Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial

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Summary

Background **In 2004, a randomised phase III trial by the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group (NCIC) reported improved median and 2-year survival for patients with glioblastoma treated with concomitant and adjuvant temozolomide and radiotherapy. We report the final results with a median follow-up of more than 5 years.**

Methods **Adult patients with newly diagnosed glioblastoma were randomly assigned to receive either standard radiotherapy or identical radiotherapy with concomitant temozolomide followed by up to six cycles of adjuvant temozolomide. The methylation status of the methyl-guanine methyl transferase gene, *MGMT*, was determined retrospectively from the tumour tissue of 206 patients. The primary endpoint was overall survival. Analyses were by intention to treat. This trial is registered with Clinicaltrials.gov, number NCT00006353.**

Findings **Between Aug 17, 2000, and March 22, 2002, 573 patients were assigned to treatment. 278 (97%) of 286 patients in the radiotherapy alone group and 254 (89%) of 287 in the combined-treatment group died during 5 years of follow-up. Overall survival was 27·2% (95% CI 22·2–32·5) at 2 years, 16·0% (12·0–20·6) at 3 years, 12·1% (8·5–16·4) at 4 years, and 9·8% (6·4–14·0) at 5 years with temozolomide, versus 10·9% (7·6–14·8), 4·4% (2·4–7·2), 3·0% (1·4–5·7), and 1·9% (0·6–4·4) with radiotherapy alone (hazard ratio 0·6, 95% CI 0·5–0·7; p<0·0001). A benefit of combined therapy was recorded in all clinical prognostic subgroups, including patients aged 60–70 years. Methylation of the *MGMT* promoter was the strongest predictor for outcome and benefit from temozolomide chemotherapy.**

Interpretation **Benefits of adjuvant temozolomide with radiotherapy lasted throughout 5 years of follow-up. A few patients in favourable prognostic categories survive longer than 5 years. *MGMT* methylation status identifies patients most likely to benefit from the addition of temozolomide.**

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Introduction

For more than three decades, postoperative radiotherapy has been standard treatment for newly diagnosed glioblastoma. Pooled analysis of six randomised trials of radiotherapy versus no radiotherapy after surgery showed significant survival benefits for radiotherapy.[1,2] However, the survival advantage after radiation was small and overall survival remained poor with almost no long-term survivors. The addition of nitrosourea-based chemotherapy gave modest further benefit: a meta-analysis of 12 randomised trials of adjuvant chemotherapy for high-grade glioma showed a 35% 1-year survival rate for glioblastoma, an improvement of 6%.[3]

In 2004, the European Organisation for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC) CE3 randomised phase III trial showed the addition of concomitant and adjuvant temozolomide to standard postoperative radiotherapy improved median survival and 2-year survival relative to postoperative radiotherapy alone.[4] Furthermore, patients whose tumour had a methylated promoter for the gene encoding O-6-methylguanine-DNA methyltransferase, *MGMT*, were more likely to benefit from the addition of temozolomide.[5] Here we present long-term results on outcome and analyse known and putative prognostic and predictive factors. At the time of the initial analysis, whether the survival advantage would last over time was unclear.

Methods

Patients

Patients were recruited from daily practice in participating centres of the European Organisation for the Research and Treatment of Cancer (EORTC) and NCIC

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See Online for webappendix

(webappendix). Eligible patients were aged 18–70 years with newly diagnosed and histologically proven glioblastoma (WHO grade IV astrocytoma), with a WHO performance status of 0–2 and adequate haematological, renal, and hepatic function. Patients on corticosteroid treatment had to receive a stable or decreasing dose for at least 14 days before randomisation. The extent of surgery was reported by the neurosurgeon as biopsy or partial or complete resection. Histology was centrally reviewed after randomisation. The methylation status of the *MGMT* gene promoter was determined retrospectively by methylation-specific PCR analysis.[5] All patients provided written informed consent, and the study was approved by the ethics committees of all participating centres.

