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Prolonged survival for patients with newly diagnosed, inoperable glioblastoma with 3-times daily ultrafractionated radiation therapy

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Ultrafractionation of radiation therapy is a novel regimen consisting of irradiating tumors several times daily, delivering low doses (<0.75 Gy) at which hyperradiosensitivity occurs. We recently demonstrated the high efficiency of ultrafractionated radiotherapy (RT) on glioma xenografts and report here on a phase II clinical trial to determine the safety, tolerability, and efficacy of an ultrafractionation regimen in patients with newly and inoperable glioblastoma (GBM). Thirty-one patients with histologically proven, newly diagnosed, and unresectable supratentorial GBM (WHO grade IV) were enrolled. Three daily doses of 0.75 Gy were delivered at least 4 hours apart, 5 days per week over 6–7 consecutive weeks (90 fractions for a total of 67.5 Gy). Conformal irradiation included the tumor bulk with a margin of 2.5 cm. The primary end points were safety, toxicity, and tolerability, and the secondary end points were overall survival (OS) and progression-free survival (PFS). Multivariate analysis was used to compare the OS and PFS with the EORTC-NCIC trial 26981-22981/CE.3 of RT alone vs radiation therapy and temozolomide (TMZ). The ultrafractionation radiation regimen was safe and well tolerated. No acute Grade III and/or IV CNS toxicity was observed. Median PFS and OS from initial diagnosis were 5.1 and 9.5 months, respectively. When comparing with the EORTC/NCIC trial, in both PFS and OS multivariate analysis, ultrafractionation showed superiority over RT alone, but not over RT and TMZ. The ultrafractionation regimen is safe and may prolong the survival of patients with GBM. Further investigation is warranted and a trial associating ultra-fractionation and TMZ is ongoing.

Keywords: glioblastoma, inoperable, low doses, radiation therapy, ultrafractionated regimen

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults and is characterized by a high rate of local recurrence due to intrinsically radioresistant tumor cell clones. For decades, the standard of care remained essentially unchanged: surgical resection of as much of the tumor as was safe followed by once-daily fractionated radiation therapy and occasionally chemotherapy.[1–4] Although the introduction of whole-brain irradiation initially allowed an almost doubling of the median survival rates, the reported median overall survival (OS) rarely exceeds 9–12 months. More recently, the addition of concomitant and maintenance chemotherapy to radiotherapy (RT) has shown to prolong median survival by approximately 3 months and increase the 2-year survival rate by 2.5-fold. The greatest benefit is achieved in patients who have undergone prior tumor resection.[5,6] Radiation therapy remains the backbone in the management of GBM, and a better understanding of radiation biology may lead to improved outcomes.[2,3]

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Resistance mechanisms of mammalian cells to RT are more complicated that once believed. Several studies indicate that some human cell lines are sensitive to killing by low radiation doses (<1 Gy), this phenomenon has been termed *low-dose hyperradiosensitivity* (HRS).[7] Cells may be sensitive as lower radiation doses may not induce DNA repair mechanisms, but higher doses may cause enough damage to trigger repair mechanisms making cells increasingly resistant to RT.[7–16] In vitro we were able to demonstrate this phenomenon in a number of various human malignant glioma cell lines, when cells were irradiated with a device used daily in clinics (a particle linear accelerator, producing photons of 10 MeV at a dose rate of 2.43 Gy/min). Interestingly, daily repeated irradiation of cells with low doses compared with irradiation with a single biologically equivalent dose resulted in significantly higher cell killing (as measured using a clonogenic assay). Strikingly, experiments conducted on glioma xenografts demonstrated that repeated irradiation with low doses (0.8 Gy, 3 times a day) is more effective than a single dose (2 or 2.4 Gy, once a day) to inhibit tumor growth.[16]

To translate these observations to the clinic, we initiated a phase I/II clinical trial using an ultrafractionation protocol (3 times 0.75 Gy for a total of 67.5 Gy). The main purpose of this study was to assess the toxicity of an ultrafractionation regimen. This protocol was initiated before concomitant radiochemotherapy became standard of care. For this pilot trial, we purposely selected patients with the unfavorable clinical prognostic factor of newly unresectable GBM.

