

Pattern of care and effectiveness of treatment for glioblastoma patients in the real world: Results from a prospective population-based registry. Could survival differ in a high-volume center?

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Background. As yet, no population-based prospective studies have been conducted to investigate the incidence and clinical outcome of glioblastoma (GBM) or the diffusion and impact of the current standard therapeutic approach in newly diagnosed patients younger than aged 70 years.

Methods. Data on all new cases of primary brain tumors observed from January 1, 2009, to December 31, 2010, in adults residing within the Emilia-Romagna region were recorded in a prospective registry in the Project of Emilia Romagna on Neuro-Oncology (PERNO). Based on the data from this registry, a prospective evaluation was made of the treatment efficacy and outcome in GBM patients.

Results. Two hundred sixty-seven GBM patients (median age, 64 y; range, 29–84 y) were enrolled. The median overall survival (OS) was 10.7 months (95% CI, 9.2–12.4). The 139 patients \leq aged 70 years who were given standard temozolomide treatment concomitant with and adjuvant to radiotherapy had a median OS of 16.4 months (95% CI, 14.0–18.5). With multivariate analysis, OS correlated significantly with KPS (HR = 0.458; 95% CI, 0.248–0.847; $P = .0127$), MGMT methylation status (HR = 0.612; 95% CI, 0.388–0.966; $P = .0350$), and treatment received in a high versus low-volume center (HR = 0.56; 95% CI, 0.328–0.986; $P = .0446$).

Conclusions. The median OS following standard temozolomide treatment concurrent with and adjuvant to radiotherapy given to (72.8% of) patients aged \leq 70 years is consistent with findings reported from randomized phase III trials. The volume and expertise of the treatment center should be further investigated as a prognostic factor.

Keywords: center volume, glioblastoma, radiotherapy, surgery, temozolomide.

Glioblastoma multiforme (GBM) is the most common and aggressive glioma in adults, with an incidence of 3 to 4 new cases per 100 000 inhabitants per year.¹ Despite advances in treatment modalities, the prognosis for GBM remains poor, with a 10% probability of survival at 5 years.²

The standard-of-care treatment for newly diagnosed GBM was established in 2005, when findings made in a randomized phase III trial (EORTC 26981–22981 /NCIC CE3 [EORTC/NCIC]) demonstrated that temozolomide concurrent with and adjuvant to radiotherapy was more effective than radiotherapy alone.³ Results obtained from one phase III clinical trial neither warrant transferability to clinical practice nor reliably demonstrate a survival benefit for the entire GBM population. The impact of this combined approach has been evaluated in many retrospective population studies,^{4–6} but no findings from a prospective study have been reported in the literature so far.

Methods

A primary brain tumor (PBT) registry, formerly known as the Project of Emilia-Romagna Region on Neuro-Oncology (PERNO), funded by the Italian Ministry of Health, was created in the Emilia-Romagna region in 2008. The region had 4 223 591 inhabitants and a homogeneous distribution of specialized tertiary cancer care hospitals in 2008, with well-distributed neurosurgery, oncology, and radiotherapy departments and no socioeconomic or geographic variations in access to health care.

The cases were recorded on the basis of clinical findings and neuroimaging results leading to a suspicion of PBT. The following data were sent to the centralized registry database on an electronic clinical record form: diagnosis code by observing center, name of recording physician, date of first observation, initials of patient, date of birth, and sex. Capture-recapture analysis⁷ was performed using independent information sources to assess the completeness of each case record. In this multiple-record system, all individual specialists from the centers ($n = 7$) participating in the PERNO project communicated the contact details of their new patients to the registry staff to be incorporated into a single, comprehensive record for each case with input from multiple sources (neuroradiologist, neurosurgeon, neuropathologist, neurologist, radiotherapist, and oncologist) during the entire period of diagnosis and treatment. Virtually all PBT patients within the Emilia-Romagna region were thus registered in the above time interval.

The registry staff assigned each case an identification code and maintained communication with other research units to assure that all patients were included in the 5 parallel subprojects (ie, GBM clinical pathways, epilepsy outcome, translational research, neuroradiological CT perfusion). The completeness of case records in the registry was verified by checking International Classification of Disease discharge codes for PBTs from neurosurgical, neurological, radiotherapy, and oncological services. Furthermore, in order to check recruitment accuracy, information was exchanged with other tumor registries in the regional provinces.

