*Neuro-Oncology* 12(7):725–735, 2010.
doi:10.1093/neuonc/noq030
Advance Access publication April 2, 2010



# Oncological patterns of care and outcome for 952 patients with newly diagnosed glioblastoma in 2004

Luc Bauchet, Hélène Mathieu-Daudé, Pascale Fabbro-Peray, Valérie Rigau, Michel Fabbro, Olivier Chinot, Loreleï Pallusseau, Charlotte Carnin, Karl Lainé, Aline Schlama, Agnes Thiebaut, Maria Cristina Patru, Fabienne Bauchet, Martine Lionnet, Michel Wager, Thierry Faillot, Luc Taillandier, Dominique Figarella-Branger, Laurent Capelle, Hugues Loiseau, Didier Frappaz, Chantal Campello, Christine Kerr, Hugues Duffau, Monique Reme-Saumon, Brigitte Trétarre, Jean-Pierre Daures, Dominique Henin, François Labrousse, Philippe Menei, and Jérome Honnorat; with the participation of Société Française de Neurochirurgie (SFNC) and the Club de Neuro-Oncologie of the Société Française de Neurochirurgie (CNO-SFNC), Société Française de Neuropathologie (SFNP), and Association des Neuro-Oncologues d'Expression Française (ANOCEF)

*Department of Neurosurgery and INSERM U583 (L.B., H.D.), Department of Neuropathology (V.R.), Hôpital Saint Eloi-Gui de Chauliac, Centre Hospitalier Universitaire de Montpellier, Montpellier, France; Department of Epidemiology, Groupe de Neuro-Oncologie du Languedoc-Roussillon (L.B., H.M.-D., V.R., M.F., L.P., K.L., F.B., Chan.C., C.K., M.R.-S.), Department of Medical Oncology (M.F.), Department of Radiation Oncology (C.K., M.R.-S.), and Registre des Tumeurs de l'Hérault (H.M.-D., B.T.), Centre de Lutte Contre le Cancer Val d'Aurelle, Montpellier, France; Department of Biostatistics, Institut Universitaire de Recherche Clinique, Montpellier, France (P.F.-P., J.-P.D.); Department of Biostatistics and Epidemiology (P.F.-P., J.-P.D.), Department of Neurology (Chan.C.), Centre Hospitalier Universitaire de Nîmes, Nîmes, France; Department of Neuro-Oncology (O.C., A.T.), Department of Neuropathology and Inserm U 911 (D.F.-B.), Hôpital de la Timone, Université de la Méditerranée, Marseille, France; Department of Neuro-Oncology, Hôpital Neurologique, Nancy, France (Char.C., L.T.); Université Lyon1, UMR-S842 INSERM Lyon, Hospices Civils de Lyon, Lyon, France (A.S., J.H.); Department of Neurology, Hôpital Neurologique, Bron, France (M.L., J.H.); Department of Neurosurgery, Centre Hospitalier Région Annecy, Pringy, France (M.C.P.); Department of Neurosurgery, Centre Hospitalier Universitaire La Milétrie, Poitiers, France (M.W.); Department of Neurosurgery, AP-HP, Hôpital Beaujon, Clichy, France (T.F.); Department of Neurosurgery, Hôpital de la Pitié-Salpêtrière, Paris, France (L.C.); Department of Neuropathology, Centre Hospitalier Universitaire Bichat, Paris, France (D.H.); Department of Neurosurgery, Hôpital Pellegrin, Université Bordeaux 2, Bordeaux, France (H.L.); Department of Pediatric and Adult Neuro-Oncology, Centre Leon Bérard, Lyon, France (D.F.); Department of Pathology and Neuropathology, Centre Hospitalier Universitaire, Limoges, France (F.L.); and Department of Neurosurgery, Centre Hospitalier Universitaire, Angers, France (P.M.)*

Received November 5, 2009; accepted December 7, 2009.

**Corresponding Author:** Luc Bauchet, MD, Department of Neurosurgery, Hospital Gui de Chauliac, CHU Montpellier, 80 avenue A. Fliche, 34295 Montpellier cedex 5, France (l-bauchet@chu-montpellier.fr).

**This report, an audit requested by the French government, describes oncological patterns of care, prognostic factors, and survival for patients with newly diagnosed and histologically confirmed glioblastoma multiforme (GBM) in France. The French Brain Tumor DataBase, which is a national multidisciplinary**

**(neurosurgeons, neuropathologists, radiotherapists, neurooncologists, epidemiologists, and biostatisticians) network, prospectively collected initial data for the cases of GBM in 2004, and a specific data card was used to retrospectively collect data on the management and follow-up care of these patients between January 1, 2004, and December 1, 2006. We recorded 952 cases of GBM (male/female ratio 1.6, median age 63.9 years, mean preoperative Karnofsky performance status [KPS] 79). Surgery consisted of resection (RS; $n = 541$) and biopsy ($n = 411$); 180 patients did not have subsequent oncological treatment. After surgery, first-line treatment ($n = 772$) consisted of radiotherapy (RT) and temozolomide (TMZ) concomitant +/− adjuvant in 314 patients, RT alone in 236 patients, chemotherapy (CT) alone in 157 patients, and other treatment modalities in 65 patients. Median overall survival was 286 days (95% *CI*, 266–314) and was significantly affected by age, KPS, and tumor location. Median survival (days, 95% *CI*) associated with these main strategies, when analyzed by a surgical group, were as follows: RS + RT-TMZ$_{(n=224)}$: 476 (441–506), biopsy + RT-TMZ$_{(n=90)}$: 329 (301–413), RS + RT$_{(n=147)}$: 363 (331–431), biopsy + RT$_{(n=89)}$: 178 (153–237), RS + CT$_{(n=61)}$: 245 (190–361), biopsy + CT$_{(n=96)}$: 244 (198–280), and biopsy only$_{(n=118)}$: 55 (46–71). This study illustrates the usefulness of a national brain tumor database. To our knowledge, this work is the largest report of recent GBM management in Europe.**