Patients and Methods

Patients

This phase I/II study was conducted in 7 French centers. Patients (≥18 years and who were able to give informed consent) with newly diagnosed, supratentorial, unresectable but histologically confirmed GBM (astrocytoma grade IV according to the WHO classification), with a WHO performance status of 0–2 were eligible. Patients were included based on local pathology, and the histology was subsequently centrally reviewed (J.F. Mosnier, CHU de Nantes, France). Patients who had undergone partial or complete tumor resection were not eligible.

Treatment

The radiation therapy regimen consisted of ultrafractionated focal irradiation with 3 daily doses of 0.75 Gy delivered at least 4 hours apart. Irradiation of the tumors was performed 5 days a week (Monday through Friday), for 6–7 consecutive weeks, 90 fractions for a total of 67.5 Gy. Irradiation was delivered to the gross tumor volume with a 2.5 cm margin for the clinical target volume. Radiotherapy was planned with dedicated computed tomography or magnetic resonance imaging (MRI) and three-dimensional planning systems; conformal ultrafractionated RT was delivered with linear accelerators with a nominal energy of 6 MeV or more. The patients were treated with thermoplastic immobilization masks to ensure adequate immobilization and reproducibility.

Patient Evaluation

Patients were assessed weekly for tolerance and toxicity during radiation therapy. The baseline examination included a cranial MRI (with and without contrast), physical and neurologic examination, and a Mini-Mental-Status score (MMS) and a quality-of-life questionnaire (EORTC—QLQ-C30, Brain Cancer Module BN-20). Baseline examination was performed at the end of the radiation therapy regimen (within the first 10 days after completion of ultrafractionation irradiation) and then every 2 months until death. The first MRI (at the end of RT) was designed to be the baseline imaging to evaluate tumor response, keeping in mind that RT artifacts could be present and should be considered in the interpretation of the MRI. Tumor progression was defined according to the modified WHO criteria (Macdonald criteria)[17] as an increase in tumor size by 25% (size of the product of the largest perpendicular diameters of contrast-enhancing tumor), the appearance of new lesions, or an increased need for corticosteroids. When there was tumor progression, patients were treated at the investigator's discretion, and the type of subsequent therapy (usually chemotherapy) was recorded.

Statistical Methods

The primary end points of the study were to document the treatment-related toxicity and tolerance of all patients treated with this novel regimen. Secondary end points were PFS and OS, reported as an intent-to-treat analysis on all 31 patients included. Survival times were calculated from the date of initial diagnosis (date of stereotactic biopsy) until death, date of progression, or last follow-up, respectively. The Kaplan–Meier technique was used to compute the estimates for PFS and OS parameters and their 95% confidence intervals. SPSS statistical software (SPSS, Inc.) was used for the primary analyses. SAS v 9.1.3 (SAS Institute, Inc.) was the statistical software used by the EORTC for survival analyses.

To estimate the efficacy of ultrafractionation therapy (ultra-RT) on patients, we compared our results with the subgroup of patients having undergone biopsy only and who are treated within the EORTC/NCIC 26981-22981/CE.3 trial.[18] This randomized trial established the combination of standard RT and concomitant and maintenance temozolomide chemotherapy (TMZ/RT) compared with once-daily fractionated RT alone.[18] The Cox regression was used to assess the effect of ultra-RT over RT or TMZ/RT without and with adjustment for possible confounding effects as reported in Gorlia et al.[19] Available factors were age and WHO performance status. MMSE was collected in about half of the patients only and was not included. Adjusted hazard

ratios (HR) were computed with 95% confidence intervals. Survival analyses were performed in the intent-to-treat population. *P* values in figures are from unadjusted analyses, and adjusted values are given in the text.

