (8·0–11·4)	32% (15–49)
Any radiotherapy					
Unmethylated	67/68	1·0	..	7·0 (5·7–8·3)	26% (16–37)
Methylated	62/63	0·97 (0·69–1·38)	0·81	8·2 (6·6–9·9)	26% (15–37)

*Three-group randomisation (n=291). †n=242. ‡*MGMT* analysis stratified for randomisation to three or two groups.

Table 2: **Survival data**

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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

342 patients were enrolled overall. 291 were randomised across three treatment groups (temozolomide n=93, hypofractionated radiotherapy n=98, and standard radiotherapy n=100) and constitute the cohort for comparisons with standard radiotherapy. 51 further patients from four centres that did not offer standard radiotherapy were randomised across only the temozolomide (n=26) or hypofractionated radiotherapy (n=25) groups. Thus, 242 patients were assessed in comparisons of temozolomide (n=119 [93+26 patients]) versus hypofractionated radiotherapy (n=123 [98+25 patients]; figure 1). Patients' characteristics were generally well balanced (table 1, appendix). Median age for patients randomised to the three treatment groups was 70 years (70 years [range 60–88] in the temozolomide group, 70 years [60–83] in the hypofractionated radiotherapy group, and 70 years [60–80] in the standard radiotherapy group); the median age for the additional 51 patients randomsied only to two treatment groups was 3 years older (73 years, range 60–83). Similar numbers of patients in each age group (60–70 years or older than 70 years) in the three-group randomisation (n=291) did not start assigned treatment: two and one, respectively, in the temozolomide group; two and two, respectively, in the hypofractionated radiotherapy group; and two and three, respectively, in the standard radiotherapy group.

Multivariate analysis on all patients (n=342) showed prognostic value for performance score (2–3 *vs* 0–1, HR 1·42 [95% CI 1·10–1·83], p=0·007) surgery (biopsy *vs* resection, 1·50 [1·17–1·92], p=0·001), and age (older than 70 years *vs* 60–70 years, 1·30 [1·03–1·64], p=0·03). We

	Temozolomide (n=90)						Hypofractionated radiotherapy (n=95)						Standard radiotherapy (n=95)					
	Grade					Total (%)	Grade					Total (%)	Grade					Total (%)
	2	3	4	5	NR		2	3	4	5	NR		2	3	4	5	NR	
Neutropenia	3	2	6	0	0	11 (12%)	0	0	0	0	0	0	0	0	0	0	0	0
Pancytopenia	0	0	2	0	0	2 (2%)*	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocytopenia	7	5	7	0	0	19 (21%)	0	0	0	0	0	0	0	0	0	0	0	0
Infection/fever	10	5	1	0	1	17 (19%)	5	1	0	0	1	7 (7%)	6	3	2	1	1	13 (14%)
Thromboembolic event	1	3	2	0	0	6 (7%)	0	4	1	0	1	6 (6%)	0	1	0	0	1	2 (2%)
Intracranial haemorrhage	1	0	0	0	2	3 (3%)	0	0	0	0	0	0	0	0	0	0	3	3 (3%)
Bleeding†	1	0	0	1‡	0	2 (2%)	1	0	0	0	1	2 (2%)	1	0	0	0	0	1 (1%)
Seizures	4	0	1	0	1	6 (7%)	1	2	3	0	1	7 (7%)	4	7	1	0	0	12 (13%)
Fatigue/asthenia	3	1	0	0	0	4 (4%)	4	1	1	0	0	6 (6%)	6	0	0	0	0	6 (6%)
Nausea	4	2	0	0	0	6 (7%)	0	0	0	0	0	0	5	0	0	0	0	5 (5%)
Vomiting	2	1	0	0	0	3 (3%)	1	0	0	0	0	1 (1%)	2	0	0	0	0	2 (2%)

Adverse events are graded according to the WHO system, except for nausea and vomiting, for which we used the National Cancer Institute Common Toxicity Criteria, version 2.0. Reported grades are the highest per patient; alopecia, disease-related events, or adverse events with frequency <1% are not reported. NR=not reported. *Reported for one patient as thrombocytopenia, leucopenia, lymphopenia, and anaemia, all grade 4, and for one patient as thrombocytopenia and pancytopenia, both grade 4. †Except intracranial. ‡Gastrointestinal bleeding during grade 2 thrombocytopenia that caused peritonitis and death.