**Keywords:** database, glioblastoma, neuro-oncology, neurosurgery, survival.

Primary central nervous system (CNS) tumors are a complex heterogeneous group of pathologic entities that may be benign, malignant, or of unpredictable evolution.[1–4] Glioblastoma multiformes (GBMs) are the most frequent malignant primitive brain tumors[5] and account for 19%–25% of all primary CNS tumors.[6–9] GBMs are a major public health problem, and patterns of care for patients with GBM evolve with time and may vary between different medical institutions.

Well-documented published data concerning GBM oncological practice in multicenter/consortium studies or at the population level are rare.[10–15] Population-based studies are very useful for describing such epidemiologic data as incidence, median age at diagnosis, sex ratio, prognostic factors, and survival and for studying associated or causal factors.[16–23] However, oncological management is usually presented with few details and often concerns a period of time in the past for which medical practices have since changed.

Clinical trials are conducted to allow safety and efficacy data to be collected for new drugs or devices. GBM phase III studies are very important but rare;[24–26] they concern a selected population and the routine practices can differ. Currently, the "standard" for treating patients with newly diagnosed GBM is based on a single phase III study.[25]

French neurosurgeons, neuropathologists, and neurooncologists, in collaboration with epidemiologists and biostatisticians, have recently established the French Brain Tumor DataBase (FBTDB). Currently, the FBTDB is the largest database for primary CNS tumors in Europe.[7,27,28] The main objective of this project is to prospectively record all such tumors in France for which histological diagnosis is available. The long-term goals of the FBTDB are to create a national registry and a network to (i) perform epidemiological studies, (ii) implement a new database and use it for setting up both clinical and basic research protocols, and (iii) allow evaluation of the medical practices of a particular area or of the entire country to harmonize the healthcare of patients affected by primary CNS tumors.

The present work is an audit requested by the French government (Institut National du Cancer—INCa) and describes the oncological patterns of care (surgery, radiotherapy [RT], and chemotherapy [CT]), prognostic factors, and survival for patients with newly diagnosed and histologically confirmed GBM in France in 2004. The preliminary results were presented at the American Society of Clinical Oncology meeting.[28]

## Materials and Methods

The FBTDB identified the patients with newly diagnosed and histologically confirmed primary CNS tumors (since January 1, 2004) and prospectively collected initial data. All neurosurgeons and neuropathologists in France participating in the FBTDB were instructed to complete a data file card for each patient who underwent surgery. Histological diagnosis was always made by experienced neuropathologists, and more than 90% of the neuropathologists worked in public academic centers. The methodology for the FBTDB accrual was described in detail previously.[7] In summary, the data file card is placed in all French operating rooms where surgery for primary CNS tumors is practiced and systematically sent along with the sample to the pathology lab. The card requests socio-demographic, clinical, radiological, surgical, and pathological data (including an optional question about cryopreservation of the samples) and is simple to complete. The first parts of the card (socio-demographic, clinical, radiological, and surgical data) are completed by the neurosurgeon. The second part is completed by the pathologist. The card is then mailed to the Tumor Registry in Herault (TRH, Registre des Tumeurs de l'Hérault, Montpellier, France), which has extensive expertise in working with tumor data and has the required authorizations for recording data with personal identifiers. The TRH compiles all cards and analyzes the data in collaboration with the University Institute of Clinical Research of Montpellier-Nîmes (IURC, Institut Universitaire de Recherche Clinique, Montpellier-Nîmes, France).

This current study includes patients with newly diagnosed and histologically confirmed GBM in 2004 (from 1 January to December 31). Histological diagnosis

according to the ICD-O-3 (WHO 2000) classification from Kleihues and Cavenee[29] was used. The 2007 WHO classification of tumors of the CNS[1] was not used because these histological diagnoses were made in 2004. Only GBM corresponding to ICD-O code 9440/3 were included (giant cell GBMs and gliosarcomas were excluded). Patients who had previous surgery for glioma or who were known to have previous low-grade glioma were excluded.

A specific data card was used to collect retrospectively data on the oncological management (surgery, RT, and CT) and the follow-up care of these patients for the period from January 1, 2004, to December 1, 2006. Attending clinicians recorded this information on the card, and 1 person was specifically assigned to collect the data cards for 1 year. Demographic, clinical, and radiographic information was collected. It was recommended to the neurosurgeon that the extent of resection (RS) be evaluated from the postoperative CT scan and/or MRI, but central review was not performed. Oncological treatments received by the patients were recorded. The starting and ending dates for RT and total dose (in grays) were requested. For CT, the starting and ending dates and name and modality of administration were also requested. In this study, the term of concomitant radiochemotherapy (CRC) was employed strictly speaking and was limited to the association of CT during the 6 weeks of RT. The term "sequence of CT" was defined as the administration of the same drug(s) with the same modality. For reasons of statistical analysis, the CRC followed by adjuvant CT were considered 2 sequences of treatment. Biopsy was considered a surgical procedure but not a treatment procedure. For the purpose of this analysis, only patients with sufficient information, including the notification of the modalities of the first treatment (or the absence of treatment), were included. The TRH compiled all the specific GBM cards and analyzed the data in collaboration with the IURC.