Results

Patient Characteristics

From September 2003 until June 2006, 31 patients were enrolled in this phase I/II study. There were 16 males and 15 females, including 4 patients who died before the beginning of irradiation. Multifocal GBM was diagnosed in 7 patients, and among them 4 received and completed ultrafractionated regimen. The median age of patients enrolled was 58 years, ranging from 37 to 76. Five patients were ≤50 years old (16.1%), 16 were ≥60 years old (51.6%), and 5 were ≥70 years old (16.1%). Seventeen patients had a performance status (PS) of ≤1, and 14 patients had a PS of 2. The median time from diagnosis at the beginning of ultrafractionated RT was 6 weeks (ranging from 2 to 10 weeks; Table 1). Unplanned interruptions in RT were brief and due to holidays, RT equipment maintenance, or technical problems. Central histopathologic review confirmed GBM in all but 1 patient (anaplastic oligodendroglioma).

Table 1. Patient's characteristics and survival status

	Evaluation			
	Treatment			Total (*n* = 124)
	EORTC/NCIC trial		Ultrafractionation	
	RT (*n* = 45)	TMZ/RT (*n* = 48)	Ultra-RT (*n* = 31)	
Extent of surgery B/PR/CR				
Biopsy	45 (100.0)	48 (100.0)	31 (100.0)	124 (100.0)
Sex				
Female	12 (26.7)	19 (39.6)	15 (48.4)	46 (37.1)
Male	33 (73.3)	29 (60.4)	16 (51.6)	78 (62.9)
Age (class)				
≤50 y	11 (24.4)	10 (20.8)	5 (16.1)	26 (21.0)
>50 and ≤60 y	21 (46.7)	16 (33.3)	12 (38.7)	49 (39.5)
>60 y	13 (28.9)	22 (45.8)	14 (45.2)	49 (39.5)
Age				
Median	55	59	58	57
Range	41–69	30–70	36–76	30–76
Performance status at entry				
0	14 (31.1)	17 (35.4)	3 (9.7)	34 (27.4)
1	24 (53.3)	22 (45.8)	14 (45.2)	60 (48.4)
2	7 (15.6)	9 (18.8)	14 (45.2)	30 (24.2)
Corticosteroids at entry				
No	2 (4.4)	6 (12.5)	2 (6.5)	10 (8.1)
Yes	43 (95.6)	42 (87.5)	29 (93.5)	114 (91.9)
Tumor location				
Frontal	10 (22.2)	9 (18.8)	5 (16.1)	24 (19.4)
Temporal	10 (22.2)	12 (25.0)	2 (6.5)	24 (19.4)
Parietal	6 (13.3)	10 (20.8)	4 (12.9)	20 (16.1)
Occipital	3 (6.7)	3 (6.3)	2 (6.5)	8 (6.5)
Multilobal/central	12 (26.7)	14 (29.2)	8 (25.8)	34 (27.4)
Other	2 (4.4)	0 (0.0)	0 (0.0)	2 (1.6)
Missing	2 (4.4)	0 (0.0)	10 (32.3)	12 (9.7)
PFS event				
No	0 (0.0)	2 (4.2)	2 (6.5)	4 (3.2)
Yes	45 (100.0)	46 (95.8)	29 (93.5)	120 (96.8)
Survival status				
Alive	2 (4.4)	2 (4.2)	2 (6.5)	6 (4.8)
Dead	43 (95.6)	46 (95.8)	29 (93.5)	118 (95.2)

Values are *n* (%).

Treatment Delivery Safety and Tolerability

A total of 27 patients started ultra-RT, and 22 completed the full course of the treatment (Fig. 1). Two patients with very large tumors progressed during the radiation therapy, and radiation therapy was discontinued prematurely after 48 and 56 Gy. One patient decided to have his care moved to another medical center, and 2 patients wished to receive standard once-daily RT for personal reasons. The most common adverse event was fatigue, as is frequently observed in standard cranial radiation therapy. The treatment was delivered to 7 patients as outpatient, while 18 patients remained hospitalized for the duration of treatment (5 days of hospitalization per week). Although the ultrafractionation regimen was a constraint to patients, it was well accepted. The completion of the quality-of-life questionnaire (EORTC—QLQ-C30, Brain Cancer Module BN-20) was required at each clinical examination; however, they were completed and reported for a minority of patients, and thus did not allow further analysis.