Study design and procedures

Patients were centrally randomised over the phone or internet at the EORTC headquarters. Patients were stratified by WHO performance status, type of surgery, and institution. The minimisation technique used is based on the variance method with semirandom assignment as implemented by Freedman and White.[6,7] Patients were randomly assigned to receive either standard focal radiotherapy or standard radiotherapy plus concomitant daily temozolomide, followed by adjuvant temozolomide. Fractionated conformal three-dimensional radiotherapy to a total dose of 60 Gy in 30 daily fractions of 2 Gy each was delivered.[4,8] Concomitant chemotherapy consisted of oral temozolomide at a daily dose of 75 mg/m² given 7 days per week from the first to the last day of radiotherapy, for at most 49 days. After a 4-week break, patients received up to six cycles of adjuvant oral temozolomide (150–200 mg/m²) for 5 days every 28 days. Prophylaxis against *Pneumocystis jirovecii* with either pentamidine or trimethoprim-sulfamethoxazole was mandatory during concomitant temozolomide and radiotherapy, irrespective of lymphocyte count, and continued recovery of the lymphocyte count to grade 1 or normal. Quality of life was assessed by use of the EORTC QLQ-C30 questionnaire and Brain Cancer Module (BN-20). A complete assessment including imaging, mini-mental state assessment, and quality of life questionnaire was done at baseline, 28 days after the completion of radiotherapy, and every 3 months thereafter. Extent of resection was based on the surgeons' judgement, with no formal assessment required. Tumour progression was defined as an increase in tumour size by 25%, the appearance of a new lesion, or an increased need for corticosteroids. If tumours progressed, patients were treated at the local investigators' discretion, and the type of second-line therapy (surgery, radiotherapy, or chemotherapy) was recorded. Toxic effects were graded according to the National Cancer Institute common toxicity criteria, version 2.

	Radiotherapy alone (n=286)	Combined therapy (n=287)
Age (years)		
<50	88 (31)	95 (33)
≥50	198 (69)	192 (67)
Sex		
Male	175 (61)	185 (64)
Female	111 (39)	102 (36)
WHO performance status		
0	110 (38)	113 (39)
1	141 (49)	136 (47)
2	35 (12)	38 (13)
Extent of surgery		
Biopsy only	45 (16)	48 (17)
Partial resection	128 (45)	126 (44)
Complete resection	113 (40)	113 (39)
Corticosteroid therapy at randomisation	215 (75)	193 (67)
Baseline MMSE		
27–30	188 (66)	196 (68)
≤26	86 (30)	81 (28)
Missing	12 (4)	10 (3)
RPA		
Class III*	39 (14)	42 (15)
Class IV†	150 (52)	152 (53)
class V‡	97 (34)	93 (32)

Data are number (%). MMSE=mini-mental state examination. EORTC=European Organisation for Research and Treatment of Cancer. RPA=recursive partitioning analysis. Patients were clinically categorised according to modified RPA classes:[8] *Age <50 years and performance status 0. †Age <50 years and performance status 1 or 2 or age ≥50 years, debulking surgery, and MMSE ≥27. ‡Age ≥50 years; biopsy only or MMSE ≤26.

Table 1: **Main characteristics of patients**

Statistical analysis

The primary endpoint was overall survival; secondary endpoints were progression-free survival, safety, and quality of life.[9] Survival analyses were done according to the Kaplan-Meier method with two-sided log-rank statistics. The study had 80% power at a significance level of 0·05 to detect a 33% increase in median survival (hazard ratio for death, 0·75). Predefined subgroups according to clinical prognostic factors were explored and data were regrouped with a modification of the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis prognostic classes.[10] All analyses were done on an intention-to-treat basis. Proportional hazard models gave estimates for the hazard ratios [HRs]. All analyses were done with SAS (version 9.1.3).

The trial is registered with ClinicalTrials.gov, number NCT00006353.

Role of the funding source

The commercial sponsor had no role in study design, data collection, analysis and interpretation, or writing of the report. The principal investigators (RS, ROM) had full access to the data and had the final responsibility for the decision to submit for publication.

Results

Between Aug 17, 2000, and March 22, 2002, 573 patients from 85 institutions in 15 countries were randomly assigned: 286 were assigned to receive initial radiotherapy alone, and 287 to receive concomitant and adjuvant temozolomide. Characteristics of patients in the two groups were well balanced (table 1). Details of treatment delivery, tolerance, and toxicity were published previously;[4] figure 1 shows the trial profile.

For 485 (85%) of 573 patients, slides or tumour tissue was available for central pathology review, and the diagnosis of glioblastoma was confirmed in 450 (93%) of these. Of the remainder, 21 (4%) had other types of high-grade glioma—either anaplastic astrocytoma or oligoastrocytoma—and for 12 (2%) the available material was insufficient for a definitive diagnosis.