As a PERNO subproject, a prospective study on the clinical pathways of patients with GBM (treatment evaluation and outcomes analysis included) was conducted between January 2009 and December 2010. For this prospective study, the main inclusion criteria were histologically proven GBM (according to the WHO classification), aged ≥ 18 years, KPS 30%–100%, no

prior surgery for primary brain tumor, and residence within the Emilia-Romagna region.

When GBM patients entered the study, the following data were recorded: details on surgery, performance status, data and modalities of radiotherapy, and chemotherapy treatments. Completed data forms were sent to the central database. Electronic audit was used to detect outlier values, inconsistencies and omissions, and any queries were faxed to the study coordinators for resolution.

MGMT methylation status was assessed using methylation-specific PCR as described elsewhere.⁸ Approval for the project protocol was obtained from the ethical committee of each respective participating center. Before patient registration, fully informed consent in writing was obtained according to International Conference on Harmonisation/Good Clinical Practice, and national regulations.

Statistical Analysis

Survival data, processed using Kaplan-Meier methods to estimate survival functions, were analyzed by means of Cox models to assess the relevance of potential prognostic factors. Due to differences in the expected prognosis and treatments recommendations, a separate evaluation was made of patients aged ≤ 70 years who were treated with temozolomide concurrent with and adjuvant to radiotherapy. A comparison was made between the referring center and the other centers in terms of age (not dichotomized), KPS, and extent of surgery using Student *t* test for the first 2 variables and the chi-square test for the latter variables. The cutoff for significance level was $P < .05$. All analyses were made using SAS System software (version 9.2). At the time of analysis, 221 patients (82.8%) had died.

Results

From January 1, 2009, to December 31, 2010, 398 PBT cases were included in the register, and 267 cases with histologically proven GBM were enrolled into the prospective subproject (Fig. 1) (Table 1). Median accrual by center was 28 (range, 6–63) cases. Ten patients migrated outside the Emilia-Romagna region for neurosurgery (3.7%), but all returned to the Emilia-Romagna region for postsurgical treatment.

Of the 257 (96.3%) patients who underwent resection within the Emilia-Romagna region, 241 (93.8%) had postsurgical scans with CT/MRI and 162 (67.2%) with contrast enhancement. The median time interval between surgery and histological diagnosis was 8 (range, 2–30) days.

Median OS in the entire population ($n = 267$) was 10.7 months (95% CI, 9.2–12.4; range, 0.1–40.6 mo).

Fifty-six of the 267 GBM patients (21.0%) did not receive postsurgical radiotherapy due to rapid clinical deterioration ($n = 41$; 15.4%), patient refusal ($n = 8$; 3.0%), postsurgical complications ($n = 6$; 2.2%), or tumor size ($n = 1$; 0.4%). The median OS in patients not receiving any postsurgical treatment was 3.0 months (95% CI, 2.3–4.5).

Two patients migrated to other Italian regions after surgery, and 209 patients (78.3%) received postsurgical treatment within the Emilia-Romagna region, with a median time interval between surgery and start of radiotherapy of 39 (range, 12.0–76.0) days and a median OS of 13.3 (95% CI, 11.9–15.6) months.

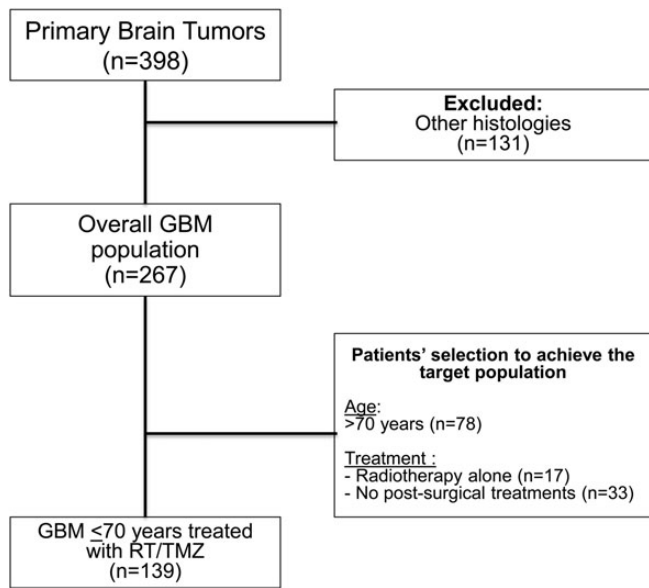


Fig. 1. Patient selection to achieve patients with glioblastoma aged ≤ 70 years and treated with radiotherapy/temozolomide.