Main adverse effects reported were:

- Fatigue grade II in 20 patients
- Headache grade I in 2 patients
- Skin reaction grade I in 11 patients
- Alopecia grade II in 12 patients.
- No nausea or seizures were noted.

Overall, the ultrafractionation regimen was well tolerated.

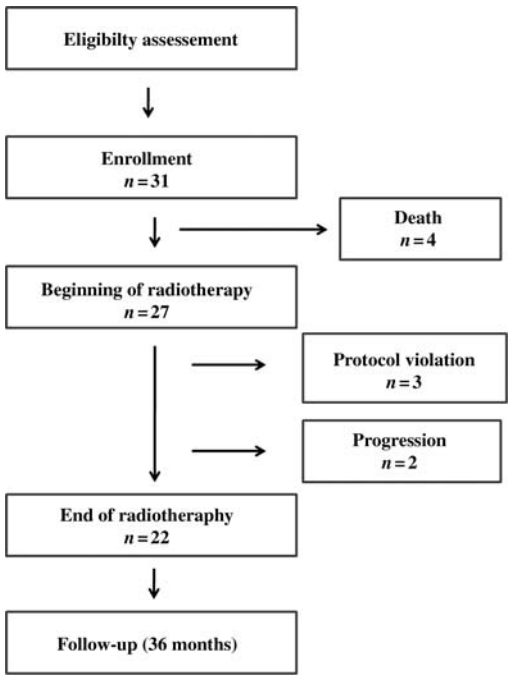

Fig. 1. Flow chart of the study.

Survival

After a median follow-up of 4 years, 2 patients remained alive (6.5%) and 29 patients had died (93.5%). The median OS was 9.5 months (95% CI, 8.5–11. 6 months). The OS rate at 6, 12, 18, and 24 months was, respectively, 74, 29, 19, and 15%. The median PFS was 5.1 months (95% CI, 4.7–8.1 months). The PFS rate at 6, 12, 18, and 24 months was, respectively, 45, 13, 6, and 6%. No difference was found in the median survival for age and gender: 8.4 months for males (95% CI, 4–10.8 months) vs 8.9 months for females (95% CI, 1.1–12.9 months), 8.4 months for $\leq$55 years (95% CI, 6.5–9 months) vs 9.5 months for $>$55 years (95% CI, 4–12.9 months). Tumor response at the end of RT was evaluated based on an MRI performed within 10 days and 2 months after the end of RT; no complete or partial response was seen, and 2 progressive disease and 8 stabilizations were observed among patients receiving ultrafractionation radiation therapy. In this trial, it was recommended that at tumor progression, fotemustine was to be used and administered as the first-line salvage chemotherapy, but patients were treated at the physician's discretion. A total of 21 patients had documented disease progression, and 16 patients received chemotherapy (fotemustine in 14 and TMZ in 2 cases). One patient underwent partial tumor resection, and 1 patient was treated with radiosurgery at progression. Responses to salvage chemotherapy were not recorded.

Historical Comparison with EORTC/NCIC Trial for PFS and OS

To further assess the effect of ultra-RT on patients, we compared our results with the results obtained in the EORTC/NCIC trial on patients with biopsy only. The EORTC/NCIC trial compared the efficiency of RT alone and RT plus TMZ (TMZ/RT).[18] All results are reported on an intent-to-treat population of 31 patients. In the EORTC/NCIC trial, there was an upper age limit of 70, while we included 5 patients between 70 and 76 years. Performance status was also less favorable in our patient population (Table 1). In the survival analyses, the prognostic value of age and performance status was not statistically significant. Consequently, there was no large difference between the unadjusted and adjusted analyses.

Ultra-RT vs EORTC/NCIC RT

In PFS analyses, ultra-RT showed a significant difference for an improved outcome over EORTC/NCIC RT (adjusted, $P = .007$, HR = 0.69, 95% CI 0.53–0.90; Fig. 2). With respect to OS, no difference could be detected (adjusted, $P = .11$, HR = 0.82, 95% CI 0.64–1.05; Fig. 3).