Statistical analysis was performed using SAS software, version 8.1. The analysis included a descriptive part of the original data and the oncological treatments received by the patients. Quantitative variables were expressed by the mean, standard deviation, quartiles, and extreme values. Qualitative variables were expressed by the numbers and percentages. Survival was estimated by the Kaplan–Meier method and defined as the time from first surgery (biopsy or RS, and corresponding to the date of the histological diagnosis) to death or censored at the date of last follow-up. The cut-off date was December 1, 2006. The log-rank test was used to compare survival by age at diagnosis ($\leq$55, ]55–65, ]65–71, $>$71 years), preoperative Karnofsky performance status (KPS) ($\leq$60, 70–80, 90–100), location of the tumor (right, left, bilateral), first treatment (RS, CRC, CT, RT), first surgery (total RS, subtotal RS, partial RS, not otherwise specified [NOS] RS, biopsy), 2 first oncological managements (biopsy or RS, followed by CT or RT or CRC), and surgery (biopsy or RS) in the CRC with temozolomide (TMZ) concomitant +/− adjuvant as first-line treatment after the surgery group. The statistical analysis included a multivariate analysis (the Cox model) to determine the effect of therapeutic factors independent of previous prognostic factors. The 7 mutually exclusive treatment patterns of interest were biopsy + CRC, biopsy + CT, biopsy + RT, RS + CRC, RS + CT, RS + RT, and all other modalities. The relative risk (RR) of mortality was estimated by their 95% confidence interval (*CI*). We regarded $P$ values $<.05$ as statistically significant. The Bonferroni correction was used to account for the inflation of alpha risk during the multiple comparison tests.

The study was approved by the French government (INCa), and all the French societies involved in the neuro-oncology field: Association des Neuro-Oncologues d'Expression Française (ANOCEF), Société Française de NeuroChirurgie (SFNC), and Société Française de Neuropathologie (SFNP).

## Results

This study included 952 patients in France with newly diagnosed and histologically confirmed GBM (corresponding to ICD-O code 9440/3 only) in 2004; the study excluded patients with previous surgery for glioma of any grade and patients with a history of low-grade glioma. Of the 43 participating neurosurgical departments located throughout France, 36 were public centers (34 academic centers and 2 general hospitals) and 7 were private institutions. In terms of the number of patients, however, the proportions were 94% from public centers and 6% from private institutions.

### *Population Characteristics*

The clinical characteristics of the patients are shown in Table 1. The male-to-female ratio was 1.6. The median age at diagnosis was 63.9 years (range, 10–84 years), and nearly one quarter of the patient population was older than 71 years. The time between the first clinical sign and histological diagnosis was $<$4 months in 89% of cases. Neurological deficit and mental status disorders were the most frequent signs and symptoms. The median KPS was 80 (range 10–100), and the mean KPS was 79. The preoperative KPS was noted in the medical reports of only 474 of the 952 patients. In this cohort, contrast enhancement was present in preoperative MRI or CT scan in more than 98% of the cases. Cryopreservation of the samples was reported to be performed in 13%, not to be performed in 28%, and not reported in 59% of the cases.

### *Oncological Management*

The oncological management of the 952 patients is shown in Table 2. Complete macroscopic or subtotal RS was performed in 378 patients (40%), RT in 654 patients (69%), and CT in 643 patients (68%); 118 patients (12%) did not receive any oncological treatment (only biopsy), 62 patients (7%) had RS alone, and 3 patients had 2 RS only.

**Table 1.** Clinical characteristics of the 952 patients at baseline

| Characteristic | *N* (%) |
|---|---|
| Sex (no. reported: 952) | |
| Male | 587 (61.7) |
| Female | 365 (38.3) |
| Age per quartile (no. reported: 952) | |
| ≤55 y | 231 (24.3) |
| ]55–65 y | 280 (29.4) |
| ]65–71 y | 209 (21.9) |
| >71 y | 232 (24.4) |
| Signs and symptoms (no. reported: 906) | |
| Epilepsy | 234 (26) |
| Headache | 257 (28) |
| High intracranial pressure | 165 (18) |
| Mental status disorders | 381 (42) |
| Sensory-motor deficit | 453 (50) |
| Other | 94 (10) |
| Time between first sign and histological diagnosis (no. reported: 822) | |
| <1 month | 279 (33.9) |
| 1–2 months | 246 (29.9) |
| 2–3 months | 139 (16.9) |
| 3–4 months | 66 (8.0) |
| ≥4 months | 92 (11.2) |
| Preoperative KPS (no. reported: 474) | |
| 90–100 | 195 (41.1) |
| 70–80 | 176 (37.1) |
| ≤60 | 103 (21.7) |
| Location of the tumor (no. reported: 813) | |
| Right | 395 (48.6) |
| Left | 375 (46.1) |
| Bilateral | 43 (5.3) |

Abbreviation: KPS, Karnofsky performance status.

After surgery, first-line treatment ($n = 772$) consisted of RT alone in 236 patients, CT alone in 157 patients, CRC in 373 patients (including RT and TMZ concomitant +/− adjuvant [RT-TMZ] in 314 patients), and other treatment modalities in 6 patients.

*Survival and prognostic factors.* At the cut-off date (December 1, 2006), 823 (86.4%) patients had died, 66 patients (6.9%) were alive (29 patients were with disease progression, 35 presented no evidence of disease, and 2 were without information on their tumor status), and 63 patients (6.6%) were lost to follow-up. Of these latter 63 patients, at the last follow-up, 24 patients were alive with progression, 12 were alive without progression, and 27 were alive without information on their tumor status.