Table 1. Characteristics of patients in the entire glioblastoma population

		n = 267
Age, y	Median age (range)	64 (29–84)
Performance status	Median	80%
	Range	30%–100%
Extent of surgery, n (%)	Biopsy	47 (17.6%)
	Partial resection	121 (45.3%)
	Complete resection	98 (36.7%)
Postsurgical treatment, n (%)	≤ 70 years (n = 189)	
	No postsurgical treatment	33 (17.3%)
	Radiotherapy alone	17 (8.9%)
	Temozolomide concomitant with and adjuvant to radiotherapy	139 (72.8%)
	> 70 years (n = 78)	
	No postsurgical treatment	25 (32.9%)
Radiotherapy alone	25 (32.9%)	
Temozolomide concomitant with and adjuvant to radiotherapy	28 (36.8%)	

Forty-three of the 267 patients (20.6%, range per center, 0%–42.9%) were enrolled in clinical trials (31 patients [11.6%] were aged ≤ 70 years, and 12, [4.5%] were aged > 70 years).

Assessment of MGMT status, undertaken in 181 of 209 (86.6%) patients, was achieved in 173 (82.8%) cases; 75 of 173 (43.3%) were methylated, and 98 of 173 (56.7%) were unmethylated.

Findings for univariate and multivariate analysis on the entire population are reported in Table 2.

Clinical Outcomes in Patients Aged ≤ 70 Years

One hundred eighty-nine patients were aged ≤ 70 years (Fig. 1) (Table 1). One hundred thirty-nine (Table 3) of 189 patients

(72.8%) were treated according to the EORTC/NCIC study.⁸ Their median OS was 16.4 months (95% CI, 14.0–18.5), being 20 months (95% CI, 15.2–27.0) in patients (n = 56) with methylated MGMT and 15.4 months (95% CI, 11.9–17.6) in those with unmethylated MGMT status (n = 60); this difference in OS was statistically significant (P = .0052 and P = .0350 for univariate and multivariate analysis, respectively).

Survival rates at 1, 2, and 3 years were 66.2% (95% CI, 58.3%–74.0%), 32.5% (95% CI, 24.5%–40.5%), and 21.3% (95% CI, 12.8–29.8%), respectively. Survival rates at 1, 2, and 3 years in MGMT methylated patients were 71.4% (95% CI, 59.6%–83.3%), 45.8% (95% CI, 32.6%–59.0%), and 34.0% (95% CI, 19.8%–48.1%), respectively, while survival rates at 1, 2, and 3 years for MGMT unmethylated patients were 63.3% (95% CI, 51.1%–75.5%), 19.8% (95% CI, 8.8%–30.8%), and zero, respectively.

Findings for univariate and multivariate analysis are reported in Table 4.

In the group of patients aged ≤ 70 years and treated according to the EORTC/NCIC study, survival rates were higher in the center that reported a higher number of patients with postsurgical treatment. With univariate analysis, it was found that having been treated in the high-volume referral center correlated with a median survival that was significantly longer than survivals obtained in other centers (24.1 months vs 15.9 months; HR, 0.533; 95% CI, 0.328–0.866; P = .0110). An exploratory analysis was therefore made to evaluate the accrual rate as a continuous variable; it was found to have no significant impact by univariate analysis on OS (P = .0673). Multivariate analysis was therefore performed to evaluate the accrual rate as a dichotomous variable (referral to high-volume center vs other centers): postsurgical treatment was correlated significantly with OS in the high-volume center (HR = 0.569; 95% CI, 0.328–0.986; P = .0446; see Table 4).

No significant differences were found between the referring center and other centers for relevant clinical factors such as age (P = .0681) and KPS (P = .8899), whereas differences were found between the centers for extent of surgery (P = .0164). Complete resections were performed in 37.8% of cases in the referral center and 52.9% of cases in other centers (P = .3462), partial resections were performed in 54.1% of cases in the referral center and 28.4% in other centers (P = .0156), and biopsies were performed in 8.1% of cases in the referral center and 18.6% of cases in other centers (P = .3996).

Discussion

The PERNO registry, the first in Italy to prospectively record the incidence of PBTs, was created in order to include all PBT cases within the Emilia-Romagna region. The present paper reports the results of a prospective subproject analyzing the newly diagnosed GBM population included in this registry and their clinical outcome.