Ultra-RT vs EORTC/NCIC TMZ/RT

In PFS analyses, no difference was seen between RT-hyper and EORTC/NCIC TMZ/RT (adjusted, $P = .54$, HR = 1.16, 95% CI 0.72–1.89, Fig. 4).

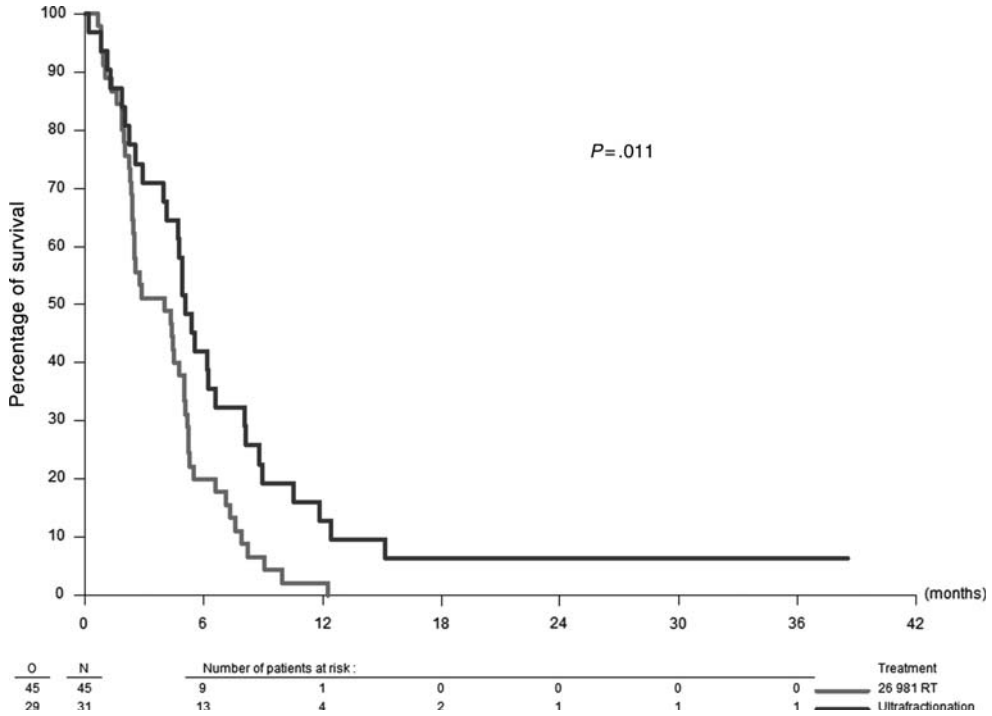

Fig. 2. Progression-free survival for EORTC/NCIC RT vs ultrafractionation.