The median overall survival was 9.4 months (286 days, 95% $CI = 266–314$ days). The survival probabilities were 39% (95% $CI = 36\%–42\%$) at 1 year, 20% (95% $CI = 17\%–23\%$) at 1.5 years, and 12% (95% $CI = 10\%–14\%$) at 2 years. The main prognostic factors were age, KPS, and bilateral location (Fig. 1). In this study, which considered only patients with GBM, we did not find any significant relation between survival and time between first clinical sign and histological diagnosis.

*Survival and oncological management.* We analyzed survival according to the oncological management, including no oncological treatment (biopsy only), surgery (partial, subtotal, "total" RS), RT, CT, and CRC (Fig. 2).

Analysis of survival, based on the absence of any oncological treatment vs at least 1 oncological treatment, showed significant differences in median survival (MS), as follows: $MS_{untreated\text{-}patients} = 1.8$ months (55 days, 95% $CI = 46–71$ days) and $MS_{treated\text{-}patients} = 10.8$ months (329 days, 95% $CI = 306–351$ days; $P < .0001$, log-rank test). However, taking into account the 4 age classes (divided into quartiles), KPS, and location of the tumor (bilateral vs nonbilateral), there were also significant differences between these 2 groups (untreated and treated patients) for each prognostic factor, with $P < .0001$ in each instance.

Analysis of survival, according to the first performed treatment (no treatment, RS, CRC, CT, or RT) regardless of treatment(s) performed afterward, showed significant overall differences, with $MS_{RS} = 12.4$ months, $MS_{CRC} = 10.8$ months, $MS_{CT} = 8$ months, and $MS_{RT} = 5.9$ months ($P < .0001$, log-rank test; Fig. 2A). When considered according to the first surgery performed, MS values for "total" RS, subtotal RS, NOS RS, partial RS, and biopsy were 14, 12.2, 11, 8.7, and 5.2 months, respectively, with a significant overall difference ($P < .0001$, log-rank test; Fig. 2B). After the Bonferroni correction, significant differences ($P < .005$) still existed between biopsy and all types of RS (biopsy vs partial RS, $P = .0008$; biopsy vs NOS RS, $P = .0002$; biopsy vs subtotal RS, $P < .0001$; biopsy vs "total" RS, $P < .0001$).

Analysis of survival, according to initial biopsy or RS, followed by RT or CT or CRC, regardless of treatment(s) performed afterward, showed overall significant differences, with $MS_{B+RT} = 5.9$ months, $MS_{B+CT} = 8$ months, $MS_{B+CRC} = 10.8$ months, $MS_{RS+RT} = 11.9$ months, $MS_{RS+CT} = 8.1$ months, and $MS_{RS+CRC} = 15.6$ months ($P < .0001$, log-rank test) (Fig. 2C). After the Bonferroni correction, significant differences ($P < .0033$) still existed between RS + CRC and all other treatment modalities (RS + CRC vs B + RT, B + CT, B + CRC, RS + RT, and RS + CT, $P < .0001$, $P < .0001$, $P < .0001$, $P = .0003$, and $P < .0001$, respectively).

In this work, the analysis of survival for the 2 main groups who had 3 sequences of treatment (RS + CRC + CT [$n = 181$] vs RS + RT + CT [$n = 75$]) did not shown any significant difference: $MS_{RS+CRC+CT} = 16$ months (487 days, 95% $CI = 451–521$ days), $MS_{RS+RT+CT} = 15.6$ months (475 days, 95% $CI = 385–513$ days), $P = .25$ by the log-rank test.

The analysis of survival concerning RS vs biopsy in the RT-TMZ group (patients who received CRC with TMZ concomitant +/− adjuvant as first-line treatment

**Table 2.** Oncological management of the 952 patients

| Surgery | First surgery ($N = 952$) | | Second surgery ($N = 91$) | |
|---|---|---|---|---|
| | No. | Percent | No. | Percent |
| Modalities | | | | |
| "Total" resection (RS) | 266 | 27.9 | 36 | 39.6 |
| Subtotal RS | 112 | 11.8 | 12 | 13.2 |
| Partial RS | 95 | 10.0 | 12 | 13.2 |
| NOS RS | 56 | 5.9 | 6 | 6.6 |
| Biopsy | 423[a] | 44.4 | 5 | 5.5 |
| Other surgery | 0 | 0 | 20[b] | 22.0 |
| Radiotherapy (RT) | | | | |
| RT: 654 patients of 952 (68.7%) | | | | |
| Median duration: 43 d; median dose: 60 Gy | | | | |
| Median/mean time from biopsy to RT: 34/39 d | | | | |
| Median/mean time from RS to RT: 41/44 d | | | | |
| Re-irradiation: 16 patients | | | | |
| Chemotherapy (CT) | | | | |
| CT first sequence: 643 patients of 952 (67.5%) | | | | |
| Drugs used in the first sequence of CT: temozolomide (TMZ): 80%, nitrosourea: 16%, other: 4% | | | | |
| Median/mean time from biopsy to CT: 21/27 d | | | | |
| Median/mean time from RS to CT: 22/42 d | | | | |
| CT second sequence: 358 patients | | | | |
| Drugs used in the second sequence: TMZ: 82%, nitrosourea: 13%, other: 5% | | | | |
| CT third sequence: 108 patients | | | | |
| Drugs used in the third sequence: TMZ: 23%, nitrosourea: 48%, other: 29% | | | | |
| Concomitant radiochemotherapy (CRC) | | | | |
| CRC as the first oncological treatment (after biopsy): 108 patients | | | | |
| Median/mean time from biopsy to CRC: 31/38 d | | | | |
| CRC as the second oncological treatment after RS: 265 patients | | | | |
| Median/mean time from RS to CRC: 37/40 d | | | | |
| CRC with TMZ concomitant +/− adjuvant as first-line treatment after surgery: 314 patients on 952 (33%) (after biopsy: 90, after RS: 224 patients) | | | | |
| CRC with other drugs (fotemustine mainly) and CRC modalities not very well-documented, as first-line treatment after surgery: 59 patients | | | | |

Abbreviation: NOS, not otherwise specified.
[a]Twelve biopsies were followed by RS just after the histological diagnosis was completed.
[b]RS with carmustine wafers: 15 patients; local immunotherapy protocol: 4 patients; radiosurgery: 1 patient.

after surgery) showed a significant difference: $MS_{RS+RT\text{-}TMZ} = 15.7$ and $MS_{B+RT\text{-}TMZ} = 10.8$ months ($P = .0005$, log-rank test; Fig. 2D).