At the time of the final analysis, 532 (93%) of 573 patients had died after a median follow-up of 61 months (range 11 days to 79 months). Survival was greater in the temozolomide group than in the radiotherapy alone group throughout follow-up (figure 2; table 2); hazard ratio (HR) for death in the radiotherapy and temozolomide group relative to the radiotherapy group was 0·63 (95% CI 0·53–0·75, p<0·0001). Progression-free survival rates were 11·2% (95% CI 7·9–15·1) at 2 years, 6·0% (3·6–9·2) at 3 years, 5·6% (3·3–8·7) at 4 years, and 4·1% (2·1–7·1) at 5 years with radiotherapy and temozolomide and 1·8% (0·7–3·8) at 2 years, 1·3% (0·4–3·3) at 3 years, 1·3% (0·4–3·3) at 4 years, and 1·3% (0·4–3·3) at 5 years with initial radiotherapy only (HR 0·56, 95% CI 0·47–0·66; p<0·0001). Grouping of patients according to previously established clinical prognostic classes (EORTC modification of RTOG recursive partitioning analysis classification,[10] referred to as recursive partitioning analysis prognostic classes) suggests the benefit is largest after combined modality treatment for patients with favourable characteristics (recursive partitioning analysis prognostic classes III and IV; figure 3, table 2). The survival benefit after combined modality treatment seems to last long into follow-up and reaches statistical significance even in patients with poor prognosis (age >60 years, class V). However, these subgroup analyses on few patients lack statistical power (interaction tests were not significant; data not shown), and do not justify drawing definitive conclusions.

When we restricted analyses to eligible patients with confirmed histology, results and conclusions remain unchanged (data not shown). Of the 29 patients surviving more than 4 years (six initially treated with radiotherapy only, 23 treated with temozolomide and radiotherapy), histology was centrally reviewed for 24, five had another high-grade glioma (one in the radiotherapy group, and four in the temozolomide and radiotherapy group).

Median survival after progression was 6·2 months for patients initially treated with radiotherapy (95% CI 5·5–7·1) and 6·2 (5·2–6·7) for patients initially treated with temozolomide and radiotherapy. Table 3 summarises management of patients after progression. Response to salvage therapy was not recorded, details on treatment after progression of a subset of patients included in a pharmacoeconomic analysis have previously been reported.[11]

In a representative subgroup of 206 patients for whom sufficient tumour material was available (mostly patients who had had tumour resection), the methylation status of the *MGMT* promoter could be determined retrospectively.[5] *MGMT* promoter methylation status was the strongest