In the Emilia-Romagna region, radiotherapy alone or combined with chemotherapy was given to 78.3% of the registered participants, the rate being 82.7% in patients aged ≤ 70 years and 67.1% in those > 70 years. The standard of care for newly diagnosed GBM patients aged ≤ 70 years has been established by the EORTC/NCIC³ trial, and 72.8% of cases considered in the present study underwent this treatment protocol (Table 1).

Table 2. Univariate and multivariate analyses of the entire GBM population

Variable	Factor	n	Univariate Analysis			Multivariate Analysis		
			Hazard Ratio		P Value	Hazard Ratio		P Value
			Estimate	95% CI		Estimate	95% CI	
Age, y	29.4–83.9	267	1.040	1.025–1.056	<.0001	1.024	1.009–1.040	.0017
KPS, %	100	38	0.319	0.201–0.505	<.0001	0.473	0.294–0.760	.0020
	≤90	229						
Extent of surgery	Complete	98	0.300 ^a	0.205–0.439	<.0001	0.383 ^a	0.259–0.566	<.0001
	Partial	121	0.565 ^a	0.397–0.804		0.604 ^a	0.424–0.860	
	Biopsy	47						
Postsurgical radiotherapy	Yes	211	0.112	0.078–0.160	<.0001	0.166	0.114–0.242	<.0001
	No	56						

^a“biopsy” is the reference class for the Hazard Ratio. Abbreviation: CI, confidence interval.

Table 3. Characteristics of patients ≤70 years treated according to EORTC 26981-22981 /NCIC CE.3 trial

n = 139		
Age	Median age	59 years
	Range	29–70 years
Gender	Male	86 (61.9%)
	Female	53 (38.1%)
Performance status, n (%)	Median (range)	90 (50–100)
	90–100	78 (56.1%)
	70–80	52 (37.4%)
	50–60	9 (6.5%)
Extent of surgery, n (%)	Biopsy	22 (15.8%)
	Partial resection	49 (35.3%)
	Complete resection	68 (48.9%)

Our survival data are comparable with those obtained in the EORTC/NCIC trial and the more recent RTOG 0525 trial,⁹ as well data obtained in retrospective registries in North America (United States and Canada)^{10,11} and South America (Columbia),¹² and seem better than data from Austria¹³ and Switzerland.¹⁴

In particular, these results are comparable with those reported in the retrospective Surveillance, Epidemiology and End Results (SEER) program,⁶ in which 65% of patients received the combined treatment according to EORTC/NCIC, followed by an OS of 15 months; 23% of patients who received no postsurgical treatment had an OS of 2 months.

Population-based data from Switzerland (Canton of Zurich)¹⁴ and the Austrian Brain Tumor Registry¹³ showed a dismal prognosis in the entire populations of GBM cases, with an OS in the general populations of 5–6 months. The Swiss registry was compiled between 1980 and 1994, before the EORTC/NCIC trial results were published (2005), and the Austrian data cover the years 2005 to 2006. In the latter preliminary spatial epidemiological analysis, the authors suggested that potential regional disparities across the Austrian health care regions may have affected differences in survival outcomes.¹³

A low socioeconomic status and its impact on patient care was also be cited as a cause of worse outcome in United States veteran cases in the national SEER cohort in which the OS for the GBM veteran patients was 6.5 months compared with 9.0 months in the SEER cohort.¹⁵

All of the above registries, despite their larger sample sizes, may be biased due to their retrospective nature: data on survival and treatment were frequently collected in a post-hoc manner.

A major advantage of this prospective population study was the solid epidemiological method (capture-recapture method) that allowed inclusion of virtually all GBM cases diagnosed within the Emilia-Romagna region. Moreover, the prospective record of patients and their treatment data allowed more comprehensive collection of demographic, treatment, and follow-up information.

The findings reported in the present study also confirm the prognostic role of *MGMT* methylation status. Moreover, the 2-year survival rates obtained are comparable with those reported in the EORTC/NCIC and RTOG 0525 studies, both for patients with *MGMT* methylated (46% in the PERNO, 49% in the EORTC/NCIC,^{2,3} and 47% in the RTOG 0525 trials) and for those with *MGMT* unmethylated (20% in the PERNO and 15% in EORTC/NCIC trials and 20% in the RTOG 0525 trial) status. Although comparisons between clinical trials and population studies are always challenging, the similarities suggest that the results obtained in the EORTC/NCIC phase III trial are transferable to the general population of GBM patients aged ≤70 years.