In our work, comparison between the CRC with the TMZ group (RT-TMZ group, $n = 314$) and the CRC with other modalities group ($n = 59$), after surgery and regardless of following treatments, did not show any significant survival difference: $MS_{RT\text{-}TMZ} = 14.6$ months (444 days, 95% $CI = 392–478$ days), $MS_{CRC\ other\ modalities} = 12.9$ months (393 days, 95% $CI = 359–463$ days), $P = .9$.

Multivariate analysis for overall survival is reported in Table 3. Here, the multivariate Cox analysis specified the RR of mortality for the sequences of biopsy or RS followed by RT, CT, or CRC, according to the main prognostic factors. Taking into account the patient age and tumor location (bilateral/nonbilateral), RR of mortality for all studied sequences were significantly superior to that of RS + CRC (Table 3). When we considered age, location, and KPS (recorded in only 474 cases), the RR of mortality for sequences RS + CT and RS + RT were superior to that of sequence RS + CRC but the differences did not reach statistical significance ($P = .10$ and .16, respectively).

## Discussion

This study of 952 patients with histologically confirmed GBM, all newly diagnosed in France in 2004, was made possible thanks to the cooperation of a large number of neurosurgeons, pathologists, neurologists, oncologists, radiation therapists, general practitioners, from throughout France, and the methodological support of epidemiologists and biostatisticians. Above all, this work shows the importance

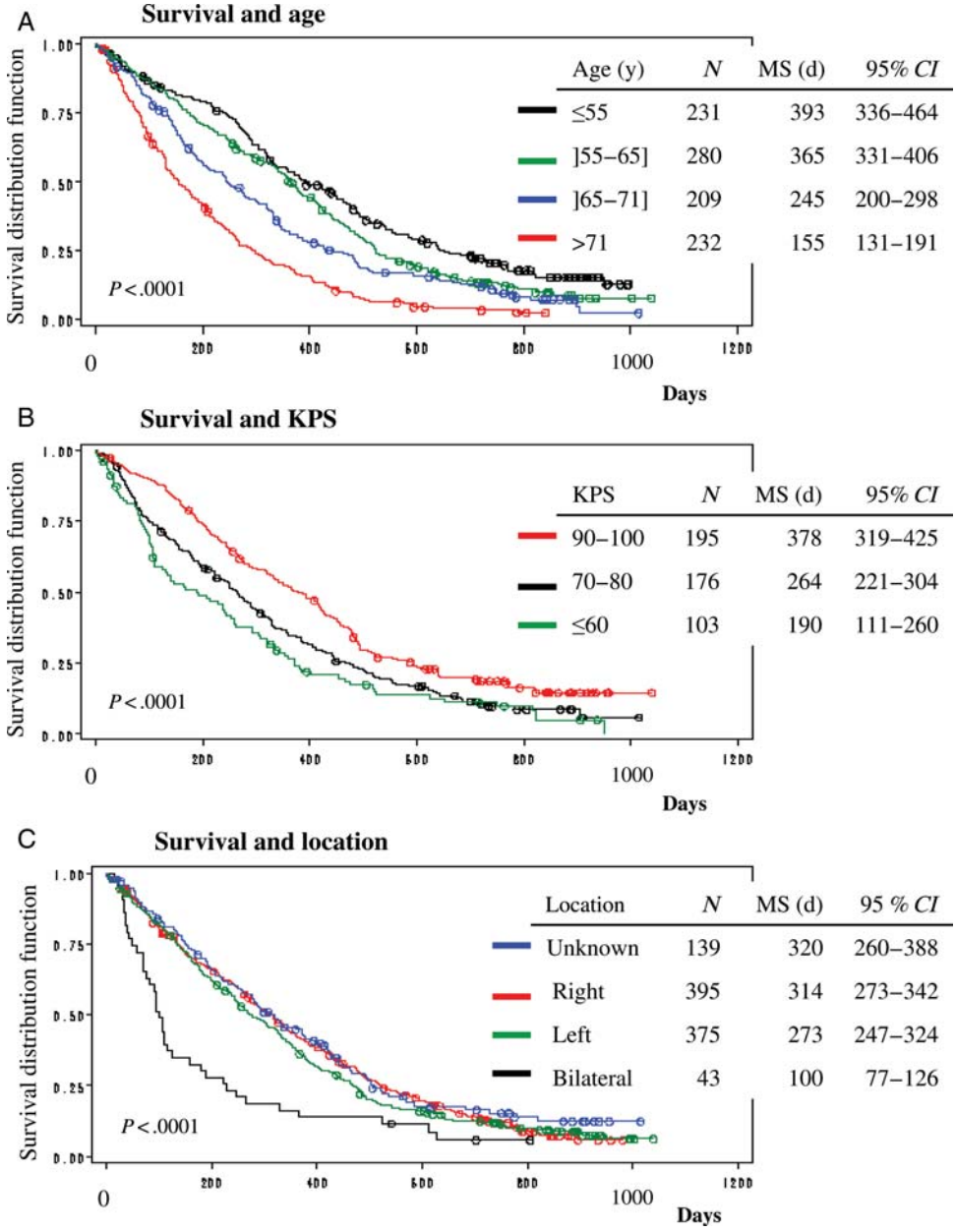


Fig. 1. Survival and prognostic factors: Kaplan–Meier estimates of survival by age at diagnosis (≤55, ]55–65, ]65–71, and >71 years) (A), preoperative KPS (≤60, 70–80, and 90–100) (B), and location (right, left, and bilateral) (C). MS, median survival; *CI*, confidence interval; KPS, Karnofsky performance status.