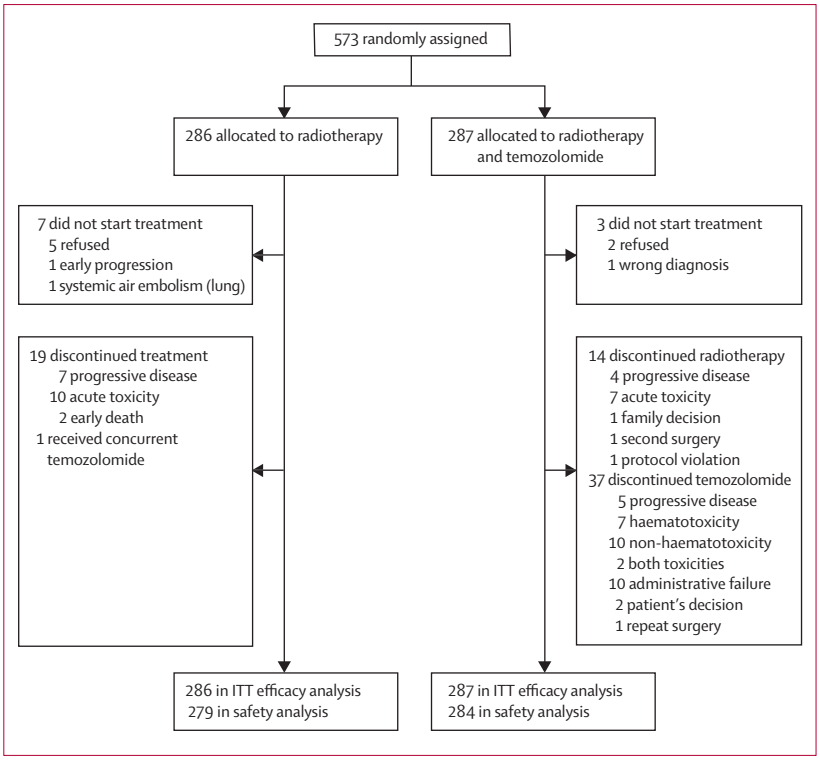

Figure 1: **Trial profile**

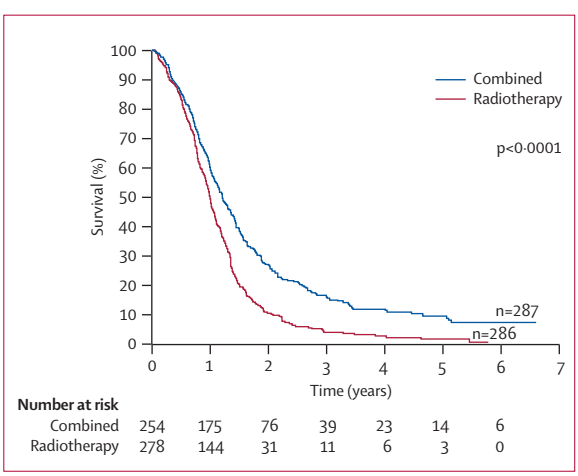

Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**

	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
Overall							
Radiotherapy	278/286	1·0	12·1 (11·2–13·0)	10·9 (7·6–14·8)	4·4 (2·4–7·2)	3·0 (1·4–5·7)	1·9 (0·6–4·4)
Combined	254/287	0·6 (0·5–0·7)	14·6 (13·2–16·8)	27·2 (22·2–32·5)	16·0 (12·0–20·6)	12·1 (8·5–16·4)	9·8 (6·4–14·0)
Complete resection							
Radiotherapy	109/113	1·0	14·2 (12·1–16·1)	15·0 (9·2–22·2)	5·3 (2·2–10·5)	4·4 (1·7–9·4)	2·9 (0·7–8·0)
Combined	96/113	0·8 (0·4–0·8)	18·8 (16·4–22·9)	38·4 (29·4–47·3)	21·4 (14·3–29·6)	15·9 (9·6–23·7)	9·9 (4·7–17·5)
Partial resection							
Radiotherapy	126/128	1·0	11·7 (9·7–13·1)	9·4 (5·1–15·2)	3·7 (1·3–8·2)	2·5 (0·6–7·0)	1·2 (0·1–5·6)
Combined	113/126	0·6 (0·5–0·8)	13·5 (11·9–16·4)	23·7 (16·7–31·4)	14·3 (8·8–21·2)	11·3 (6·3–17·8)	11·3 (6·3–17·8)
Biopsy only							
Radiotherapy	43/45	1·0	7·8 (6·4–10·6)	4·6 (0·8–13·7)	4·6 (0·8–13·7)	0	0
Combined	45/48	0·7 (0·5–1·1)	9·4 (7·5–13·6)	10·4 (3·8–20·9)	7·8 (2·3–17·9)	5·2 (1·0–14·8)	5·2 (1·0–14·8)
Age <50 years							
Radiotherapy	83/88	1·0	13·6 (11·6–15·6)	14·8 (8·3–23·0)	6·5 (2·5–13·1)	4·9 (1·5–11·3)	4·9 (1·5–11·3)
Combined	79/95	0·6 (0·4–0·8)	17·4 (15·3–21·5)	34·7 (25·3–44·3)	25·4 (17·0–34·7)	20·1 (12·4–29·1)	17·0 (9·8–25·9)
Age ≥50 years							
Radiotherapy	195/198	1·0	11·9 (10·6–12·6)	9·1 (5·6–13·7)	3·4 (1·4–6·7)	2·3 (0·8–5·2)	0·7 (0·1–3·5)
Combined	175/192	0·7 (0·5–0·8)	13·6 (11·8–15·1)	23·5 (17·7–29·7)	11·4 (7·3–16·5)	8·2 (4·7–12·9)	6·4 (3·2–11·0)
Age 50–60 years							
Radiotherapy	109/111	1·0	12·0 (10·0–14·2)	11·8 (6·6–18·6)	4·2 (1·5–9·4)	2·1 (0·4–6·6)	1·1 (0·1–5·1)
Combined	101/109	0·7 (0·5–0·9)	14·6 (13·6–17·9)	24·8 (17·1–33·2)	11·0 (6·0–17·7)	8·0 (3·8–14·2)	6·4 (2·6–12·6)
Age >60 years							
Radiotherapy	86/87	1·0	11·8 (10·4–12·7)	5·7 (2·1–12·0)	2·3 (0·4–7·2)	2·3 (0·4–7·3)	0
Combined	74/83	0·7 (0·5–0·97)	10·9 (8·9–14·9)	21·8 (13·5–31·2)	12·3 (6·1–20·8)	8·8 (3·6–16·9)	6·6 (2·1–14·7)
RPA class III							