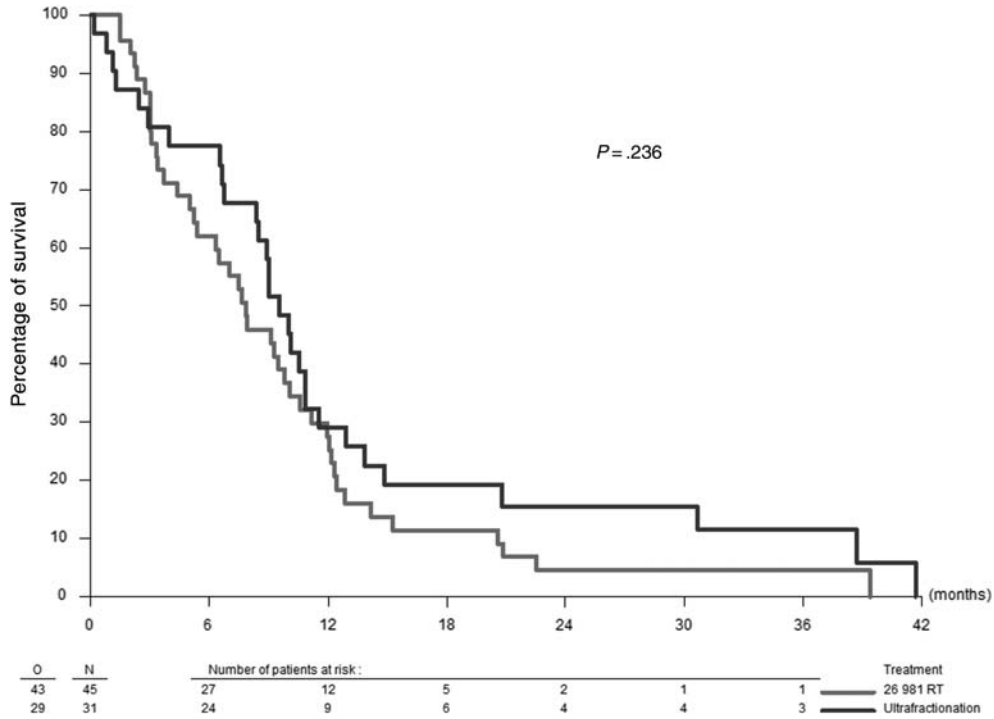

Fig. 3. Overall survival for EORTC/NCIC RT vs ultrafractionation.

Ultra-RT was also not significantly different from EORTC/NCIC TMZ/RT in OS analyses (adjusted, $P = .87$, HR = 0.96, 95% CI 0.60–1.55; Fig. 5).

In our study, median and 2-year survival was 9.5 months and 15.5%, compared with 7.9 months and 4.6% in the RT arm of EORTC/NCIC trial; however, the patients treated with chemo-RT in that trial reached a similar outcome to our results with a median and 2-year survival rate of 9.4 months and 10.4%, respectively (Tables 2 and 3).

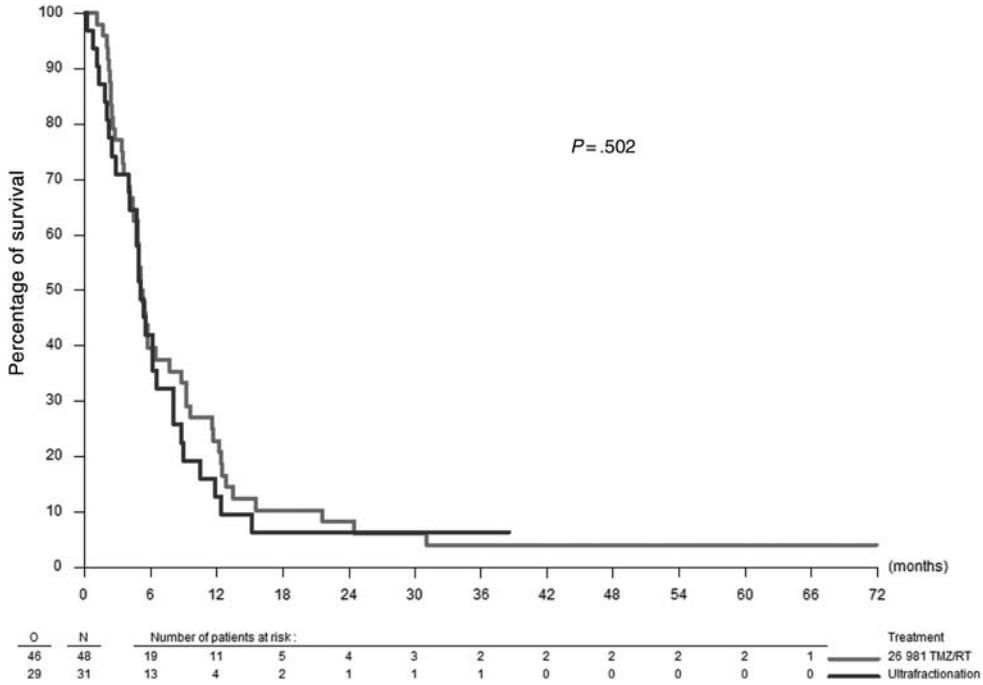

Fig. 4. Progression-free survival EORTC/NCIC TMZ/RT vs ultrafractionation.