of multidisciplinary networks and databases that involve clinicians and epidemiologists.[30] The main results of this study conducted by the FBTDB are: (i) a precise inventory of oncological management (surgery, RT, and CT) at a national level, (ii) a study of patient survival, including univariate and multivariate analyses, and (iii) the confirmation of the effect of surgical RS and CRC at the population level.

### *Population Characteristics*

Many registry reports and previous studies have reported an obvious predominance of male patients with GBM, for example, male-to-female ratios of 1.4 for CBTRUS,[6] 1.4 for the Ontario Cancer Registry,[16] 1.3 for the Austrian Brain Tumor Registry,[8] 1.5 for the Gironde Registry (French area registry),[9] 1.5 for the Glioma Outcomes Project (GOP; consortium study),[11] 1.7 in Stupp et al. (clinical trial),[25] 2.0 in Westphal et al. (clinical trial),[24] 1.6 in Filippini et al. (single-institution study),[31] and 1.6 in the current study.

In the current study, the median age at diagnosis was 63.9 years and was in accordance with data from registries (eg, 64 years in CBTRUS).[6] It is important to note that the median age at diagnosis is often lower in clinical trials (eg, 56 years in Stupp et al.[25] and 53 years in

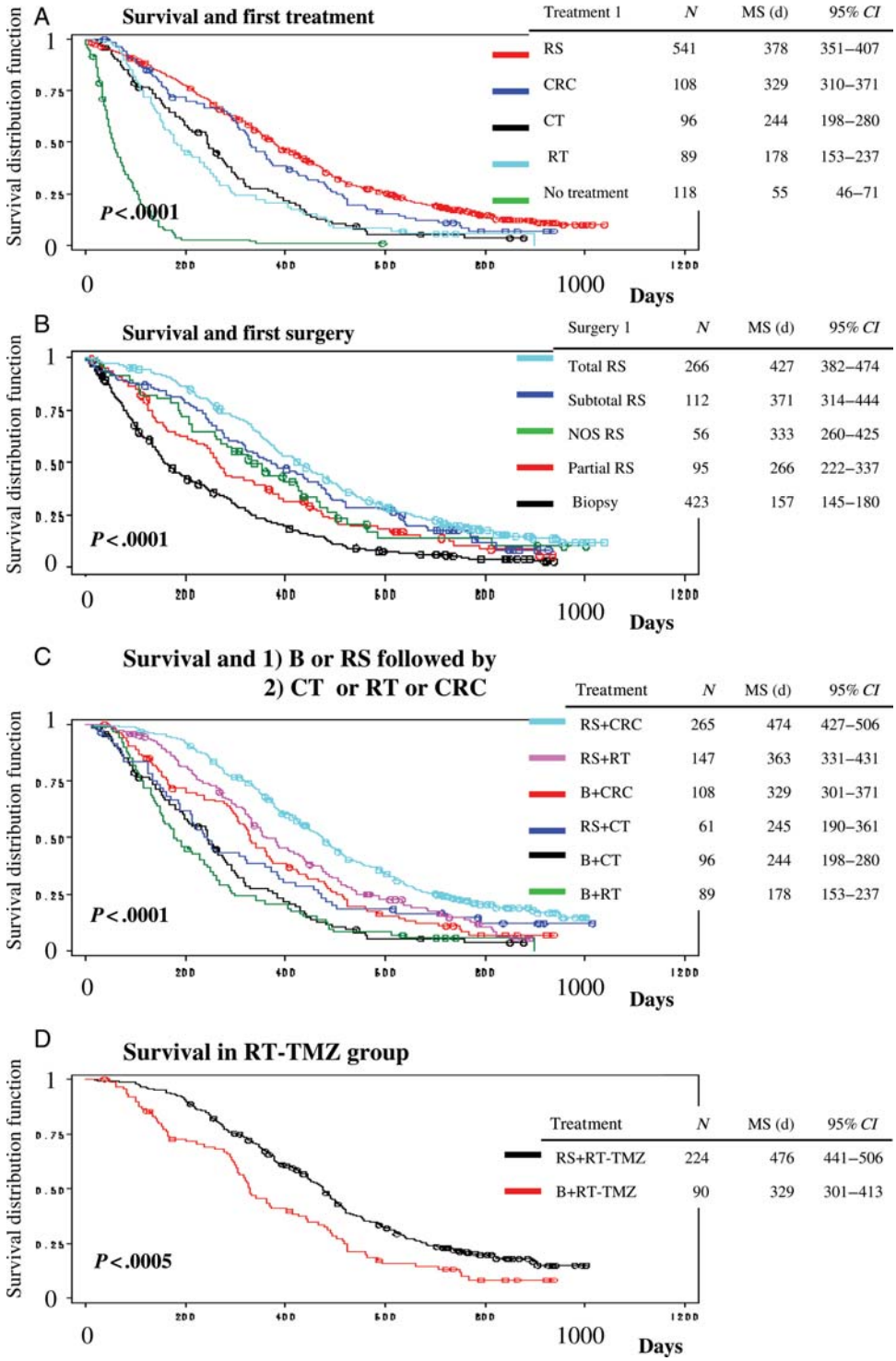


Fig. 2. Survival and treatment patterns: Kaplan–Meier estimates of survival by first treatment (RS, CRC, CT, RT, and no treatment) (A), first surgery (total RS, subtotal RS, partial RS, not otherwise specified RS, and biopsy) (B), first 2 oncological managements (biopsy or RS, followed by CT or RT or CRC) (C), and surgery (biopsy vs RS) in the CRC with TMZ concomitant +/− adjuvant in first-line treatment after surgery (D). RS, resection; CRC, concomitant radiochemotherapy; CT, chemotherapy; RT, radiotherapy; MS, median survival; *CI*, confidence interval; NOS, not otherwise specified; B, biopsy; RT-TMZ, radiotherapy and TMZ concomitant +/− adjuvant in first-line treatment after surgery.

Westphal et al.[24]) and in some single-institution studies (eg, 58 years in Filippini et al.[31]). Age is an important prognostic factor;[20,32] this underlines the importance of population studies to compare oncological management and survival between 2 different countries or areas.

In our study, the clinical presentation of patients (Table 1) was quite similar to that of the GOP (seizure:

**Table 3.** Relative risk of mortality: multivariate Cox analysis with age at diagnosis (≤55, ]55–65, ]65–71, and >71 years) and location (bilateral/nonbilateral) of the tumor ($N = 952$)

| Variable | No. | *P* value | Hazard ratio | 95% *CI* |
|---|---|---|---|---|
| RS + CRC | 265 | | 1 | |
| All other modalities[a] | 186 | <.0001 | 7.859 | 6.243–9.893 |
| B + CRC | 108 | .0002 | 1.606 | 1.255–2.056 |
| B + CT | 96 | <.0001 | 2.431 | 1.873–3.155 |
| B + RT | 89 | <.0001 | 2.649 | 2.038–3.442 |
| RS + CT | 61 | .0010 | 1.674 | 1.232–2.275 |
| RS + RT | 147 | .0054 | 1.376 | 1.099–1.722 |

Abbreviations: RS, resection; CRC, concomitant radiochemotherapy; B, biopsy; CT, chemotherapy; RT, radiotherapy.