Radiotherapy	36/39	1·0	14·8 (11·1–17·0)	20·5 (9·6–34·2)	10·3 (3·3–22·0)	6·8 (1·5–18·3)	6·8 (1·4–18·3)
Combined	31/42	0·5 (0·3–0·9)	18·7 (16·4–36·0)	40·5 (25·7–54·7)	31·5 (17·8–46·2)	28·0 (14·8–42·9)	28·0 (14·8–43·0)
RPA class IV							
Radiotherapy	146/150	1·0	13·3 (12·2–15·0)	11·3 (6·9–17·0)	4·1 (1·6–8·4)	3·3 (1·2–7·4)	1·6 (0·2–6·5)
Combined	136/152	0·6 (0·5–0·8)	16·3 (14·1–18·4)	29·1 (22·1–36·5)	15·8 (10·5–22·0)	11·3 (6·8–17·1)	8·9 (4·7–14·7)
RPA class V							
Radiotherapy	96/97	1·0	9·1 (7·9–11·8)	6·3 (2·6–12·3)	2·1 (0·4–6·6)	1·0 (0·1–5·1)	0
Combined	87/93	0·7 (0·5–0·9)	10·7 (9·0–12·6)	18·2 (11·1–26·6)	9·9 (4·8–17·3)	6·8 (2·6–13·9)	3·4 (0·7–9·9)
***MGMT* unmethylated**							
Radiotherapy	54/54	1·0	11·8 (10·0–14·4)	1·8 (0·1–8·6)	0	0	0
Combined	54/60	0·6 (0·4–0·8)	12·6 (11·6–14·4)	14·8 (7·2–25·0)	11·1 (4·7–20·7)	11·1 (4·7–20·7)	8·3 (2·7–18·0)
MGMT* methylated							
Radiotherapy	43/46	0·5 (0·3–0·7)	15·3 (13·0–20·9)	23·9 (12·9–36·9)	7·8 (2·2–18·3)	7·8 (2·2–18·3)	5·2 (1·0–15·0)
Combined	37/46	0·3 (0·2–0·4)	23·4 (18·6–32·8)	48·9 (33·7–62·4)	27·6 (15·4–41·4)	22·1 (11·0–35·7)	13·8 (4·5–28·2)

Data are percentage survival (95% CI) unless otherwise stated. *HR relative to radiotherapy unmethylated.

Table 2: **Kaplan-Meier overall survival including subgroup analyses**

prognostic factor for survival (HR 0·49, 95% CI 0·32–0·76, p=0·001; table 2, figure 4). Survival was significantly longer in patients treated with temozolomide and radiotherapy than in patients treated with radiotherapy alone, both in patients with a methylated and unmethylated *MGMT* promoter (table 2). Nevertheless, analysis of progression-free survival shows an advantage only for patients whose tumour had a methylated *MGMT* promoter and who were treated with temozolomide and radiotherapy (overall Wald test p<0·0001).[5] Of patients treated initially with radiotherapy only, slightly more with methylated *MGMT* promoters received salvage chemotherapy than did those with unmethylated *MGMT* (86·7% methylated *vs* 77·8% unmethylated, p=0·30; webappendix).