Table 3: **Adverse events for patients in the three-group randomisation who started assigned treatment**

found an interaction between treatment and age (p=0·03), but not type of surgery (p=0·81) or performance score (p=0·10).

Most patients in the three-group randomisation started radiotherapy, but fewer patients completed irradiation according to protocol in the standard radiotherapy group than in the hypofractionated radiotherapy group (72 [72%] of 100 patients *vs* 93 [95%] of 98; appendix). The most frequent reasons for not completing radiotherapy were deterioration or disease progression or physician's or patient's choice (figure 1). Temozolomide was started in 90 (97%) of 93 patients assessed as part of the three-group randomisation. 80 (86%) received at least two cycles of chemotherapy, and 32 (34%) completed all six cycles. The median number of cycles administered was four. Patients discontinued temozolomide mainly because of disease progression (figure 1). The completion rate was equal by age group for patients who received temozolomide or hypofractionated radiotherapy, but there was a difference between age groups in patients who received standard radiotherapy, although it was not significant (27 [66%] of 41 patients aged older than 70 years *vs* 45 [76%] of 59 aged 60–70 years, p=0·65; appendix). In the comparison of temozolomide (n=119) and hypofractionated radiotherapy (n=123), the rates of completion of assigned treatment did not differ from those for patients randomised across three treatment groups (appendix).

Second-line treatment was given to 94 (32%) of the 291 patients in the three-group randomisation; 123 (42%) received no further therapy, and data were not reported for 74 (26%). More patients in the temozolomide group received second-line treatment than did those in the radiotherapy groups (38 [41%] of 93 in the temozolomide group *vs* 29 [30%] of 98 in the hypofractionated radiotherapy *vs* 27 [27%] of 100 in the standard radiotherapy group), although these differences were not significant. 34 (37%) of 93 temozolomide patients received second-line radiotherapy, whereas 52 (26%) of 198 patients in the radiotherapy groups received second-line chemotherapy. In the comparison of temozolomide (n=119) and hypofractionated radiotherapy (n=123), rates for use of second-line therapy were similar to those for the three-group comparison (appendix).

Survival analyses were done as three pairwise comparisons: temozolomide (n=93) versus standard radiotherapy (n=100), hypofractionated radiotherapy (n=98) versus standard radiotherapy (n=100), and temozolomide (n=119) versus hypofractionated radiotherapy (n=123). Thus, the power for the comparison of temozolomide or hypofractionated radiotherapy versus standard radiotherapy (n=291) was around 70%, and that of temozolomide versus hypofractionated radiotherapy (n=242) was around 80%, owing to the additional 51 patients. Survival was significantly better in patients who received temozolomide than in those who received standard radiotherapy, but did not differ significantly between patients who received hypofractionated or standard radiotherapy (figure 2A, table 2). Survival did not differ between treatments for patients aged 60–70 years (figure 2B, table 2). By contrast, for patients older than 70 years, survival was better with temozolomide and with hypofractionated radiotherapy than with standard radiotherapy (figure 2C, table 2). 1-year survival was slightly higher in patients who received temozolomide (table 2). For temozolomide versus hypofractionated radiotherapy, median survival was similar (log-rank p=0·12, table 2, appendix). Survival did not differ by treatment within age groups (table 2, appendix). Survival did not differ