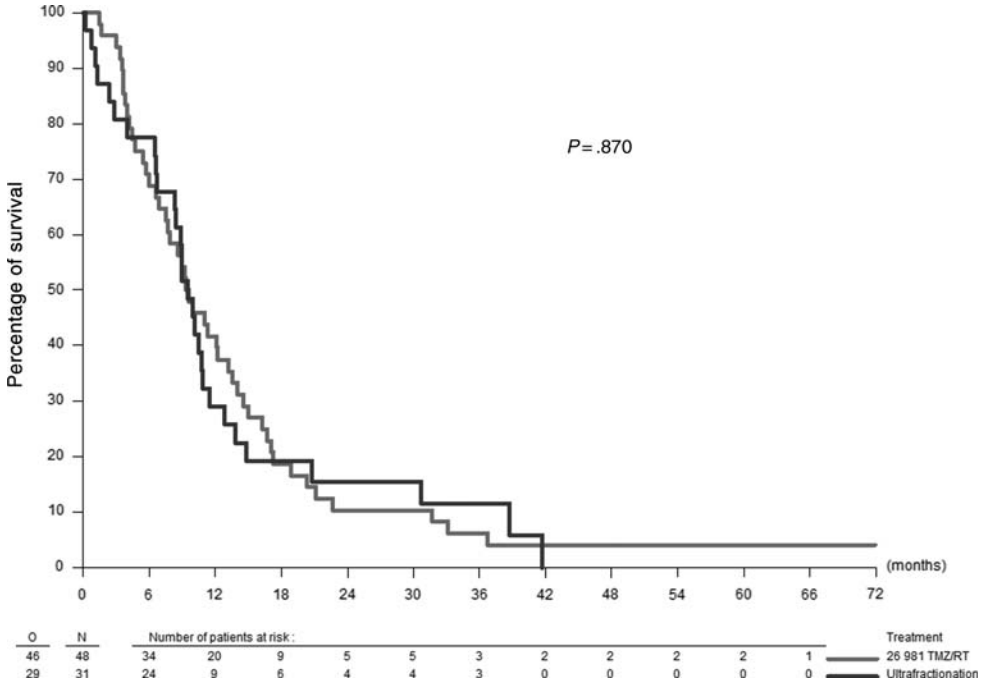

Fig. 5. Overall survival EORTC/NCIC TMZ/RT vs ultrafractionation.

Table 2. Progression-free survival (multivariate analysis)

Treatment	Patients (*n*)	Observed events (O)	Median (95% CI) (mo)	% at 1 y (95% CI)	% at 2 y (95% CI)
EORTC/NCIC RT	45	45	4.04 (2.46, 5.06)	2.22 (0.18, 10.15)	0.00
EORTC/NCIC TMZ/RT	48	46	5.13 (4.47, 8.84)	22.92 (12.30, 35.49)	8.33 (2.67, 18.21)
Ultra-RT	31	29	5.09 (4.73, 8.08)	12.90 (4.07, 26.98)	6.45 (1.15, 18.62)

Table 3. Overall survival (multivariate analysis)

Treatment	Patients (*n*)	Observed events (O)	Median (95% CI) (mo)	% at 1 y (95% CI)	% at 2 y (95% CI)
EORTC/NCIC RT	45	43	7.85 (6.37, 10.58)	27.56 (15.40, 41.15)	4.59 (0.84, 13.73)
EORTC/NCIC TMZ/RT	48	46	9.40 (7.52, 13.57)	41.67 (27.72, 55.03)	10.42 (3.82, 20.86)
Ultra-RT	31	29	9.53 (8.48, 11.56)	29.03 (14.52, 45.27)	15.48 (5.34, 30.48)

Discussion

Radiation therapy remains the backbone of care for GBMs, even in patients who have undergone a prior presumed complete resection. The infiltrative nature of these tumors makes a truly complete resection nearly impossible in most cases.[1–4] Standard fractionated RT delivers a total radiation dose of 60 Gy, given in 30 fractions over 6 weeks. The target is mostly enhancement of the tumor as visualized on CT or MRI, with a wide margin of 2–3 cm.[2–4,20] Although the radiation therapy is not a curative treatment for GBMs, it is allowing the prolongation of life with optimization of quality of life.[20–23] Still, radiation therapy may be improved and the development of new modalities of RT is urgently needed.