Acute toxicity was acceptable and quality of life was maintained in both treatment groups, as previously reported.[4,9] Non-haematological late toxicity was defined as toxicity not reported until 9 months after completion of radiotherapy. Severe late toxicity (grade 3 or 4 according to common toxicity criteria) was reported in only

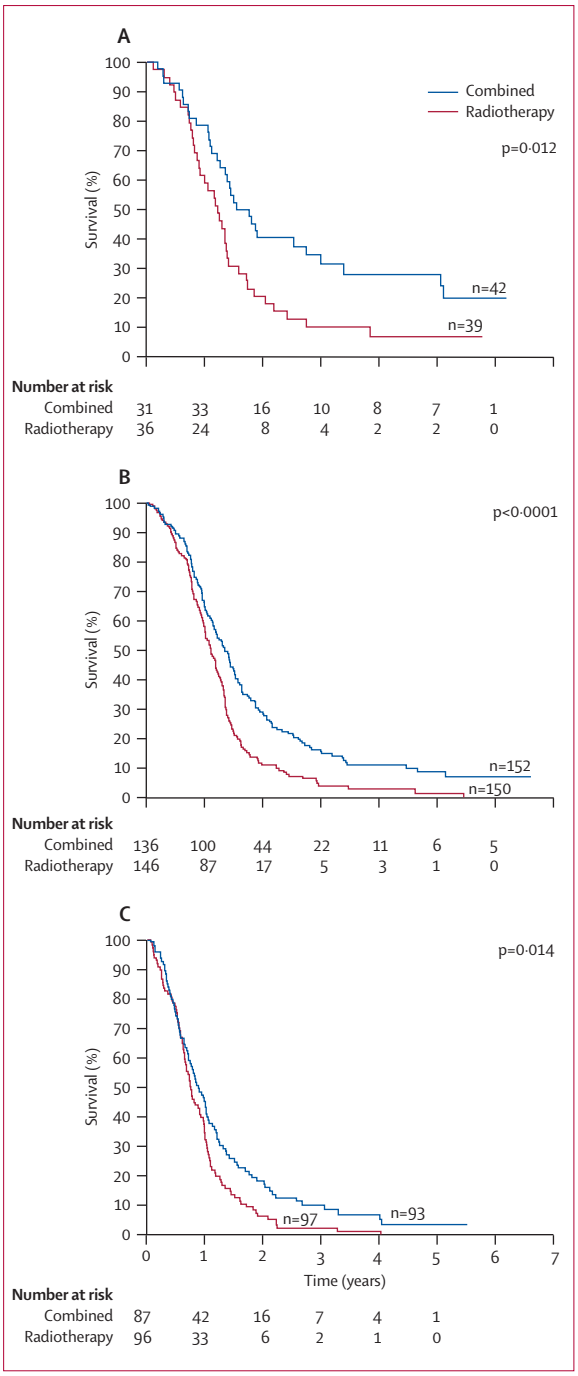

Figure 3: **Kaplan-Meier estimates of overall survival by treatment**
Recursive partitioning analysis (RPA) class III (A). RPA class IV (B). RPA class V (C).

	Radiotherapy (n=282)*	Combined (n=272)*
Second surgery	63 (22)	64 (24)
Repeat irradiation	11 (4)	13 (5)
Salvage chemotherapy	197 (70)	148 (54)
Supportive care only	73 (26)	106 (39)

Data are number (%). Some patients had more than one treatment. *Number of patients who progressed.