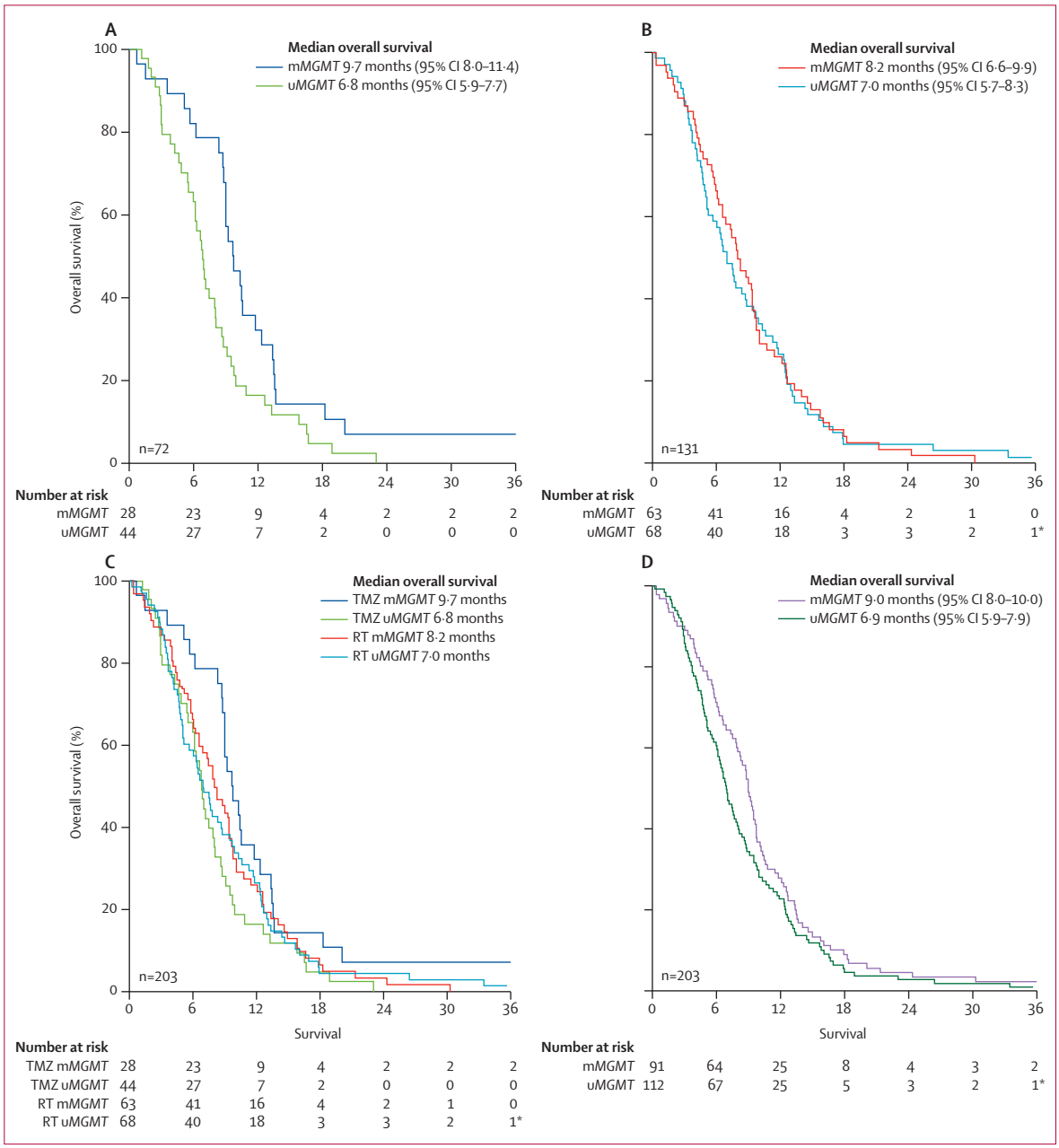

Figure 3: **Kaplan-Meier analysis of overall survival in patients tested for *MGMT* promoter methylation status**
Hypofractionated and standard radiotherapy were combined in a pooled analysis. (A) m*MGMT* versus u*MGMT* status in the temozolomide group. (B) m*MGMT* versus u*MGMT* status in the combined radiotherapy group. (C) Comparison of m*MGMT* versus u*MGMT* status in the temozolomide group and m*MGMT* versus u*MGMT* status in the combined radiotherapy group (data from parts A and B combined). (D) Comparison of m*MGMT* versus u*MGMT* status, irrespective of treatment. OS=overall survival; mMGMT=methylated *MGMT* promoter; uMGMT=unmethylated *MGMT* promoter; TMZ=temozolomide; RT=radiotherapy. *Patient censored at 35 months.

between patients included before and after Oct 15, 2004, when patients younger than 65 years fit for radiochemotherapy were excluded (log-rank p=0·36). At the time of data analysis (Jan 1, 2011), only four patients remained alive, and a further three were lost to follow-up.