The HRS phenomenon, noted in certain human malignant glioma cell lines, may be translated into an innovative and new treatment regimen for GBMs. Our previous studies on xenografts had shown that ultrafractionation, which is taking advantage of the HRS, could be effective on GBM.[16] These results were encouraging and supported the development of this phase I/II study. Since the safety and tolerance of this new regimen of radiation therapy, three doses per day at least 4 hours apart, was unknown, the present study was designed to assess toxicity and feasibility. Our study demonstrates that such a radiation therapy regimen is practicable and well tolerated. Our results obtained in a patient population with very unfavorable prognostic factors (biopsy only, PS 2%–45%, 16% of patients >70 years, 4 patients died before treatment start) are encouraging with a trend toward improved outcome when compared with a somewhat more favorable group of patients treated with initial RT only within the EORTC/NCIC trial. Furthermore, the results of these two studies were substantially better than prior reports of standard RT plus adjuvant chemotherapy.[24] Our results with ultrafractionation alone are comparable with the results with TMZ/RT in the EORTC/NCIC trial. At 2-years, 15.48% (95% CI 5.34–30.48) of our patients were still alive, compared with 4.59% (95% CI 0.48–13.73) and 10.42% (95% CI 3.82–20.86) of patients treated with standard RT and TMZ/RT in the EORTC/NCIC trial. This effect cannot be explained by salvage second-line therapies, as over half of these patients did not receive any further treatment.

Attempts to evaluate alternative fractionation regimens have been developed, eg, hyperfractionation and accelerated fractionation. In the case of hyperfractionation, the dose per fraction is decreased, the number of fractions increased, the total dose is increased, and the total treatment time remains similar to conventional therapy time. In accelerated fractionation regimens, the total dose and dose per fraction remain unchanged, but the number of fractions per day is increased and thus the overall treatment time is reduced and treatment intensity increased.[25] Few clinical studies were developed and tested on malignant glioma patients with these alternative regimens,[26–33] and in those reported, adjuvant chemotherapy was frequently administered. The results reported were similar to the historical data, but few neurologic toxicities were noted. Unfortunately, no significantly improved outcome was demonstrated.[26–33] The rationale for an ultrafractionation regimen is radically different since it is taking advantage of the HRS. The dose per fraction is lower and extrapolated from experimental studies where cells and xenograft tumors were hypersensitive to the irradiation. It is the first time that an ultrafractionation radiation therapy regimen was clinically performed. The efficacy of our ultrafractionation regimen can be explained by the *HRS*, and is unlikely due to the modest increase in total dose (67.5 Gy versus 60 Gy), since all previous attempts of dose escalation did not demonstrate any improved outcome. Indeed, the tumor became more radiosensitive as the total doses delivered increased, with respect to cerebral toxicity.

It is established that the dose per fraction is correlated to the tolerance; low dose per fraction is correlated with the development of late radiation-associated side effects. No neurologic symptomatology evoking a post-RT leuco-encephalopathy was recorded. However, the true long-term effects cannot be evaluated in this poor-patient population. Fatigue was the main adverse event recorded as is usually observed with standard cranial irradiation. Our results suggest that ultrafractionation radiation therapy could improve or influence GBM patient's outcome at least in a subset of patients. Overall, it is tempting to speculate that a treatment combining ultrafractionation and TMZ may improve the efficacy of both treatments, and prospective evaluation is warranted.

Of course there are limitations to our pilot study. We treated a negatively selected patient population, and the sample size is relatively small. Of 31 patients included, 4 patients never started treatment and only 22 completed the prescribed regimen; however, the conclusions remain unchanged if we analyze only the treated population. Nevertheless, the treatment regimen proved to be feasible, was well tolerated, and merits further evaluation in combination with current standard concomitant chemotherapy agents.

Conflict of interest statement. None declared.

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