Table 3: **Salvage treatment by treatment group after progression**

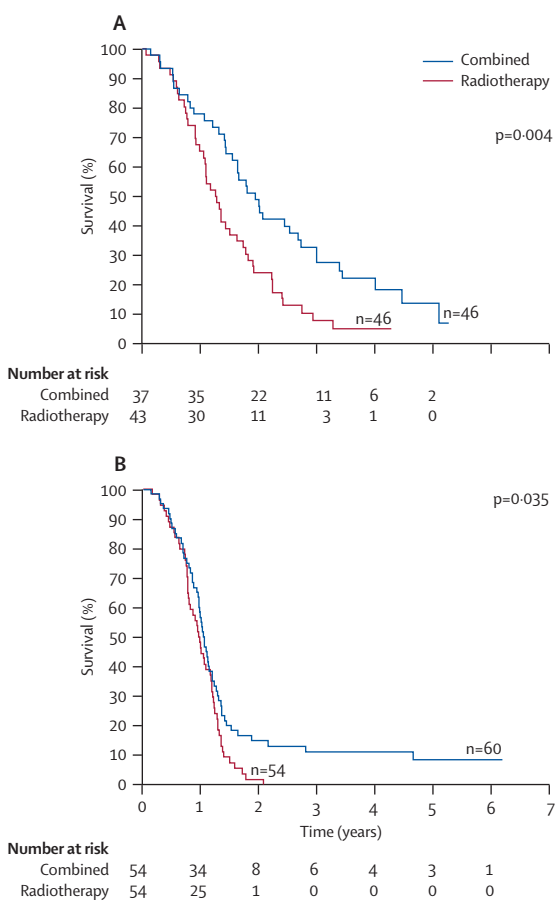

Figure 4: **Kaplan-Meier estimates of overall survival by *MGMT* status**
Patients with methylated *MGMT* (A). Patients with unmethylated *MGMT* (B).

three patients (one with visual deficit and one with seizures in the temozolomide group and one in the radiotherapy group with fatigue).

Discussion

For many years, attempts to improve the dismal prognosis of patients with glioblastoma—including changes to radiotherapy schedules, doses, and techniques[2,12,13] and the addition of nitrosourea-based chemotherapy combinations—have had little success.[3] In the late 1990s, temozolomide[14,15] seemed promising for the treatment of recurrent anaplastic glioma; however, in glioblastoma, the objective response rates were only 5–8%.[16,17] A pilot phase II study[18] showed that concomitant temozolomide with conventionally fractionated radiotherapy, followed by six cycles of the drug is feasible. An analysis of recurrence showed no difference between initial radiotherapy alone or temozolomide and radiotherapy, which supports the

hypothesis that initial combined therapy might effectively reduce tumour bulk and aggressiveness, but does not modify the disease course.[19]

In the phase III EORTC-NCIC study reported here, combined initial treatment for glioblastoma with temozolomide and radiotherapy improves survival compared with radiotherapy alone. The survival advantage of combined treatment lasts for up to 5 years of follow-up; nevertheless, most patients successfully treated with combined therapy eventually had tumour recurrence and died. Survival does not plateau, and combined treatment is unlikely to be curative for many patients. Most patients treated with radiotherapy alone in the present study have received salvage chemotherapy at recurrence or progression, and about half the patients initially treated with temozolomide received further chemotherapy at progression; salvage therapy was prescribed to more patients initially treated with radiotherapy alone. Survival nevertheless favours combined treatment, which supports the conclusion that the addition of chemotherapy early in the disease course and concomitantly with radiotherapy is the best strategy to incorporate new drugs. The date of progression was determined by the local investigator; and some patients probably had pseudoprogression, which was most likely in those given temozolomide who have a methylated *MGMT* promoter.[20] The high number of treatments given after progression or recurrence is evidence of a general change in attitude and a less pessimistic view of primary brain tumours. This change is also apparent in the outcome of patients treated in the control group, which is among the best reported for standard therapy. In many clinical trials, median overall survival was only 9–10 months.[13,21]

One question arising from the EORTC-NCIC trial is the contribution of the concomitant and the adjuvant drug doses. The trial was not designed to answer that question, but the issue is now being investigated in the ongoing EORTC-Intergroup trial on anaplastic astrocytoma (CATNON trial).[22] Preclinical data support a positive interaction between concurrent temozolomide and radiation: temozolomide and radiotherapy inhibit cell growth in a glioblastoma cell-line model;[23] temozolomide induces an arrest in G2/M in glioblastoma cell lines, and this is the most radiosensitive phase of the cell-cycle;[24] temozolomide has a radiation-enhancing effect in some glioma cell lines;[25] temozolomide inhibits radiation-induced invasion via inhibition of integrins;[26] and temozolomide increases radiation-induced DNA double-strand breaks and cell death in a glioblastoma model, but only when the drug is given concomitantly with radiotherapy and not sequentially.[27]

As in many other types of cancers, pretherapeutic prognostic factors play a major part in outcome of glioblastoma,[28–30] and these factors can have greater effects than treatment. The updated analysis shows that all prognostic subgroups benefit from combined treatment, including patients with impaired performance status or recursive partitioning analysis prognostic class V, the latter being only of borderline significance in our first report.[10] In the more favourable prognostic class III, survival at 2 years was 41%, and 28% at 5 years. Our data suggest that patients with good prognoses benefit most from combined treatment, although our study was not powered for statistical sensitivity analyses.