Adverse events were reported for all patients who started randomised treatment (n=329). Common adverse events were seizures, seen in 32 (10%) of patients, fatigue in 28 (9%), and thromboembolic disease in 17 (5%), and were probably disease related. Nausea and vomiting and haematological toxic effects were more frequently seen in patients treated with temozolomide than in those treated with radiotherapy. Grade 3–5 infections were similar among patients who received temozolomide or radiotherapy. Two patients had fatal infections (one in

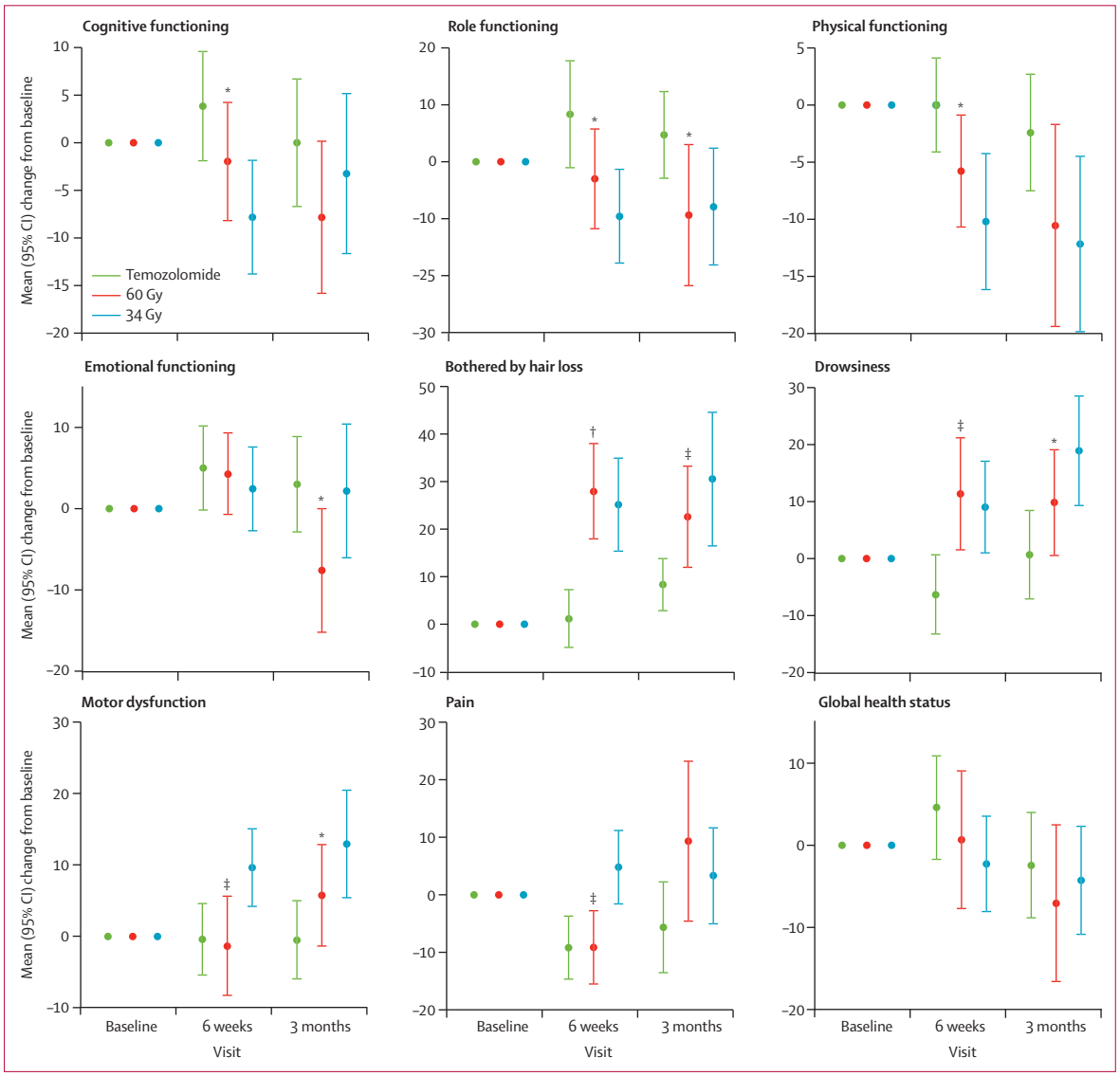

Figure 4: **Health-related quality of life analysis for global health status, function scales, and symptom scales, where differences between treatment groups were significant, in all patients with baseline values**