[a]Included 118 patients with biopsy only, 62 patients with 1 RS only, and 6 patients with other modalities of treatment.

23%, nausea/vomiting: 15%, memory loss: 39%, cognitive changes: 39%, sensory-motor deficit: 48%),[11] with only headache more frequent (57%) in the US study. The mean KPS score was the same (79) in both studies. Unfortunately, the preoperative KPS was recorded for only 474 patients in our study. Certainly, it would be possible to estimate it retrospectively in some cases, but the current work aimed to describe actual practice, so we only noted what was specified. French neurosurgeons have to improve by writing the preoperative KPS in their medical records. We could also note that KPS is not recorded in the SEER registry.[22]

In this study, pathological review was not performed for 2 reasons: (i) the aim of the study was to describe the French medical practice, and (ii) it has been established by the Brain Tumor Epidemiology Consortium (BTEC) that GBMs have enough general agreement over time, across regions, and between individual pathologists that one can consider using existing diagnostic data without further review (as long as uniform guidelines such as those provided by the WHO are used).[33] Furthermore, we probably selected a homogeneous population of GBM cases (GBM cases corresponding to ICD-O code 9440/3 only were included, cases with any previous history of glioma were excluded, and time between first clinical sign and histological diagnosis was <4 months in 89% of cases).

Surgery was performed for 94% of the patients in public centers. This is in accordance with previous data from French institutions estimating that more than 90% of all brain tumor patients had surgery performed in public centers.[34] The small number of patients who had surgery performed in nonacademic institutions does not allow us to compare the medical practices between academic and nonacademic institutions, as has been done in the United States.[11,17,35]

*Oncological management.* For the 952 patients considered here, the first surgery was RS in 529 cases (56%) and biopsy in 423 cases (44%). There is a noticeable difference here in our French series compared with US, Australian, and Italian data. The GOP described a biopsy rate for GBM of 20%.[10] In the San Francisco Bay area SEER registry, during the period 1991–2001, 27.3% of GBM patients had a biopsy.[17] In the Australian publication,[12] the percentage of biopsies was 23%, but this series did not contain exclusively GBM, 13% of patients did not have a histological diagnosis, and the performed surgery was not specified in 9%. In the Italian single-institution study,[31] biopsies were performed in 12% of the cases, and in the Italian consortium study,[14] the percentage of biopsies was 25% for all astrocytoma grades that were treated with RT. However, recent data from the FBTDB (not yet published) show a decrease in the percentage of biopsies compared with the percentage of RS in GBM patients for the years 2006 and 2007, compared with 2004.