The role of surgery, in particular extensive surgery, in gliomas is a controversial topic. A recent randomised trial showed that fluorescence-guided maximum surgical resection will improve progression-free survival at 6 months.[31] In our trial, the extent of surgery was only recorded as reported by the neurosurgeons, without mandating immediate postoperative imaging and central review. Despite these limitations, patients who had complete tumour resection survived longer than did those with partial resection. The worst outcome was in patients with unresectable tumours who had biopsy only.

Prediction of benefit from therapeutic interventions remains a challenging task in oncology and is a prerequisite for individualised antitumour therapy.[32] Cytotoxicity of temozolomide is mediated mainly through methylation of the O6-position of guanine; this DNA damage is rapidly repaired by MGMT.[33–35] Epigenetic silencing of *MGMT* has been proposed as a predictive factor for benefit from chemotherapy with alkylating agents.[36,37] In a representative subgroup of patients, we determined the methylation status of the *MGMT* promoter; overall survival was best in patients with a methylated promoter treated with temozolomide and radiotherapy.[5] With long-term follow-up, survival of patients with an unmethylated promoter treated with combined therapy was also significantly longer than if treated with initial radiotherapy alone; however, this finding is based only on very few patients from whom molecular information is available and who were alive after more than 2 years. Tumour cells that do not express MGMT are probably more susceptible to chemotherapy with alkylating drugs, and only patients with methylated *MGMT* promoter treated with temozolomide and radiotherapy have long-term progression-free survival. These findings suggest a predictive value of the MGMT status for benefiting from chemotherapy with temozolomide. This study was not powered to show statistical significance for subgroup analyses and determination of interaction between treatment and *MGMT*-status; however, our findings are consistent with those of other reports.[36–39] Furthermore, overall survival as the primary endpoint is confounded by salvage chemotherapy with various alkylating drugs, including temozolomide, offered to most patients. The definitive predictive (and prognostic) value of *MGMT* promoter methylation status is being assessed in the ongoing RTOG/EORTC intergroup trial.[40]

Many patients with glioblastoma survive for several years; however, true long-term survival and cure

are not possible. In *MGMT*-promoter methylation we have identified the first predictive biomarker in brain tumours that allows selection of patients who will benefit most from treatment with temozolomide and radiotherapy. To adapt treatment to individual tumours' molecular profile, alternative strategies for patients with an unmethylated *MGMT* are needed together with further improvements for those with methylated *MGMT*. Additional deregulated molecular pathways underlying treatment resistance need to be targeted.[41] Several trials are investigating the addition of other treatments to temozolomide and radiotherapy, such as antiangiogenic drugs, inhibitors of the epidermal growth factor receptor or mammalian target of rapamycin, or integrins.[42–51] Until better treatments are available, radiotherapy with concomitant and adjuvant chemotherapy is the current standard of care. Rational choice of drugs, mechanism-based translational research, and systematic assessment of new targets and drugs are needed to improve outcome for patients with glioblastoma.

Contributors

RS and MJvdB wrote the protocol and designed the trial. ROM designed the radiotherapy and assured radiotherapy quality. JGC, CJV, and EE provided additional scientific advice, guidance, and reviewed the protocol. MJT did the quality of life analysis. RS and ROM coordinated the study. The *MGMT* biomarker study was designed and organised by MEH who also provided the research funds. All authors (except MEH, RCJ, SKL, KM, PW, EE, DL, AA, and TG) recruited patients to the study. RCJ, SL, KM, and PW did the pathology review, for which MEH provided organisational assistance. All data were collected by the participating centres, processed at the EORTC and NCIC data centres, and reviewed by RS, R-OM, and AA. TG did statistical analyses. The report was written by ROM and RS with contribution, review, and approval from all authors.

Conflicts of interest

RS, MJvdB, MEH, and MW have received research funding, honoraria for consultancy and speaking engagements (including travel and accommodation) from Schering-Plough and Merck KGaA, Darmstadt, Germany. ROM, WPM, PH, CM, and CJV have received research funding, honoraria for consultancy and speaking engagements (including travel and accommodation) from Schering-Plough. MEH has received research funding and consultancy honoraria from OncoMethylome Science, Liège, Belgium. CJV has received research funding and consultancy honoraria from UCB Pharma, Brussels, Belgium. SV has received honoraria for advisory services (including travel and accommodation) from Schering Plough.

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