Questionnaires were completed by 284 patients at baseline, 192 at 6 weeks, and 132 at 3 months. Changes from baseline were not reported at 6 months owing to the low number of questionnaires completed. TMZ=temozolomide. 34 Gy=hypofractionated radiotherapy. 60 Gy=standard radiotherapy. *p<0·05. †p<0·001. ‡p≤0·01.

the temozolomide group during neutropenia and one in the standard radiotherapy group who was taking high-dose steroids). One patient in the temozolomide group with grade 2 thrombocytopenia died from complications after surgery for a gastrointestinal bleed that caused peritonitis. The main adverse events in patients randomised across three groups are summarised in table 3 and the appendix. Adverse events for temozolomide versus hypofractionated radiotherapy are summarised in the appendix.

Histological slides for central review were available for 299 (87%) of 342 patients. For 14 cases, only scanned slides were available. Glioblastoma was confirmed in 291 (97%) of 299 patients. Of the remaining patients, the sections did not allow for a definitive diagnosis in three, and WHO grade II or III diagnoses were made in five (anaplastic oligoastrocytomas, n=2; anaplastic oligodendrogliomas, n=2; and low-grade glioma, n=1). The IDH1 Arg132His mutation was rare and identified in only two cases (<1%)—one of anaplastic oligoastrocytoma and one of glioblastoma—of the 250 evaluable cases.

MGMT promoter methylation could be assessed in tumour tissue from 258 (75%) of the 342 patients enrolled. 55 (21%) samples were judged invalid (appendix). *MGMT* promoter was methylated in 91 (45%) of remaining 203 successfully assessed cases. For patients whose *MGMT* promoter methylation status could be determined, 159 (78%) had undergone resection

***Panel:* Research in context**

Systematic review

In 1999 we searched PubMed for relevant reports of phase 2 and 3 trials and other relevant articles on the treatment of elderly with glioblastoma and poor outlook. We used the search terms "elderly", "glioblastoma", "malignant glioma", "radiotherapy", "hypofractionated radiotherapy", and "chemotherapy". At that time we found no data on potential predictive markers for treatment outcomes. After the trial started, three prospective phase 3 trials and several phase 2 trials were reported that specifically addressed optimum management of elderly patients with glioblastoma and poor outlook. A French study of radiotherapy to 50·0 Gy and best supportive care compared with best supportive care alone in patients older than 70 years showed a significant advantage with radiotherapy (median survival 7 *vs* 4 months).[23] In a subsequent phase 2 trial, the same researchers showed that temozolomide chemotherapy was associated with improved quality of life and functional status in patients who presented with very poor performance status, especially in those with tumour *MGMT* promoter methylation. A Canadian study of hypofractionated radiotherapy to 40·0 Gy over 3 weeks versus standard radiotherapy to 60·0 Gy over 6 weeks reported no difference in survival.[24] Short hypofractionated radiotherapy regimens are increasingly being advocated for elderly patients. The German NOA-08 trial showed that dose-dense temozolomide in cycles of 1 week on, 1 week off in patients older than 65 years was non-inferior to standard radiotherapy to 60·0 Gy.[25] This trial also confirmed the predictive value of *MGMT* promoter methylation for benefit from temozolomide chemotherapy.

Interpretation

Our results are in concordance with those in previous reports, but additionally highlight that standard radiotherapy seems poorly tolerated in patients older than 70 years and can be avoided in those with predicted short survival. A high number of patients were unable to complete the standard radiotherapy schedule compared with the 2-week hypofractionated schedule. Our findings support the predictive value of *MGMT* promoter methylation status for response to temozolomide chemotherapy, but we found no similar predictive value for response to radiotherapy. Our data, as well as those of the NOA-08 trial, suggest that testing of *MGMT* promoter methylation status would be useful in elderly patients with glioblastoma to facilitate treatment recommendations. The European Organisation for Research and Treatment of Cancer and National Cancer Institute of Canada study[3,4] on concomitant and adjuvant radiotherapy and temozolomide for patients aged up to 70 years showed a survival benefit with combined chemotherapy and radiotherapy, but the advantage decreased with increasing age, especially for patients older than 65 years. An ongoing trial by the same investigators (NCT0048267) is exploring whether combined hypofractionated radiotherapy and temozolomide will be useful for patients older than 65 years with glioblastoma. The accumulating data suggest that elderly patients do benefit from active antitumour therapy, and that short-course hypofractionated radiotherapy or temozolomide chemotherapy might be valid alternatives to standard irradiation.