The extent of RS in GBM patients (partial, subtotal [>90%], and total), which generally refers to the contrast enhancement, is not often specified in population studies, and postoperative imaging reviews are rarely performed. Here, at least 40% of patients had a total or subtotal RS. North American surgical studies give a higher percentage.[11] On the other hand, total RS was achieved in 28% of the cases in our series and in 25% of the cases in the Australian series.[12]

In our study, there was no local treatment with CT during the first surgery (carmustine wafers were not approved in France for first-line treatment for GBM in 2004). In the GOP study, 15% of patients had local CT using carmustine wafers.[11]

The percentage of patients with GBM having a second surgery is rarely mentioned in population studies. In the series of the French team of Mineo et al.,[36] this rate was 8%. In our study, 91 patients (9.6%) had a second surgery, which was a lower proportion than in the Italian single-institution study of Filippini et al.,[31] in which 26% of all patients had a second surgery, and in the US publication.[37]

RT was performed in 68.7% of our patients, 68% in the Australian series,[12] 89% in the GOP,[11] and 82% in the San Francisco Bay area SEER registry,[17] but dose and duration were not often specified. Details on RT management are presented in 2 glioma studies.[13,14] In our study, the median dose (60 Gy) and the median duration of treatment (6.1 weeks) were equal to those of the clinical trial completed by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada Clinical Trials Group (NCIC).[25,38] Over 90% of our patients had complete treatment, and causes of discontinuation were mainly related to tumor progression. This result obtained in our population study is just slightly inferior to that of the clinical trial of Stupp et al.[25]

Mean times (median times) between biopsy and RT and between RS and RT were 39 (34) days and 44 (41) days, respectively. Given the rapid evolution of GBM, these delays could be shortened, as has been already suggested in some clinical trials.[39] Moreover, it has been recently shown that increasing the time between surgery and RT reduced the survival of patients.[40,41]

Different chemotherapies have been used in GBM treatment, but until 2005 the standard therapy consisted

of surgical RS followed by RT only.[42] Few data are therefore available about the use of CT in GBM population studies.[43] CT was performed in 67.5% of patients in our study, 54% in the GOP study,[11] 56% in the study of Rosenthal et al.,[12] and 21.5% of patients in the San Francisco Bay area SEER registry.[17] However, all of these other series have compiled earlier cases than in our series.

In the current work, 39% of patients had CRC after surgery. To our knowledge, there is still no published study on a large population that details the results of CRC in GBM patients.[44]

The randomized phase III trial by the EORTC and NCIC was published in 2005.[25] This means that many French neurooncologists have been innovative in GBM treatment, on the basis of phase II trials,[45] and our period of studies captured an important era of change in the management of GBM.

### *Survival*

In this study, which considered only GBM patients, median overall survival was 9.4 months, and the corresponding values were 5.3 and 7.3 months according to the studied group in the San Francisco Bay area SEER registry,[17] 7.4 months in the Australian study,[12] and 9.4 months in the GOP.[10] It is extremely difficult to compare 2 median overall survivals without first considering the prognostic factors. In strong accordance with the literature, we found that age, KPS, and tumor location are important prognostic factors.[5,31,32,46] This explains, at least in part, why differences exist between studies and why median overall survivals are often higher in clinical trials. Of course, the different methods of medical care also affect survival. In accordance with previous studies,[10,26,47–49] we confirmed the positive effect of RS on survival at the population level. The fact remains that the neurosurgical indications must be discussed according to the aspect and topography of the lesion and the neurological status, general condition, and age of the patient. Recursive partitioning analysis used in clinical trials[32,50] is one way to predict survival and could help select the best treatment for each patient. Nomograms for predicting survival of patients with newly diagnosed GBM have recently been proposed.[51]

The effect of RT in high-grade gliomas has been previously demonstrated and confirmed,[52] even in elderly patients (70 years of age or older).[53] The effect of CT was controversial until the meta-analysis based on 12 randomized trials showed a small but real effect (Glioma Meta-analysis Trialists Group),[54] which confirmed the preliminary work of Fine et al.[55]

As mentioned above, the randomized trial published by the EORTC and the NCIC showed that the addition of TMZ to RT for the treatment of patients with newly diagnosed GBM significantly improved survival.[25,38] On the basis of 1 phase III completed trial, RT plus concomitant and adjuvant TMZ has rapidly become the new standard of care in Europe and North America. To our knowledge, our study is the first work that is in accordance with this experimental study at the population level and which compares the patterns of care for patients with newly diagnosed GBM in the same year (2004) and in 1 nation.

## Conclusion

This study illustrates very well the usefulness of a national brain tumor database. Indeed, thanks to our FBTDB, the multidisciplinary cooperation (neurosurgeon, neuropathologist, oncologist, radiotherapist, epidemiologist, biostatistician, and others) made it easy to have an access to data on the oncological management of GBM patients in France between 2004 and 2006. It shows that we can collect follow-up data for a huge number of GBM patients throughout the country. Although experimental studies are important for finding new therapeutic strategies, population studies are the only way to know what we do to patients and make it possible to evaluate patient's medical care. The results confirm that French oncological management is in agreement with the current recommendations, with a special emphasis on surgery,[10,26] and the pivotal clinical trial that defined an RT and TMZ combination as the new standard of care in patients with newly diagnosed GBM.[25,38] To our knowledge, this work is the largest report to date of recent GBM management in Europe. Such a database may allow us to open the door to future clinical and fundamental research studies in the field of neuro-oncology.

## Acknowledgments

First, we would like thank the patients and families. We also thank all pathologists, neurosurgeons, neurologists, oncologists, general practitioners, biostatisticians, clinical research technicians, and all those who participated in this important collaborative work.

*Conflict of interest statement*. None declared.

## Funding

This work was conducted with the financial support of grants from the French Institut National du Cancer (INCa), Ligue Nationale Contre le Cancer, Schering-Plough Laboratory, Association des Neuro-Oncologues d'Expression Française, Société Française de Neurochirurgie, Associations pour la Recherche sur les Tumeurs Cérébrales (ARTC and ARTC Sud), Département de l'Hérault, Rotary Club (AGLY), Archimedes Pharma Laboratory, and Groupe de Neuro-Oncologie du Languedoc Roussillon.

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