Our data confirms the role of known prognostic factors (performance status and *MGMT* status), while the extent of surgery appears to have a borderline effect (by multivariate analysis; *P* = .698) in patients aged ≤70 years treated according to the EORTC/NCIC trial protocol. However, the extent of surgery was evaluated by taking into account postsurgical CT/MRI with or without contrast enhancement performed within 48 hours after surgery in 60% of patients and on the basis of the neurosurgical report in about 40% of patients.

For the first time in the field of neuro-oncology, we have investigated the impact of center volume and expertise in postsurgical treatment as a variable that may influence the outcome of GBM

Table 4. Survival and uni- and multivariate analysis for patients ≤70 years treated according to EORTC26981 – 22981 /NCIC CE.3 protocol

Variable	Factor	n	Survival			Univariate analysis			Multivariate analysis		
			OS (mo)	95% CI	P-value	Hazard ratio		Hazard ratio		P-value	
						Estimate	95% CI	Estimate	95% CI		
Age	29–70 y	139	16.4	14.0–18.5	1.033	1.007–1.061	1.015	0.983–1.047	0.3675		
	100	31	26.6	19.0–30.1	0.451	0.264–0.771	0.458	0.248–0.847	0.0127		
	≤90	108	14.3	12.1–17.0							
MGMT status	Methylated	56	20.0	15.2–27.0	0.530	0.339–0.827	0.612	0.388–0.966	0.0350		
	Unmethylated	60	15.4	11.9–17.6							
Extent of surgery	Complete	68	17.9	15.2–22.7	0.323 ^a	0.190–0.548	0.463 ^a	0.240–0.892	0.0698		
	Partial	49	18.1	12.9–24.9	0.330 ^a	0.188–0.579	0.539 ^a	0.274–1.061			
Enrolled in clinical trial	Biopsy	22	10.6	5.7–12.9	0.509	0.298–0.869	0.756	0.412–1.386	0.3656		
	Yes	30	24.9	16.3–NA							
Treated in high-volume center	No	109	15.6	12.3–17.8	0.533	0.328–0.866	0.569	0.328–0.986	0.0446		
	Yes	37	24.1	15.4–NA							
	No	102	15.9	12.3–17.8							

^a“biopsy” is the reference class for the Hazard Ratio. Abbreviations: CI, confidence interval; mo, months; NA, not achieved; y, year.

patients, as it does in other cancer types (eg, lung,¹⁶ rectal,¹⁷ and ovarian cancer¹⁸), and we found that center expertise has an impact ($P = .0446$) on the survival of patients.

The HR of 0.569, found by multivariate analysis, suggests a potential reduction of mortality in the range of 40%. From a clinical viewpoint, the median OS for cases treated in a center with high volume and expertise in postsurgical treatment showed a difference (~ 8 months); this should be confirmed in a larger prospective study. However, the OS of ~ 16 months found in cases treated in lower volume centers is in line with data reported in the EORTC/NCIC trial.^{2,3}

Unlike settings for other cancer types, such as lung carcinoma, where hospitals with a high volume of surgical resections are followed by increased survival¹⁶ or, in the rectal and esophageal cancer setting where surgeon volume^{17,19} plays a significant role in prolonging survival, the results in our setting were not clearly attributable to the surgeon. By multivariate analysis, the extent of surgical resection had only a borderline effect on OS. In cases with ovarian carcinoma, findings at multivariate analysis demonstrated that OS correlated with adherence to NCCN guidelines, even if adherence was greater in high-volume rather than low-volume hospitals and in physicians who treated more patients. The same claim cannot be made for our GBM population, which was homogeneous (aged ≤70 years) and had standardized treatment with temozolomide concomitant and adjuvant to radiotherapy. Our findings may have depended on several factors such as expertise in neuroradiological interpretation, management of adverse events, and use of third-line treatments as well as improvements in administering the best supportive care. Moreover, the volume analysis was made following protocol, case accrual being achieved within the Emilia Romagna region, which is only partially representative of the size of the practice in the high-volume center.

Given the number of variables tested, there is concern regarding some potential prognostic associations that would be difficult to estimate within a relatively small patient population, and improvements in immediate postsurgical disease assessment are needed. Therefore, the exploratory data reported in the present prospective population-based registry study should be confirmed by a larger prospective study.

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Conflict of interest statement. None declared.

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Appendix: The PERNO Study group

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