and 44 (22%) biopsy. These rates were similar to those in the total study population (72% and 28%, respectively). We did a pooled analysis of both radiotherapy groups to assess whether *MGMT* promoter methylation status had predictive value for survival in relation to type of treatment in the 203 patients. Of patients who received temozolomide, those with *MGMT* promoter methylated tumours had better survival than did those with unmethylated *MGMT* promoter status (table 2, figure 3A). By contrast, the *MGMT* promoter methylation status did not affect survival in patients treated with radiotherapy (table 2, figure 3B). We tested for heterogeneity (interaction) across groups to assess whether the HRs for temozolomide and radiotherapy differed by *MGMT* promoter methylation status (figure 3C). The result was of borderline significance (p=0·061). Methylation status, irrespective of treatment, had no effect on overall survival (figure 3D).

Baseline data for health-related quality of life were available for 284 (83%) of 342 patients. Of those alive at follow-up, 192 (59%) of 325 completed questionnaires at 6 weeks, and 132 (44%) of 300 did so at 3 months. Because of the low number of questionnaires collected at 6 months, these data are not reported. The data at 3 months should be interpreted with caution because of the low number of completed questionnaires. Primary domains of interest were physical, role, emotional, social, and cognitive functioning, and global health status. Patients in the temozolomide group generally reported better quality of life than did patients in the radiotherapy groups, but the ratings for global health status were equal (figure 4).

Discussion

Our trial confirms that the overall prognosis for elderly patients with glioblastoma is poor, particularly in patients older than 70 years treated with standard radiotherapy (panel). We found that temozolomide chemotherapy is a potential alternative to radiotherapy in elderly and frail patients. Of note is that a substantial number of patients were unable to complete the planned standard radiotherapy regimen, which could partly explain the inferior survival in this group. Radiotherapy was discontinued mainly owing to deterioration, disease progression, physician's choice, or patient's choice. A 6-week radiotherapy regimen, therefore, seems to be associated with substantial risks of morbidity and early discontinuation. The lower crossover to second-line treatment by patients in the standard radiotherapy group than by those in the temozolomide group does not explain the observed survival differences.

Our results are in accordance with previously reported randomised trials in elderly patients with glioblastoma. In a French trial,[23] radiotherapy (50·0 Gy in 28 fractions), compared with best supportive care, was associated with improved median survival (7 *vs* 4 months) and retained health-related quality of life in patients older than 70 years. A randomised Canadian trial[24] suggested no difference in outcome between patients aged 60 years or older treated with 6 weeks or 3 weeks of radiotherapy.

The NOA-08 trial[25] compared 60·0 Gy radiotherapy administered in 1·8–2·0 Gy fractions with dose-dense temozolomide in cycles of 1 week on, 1 week off in patients older than 65 years who had anaplastic astrocytoma or glioblastoma. Survival did not differ between treatment groups. Median survival for those who received 60·0 Gy radiotherapy was 9·6 months (95% CI 8·2–10·8), whereas in this trial it was 6·0 months (95% CI 5·1–6·8). This difference might be explained by the fact that we assessed all randomised patients, whereas in the NOA-08 trial nearly 10% of

randomised patients (those who never started trial therapy—ie, those with the poorest outlook) were excluded from the survival analysis.

In the pivotal EORTC and National Cancer Institute of Canada (EORTC-NCIC) randomised, phase 3 trial, concomitant administration of temozolomide and radiotherapy followed by maintenance temozolomide was established as current standard treatment for fit patients up to age 70 years.[3,4] Although combined therapy was most beneficial in the youngest patients, a smaller survival advantage was seen for those aged 60–70 years, albeit diminishing notably after age 65 years.

A phase 2 trial has raised concerns of increased risk of neurocognitive toxic effects with combined treatment in elderly patients.[8] Therefore, radiochemotherapy might not be suitable for all elderly patients with glioblastoma, although further study to define the optimum treatment strategy in this population is warranted. From October, 2004, we excluded patients younger than 65 years who were fit for combined treatment. Survival before and after this date was similar, which suggests that the selection of patients did not change substantially over the duration of recruitment.

This trial has some limitations. The power was lower than initially planned because recruitment of patients was stopped early. The recruitment of patients was slower than anticipated, which was probably due partly to the results of the EORTC-NCIC trial, which favoured combined temozolomide and radiotherapy, and partly to patients with glioblastoma frequently being judged too frail to be suitable for study protocols. The length of follow-up enabled observation of an increased number of events, and the trial was closed after 342 patients had been enrolled.

A potential, confounding effect of second-line therapy could not be assessed because data on progression-free survival were deliberately not collected. The prevailing view of treatment in elderly patients with glioblastoma at the time the study started was anticipated to be an obstacle to further imaging and treatment in patients with poor outlook, in addition to the difficulty in correctly assessing the date of radiological progression after radiotherapy.

Reported treatment-related adverse events were mostly mild and were similar for the two radiotherapy groups; nausea and vomiting and myelosuppression were seen mainly in chemotherapy-treated patients. Most reported adverse events were related to the underlying disease rather than to treatment.

Temozolomide alone seemed to improve symptoms and function scores in several health-related quality-of-life domains, which supports findings in other trials.[26,27] A small phase 2 trial reported a median survival of 6·4 months with temozolomide alone as first-line therapy in patients older than 70 years who had glioblastoma with good performance status at presentation.[14] Another phase 2 trial of temozolomide alone in patients older than 70 years with glioblastoma and poor performance scores (Karnofsky score 60 or lower) showed improvements in quality of life and performance status that enabled a substantial proportion of patients to regain some independence, especially in patients with *MGMT* promotor methylation.[28] Median survival was 5·8 months.

MGMT promoter methylation has previously been shown to be a prognostic marker of outcome, and is a strong predictor of benefit with temozolomide chemotherapy.[8,25,28,29] Our results support the predictive value of *MGMT* promoter methylation in elderly patients with glioblastoma: survival was significantly longer in patients treated with temozolomide and who had methylated *MGMT* promoter status than in those who did not have *MGMT* promoter methylation (log-rank p=0·02). Conversely, outcomes did not differ between patients in the radiotherapy groups with or without *MGMT* promoter methylation. Although our analysis was done post hoc in a limited number of patients (n=203), and despite crossover to second-line therapy for about a third of patients, the test for heterogeneity (interaction) across the groups temozolomide without *MGMT* promoter methylation and radiotherapy without *MGMT* promoter methylation and temozolomide with *MGMT* promoter methylation and radiotherapy with *MGMT* promoter methylation reached borderline significance (p=0·061). Our findings are supported by those of the NOA-08 trial,[25] where the researchers concluded that treatment decisions for elderly patients with glioblastoma could be aided by assessment of *MGMT* promoter methylation status.[24]

In conclusion, outcomes of patients with glioblastoma who are treated with standard radiotherapy over 6 weeks, especially those older than 70 years, are poor. Our findings suggest that temozolomide chemotherapy or hypofractionated radiotherapy over 2 weeks might be valid alternative strategies, and that *MGMT* promoter methylation status might be a useful biomarker to help make treatment decisions.

Contributors

AM designed the study. AM and RH wrote the protocol and initiated the study. AM was the principal investigator, collaborated with study centres and authorities, organised study-group meetings, collaborated with the statistician, and did the literature search. BHG was the coordinator for participating centres in Norway. DF was the coordinator for participating centres in France. HS was the coordinator for participating centres in Denmark. UA was the coordinator for participating centres in Turkey. AM, BHG, CM, RS, DF, HS, UA, BT, and RH were involved in data collection. RS, BT, BL, MEH, JR, and RH analysed the data. BT analysed the data for health-related quality of life, BL did the pathology review, and JR prepared the figures. AM, BHG, RS, DF, HS, MEH, and RH interpreted the results. All authors contributed to the writing and review of the report and approved the final draft for submission.

Conflicts of interest

AM has received consultancy fees for advisory board and travel expenses from Schering-Plough. BHG has received travel expenses from Schering-Plough. RS has served on advisory boards for Merck and Merck Sharp and Dohme. MEH has acted as adviser to MDxHealth and has participated on an advisory board for Merck Sharp and Dohme. RH has served on the advisory board for Schering-Plough. The other authors declare that they have no conflicts of interest.

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