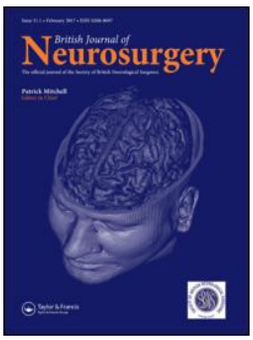

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ORIGINAL ARTICLE

The prognosis of glioblastoma: a large, multifactorial study

Chen Luo[a,b,c,d*], Kun Song[a,b,c,d*], Shuai Wu[a,b,c,d], N. U. Farrukh Hameed[a,b,c,d], Nijiati Kudulaiti[a,b,c,d], Hao Xu[a,b,c,d], Zhi-Yong Qin[a,b,c,d] and Jin-Song Wu[a,b,c,d]

[a]Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China; [b]Neurosurgical Institute of Fudan University, Shanghai, China; [c]Shanghai Clinical Medical Center of Neurosurgery, Shanghai, China; [d]Shanghai Key Laboratory of Brain Function and Restoration and Neural Regeneration, Shanghai, China.

ABSTRACT

Objective: Glioblastoma is the most common and fatal primary brain tumor in adults. Even with maximal resection and a series of postoperative adjuvant treatments, the median overall survival (OS) of glioblastoma patients remains approximately 15 months. The Huashan Hospital glioma bank contains more than 2000 glioma tissue samples with long-term follow-up data; almost half of these samples are from glioblastoma patients. Several large glioma databases with long-term follow-up data have reported outcomes of glioblastoma patients from countries other than China. We investigated the prognosis of glioblastoma patients in China and compared the survival outcomes among patients from different databases.

Methods: The data for 967 glioblastoma patients who underwent surgery at Huashan Hospital and had long-term follow-up records were obtained from our glioma registry (diagnosed from 29 March 2010, through 7 June 2017). Patients were eligible for inclusion if they underwent surgical resection for newly diagnosed glioblastomas and had available data of survival and personal information. Data of 778 glioblastoma patients were collected from three separate online databases (448 patients from The Cancer Genome Atlas (TCGA, https://cancergenome.nih.gov), 191 from REpository for Molecular BRAin Neoplasia DaTa (REMBRANDT) database (GSE108476) and 132 from data set GSE16011(Hereafter called as the French database). We compared the prognosis of glioblastoma patients from records among the different databases and the changes in survival outcomes of glioblastoma patients from Huashan Hospital over an 8-year period.

Results: The median OS of glioblastoma patients was 16.3 (95% CI: 15.4–17.2) months for Huashan Hospital, 13.8 (95% CI: 12.9–14.9) months for TCGA, 19.3 (95% CI: 17.0–20.0) months for the REMBRANDT database, and 9.1 months for the French database. The median OS of glioblastoma patients from Huashan Hospital improved from 15.6 (2010–2013, 95% CI: 14.4–16.6) months to 18.2 (2014–2017, 95% CI: 15.8–20.6) months over the study period (2010–2017). In addition, the prognosis of glioblastoma patients with total resection was significantly better than that of glioblastoma patients with sub-total resection or biopsy.

Conclusions: Our study confirms that treatment centered around maximal surgical resection brought survival benefits to glioblastoma patients after adjusting to validated prognostic factors. In addition, an improvement in prognosis was observed among glioblastoma patients from Huashan Hospital over the course of our study. We attributed it to the adoption of a new standard of neurosurgical treatment on the basis of neurosurgical multimodal technologies. Even though the prognosis of glioblastoma patients remains poor, gradual progress is being made.

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Introduction

Glioblastomas account for up to 47.7% of primary central nervous system (CNS) malignant tumors.[1] The annual incidence of glioblastoma is approximately 3.20 cases per 100,000 according to data from the central brain tumor registry of the USA (CBTRUS 2016).[2] Despite optimal surgical and postoperative adjuvant therapies, glioblastomas are almost invariably fatal due to their invasive and aggressive nature.[3–5]

The 5-year survival rate of glioblastoma patients is approximately 5.5% in the USA, and the median overall survival (OS) is only approximately 1 year.[2,6,7] The median OS of glioblastoma patients in cases of gross total resection was reported to be 15.5 months compared to 11.7 months for those with subtotal resection and 5.9 months for those without resection.[8] The leaders of several large, glioma-focused databases containing long-term follow-up data from patients in Western countries have presented their findings on glioblastoma.[6,7,9] In addition, there have also been several reports involving single-center glioblastoma survival data. For example, Li et al. summarized 1229 glioblastoma patients' data from the University of Texas MD Anderson Cancer Center, which revealed that the median OS of glioblastoma patients was approximately 13.4 months and the prognosis of glioblastoma patients was closely related to the extent of

CONTACT Zhi-Yong Qin wisdomqin@vip.163.com Department of Neurosurgery, Huashan Hospital Shanghai Medical College, Fudan University, 12 Middle Wulumuqi Road, Shanghai, 200040, PR China
*Co-first authors, these authors contributed equally to this work.

Supplemental data for this article can be accessed here.

resection (EOR).[9] Moreover, Eriksson reported that the treatment and prognosis of glioblastoma patients both improved over two decades in a northern Swedish health care region (the median OS increased from 6.9 to 10.3 months).[10]

Despite decades of meticulous research, the survival of glioblastoma patients remains dismal.[2,3,5,7] There are several reports about the prognosis of glioblastoma patients with a median OS varying from 8 to 20 months.[6–9,11] However, most of these glioblastoma patients were from Western countries.[6,7,9] Large-scale clinical prognostic data reports of glioblastoma patients from China are rare. Herein, a large, single-center study from Huashan Hospital was conducted from 2010 to 2017. We collected data for 967 glioblastoma patients who received regular follow-up care. We then summarized the prognoses of glioblastoma patients from Huashan Hospital. The differences in prognosis from patients from other databases and the survival changes of glioblastoma patients from Huashan Hospital were also compared.

Methods

Study population and ethics statement

This retrospective study was approved by the institutional review boards of Huashan Hospital, Fudan University, Shanghai, China. Written informed consent was obtained from all participants in all studies.

Clinical data of 2663 patients with tissue diagnosis of neuroepithelial tissue tumors were obtained from the glioma registry of Huashan Hospital from March 2010 to June 2017. We retrospectively identified all patients who were histopathologically diagnosed as WHO grade IV glioblastoma and received craniotomy but not biopsy. Clinical characteristics were collected through patients' history review. EOR was defined according to surgeon's operation note. Survival information was collected by outpatient follow-up and telephone interview. The range of the follow-up period was 0–96 months (median follow-up period: 12.2 months, 95% CI:12.1–12.2 months), with a follow-up rate of 98.7%. Follow-up data were collected and analyzed by two technicians. An experienced neuropathologist reviewed the diagnoses of patients according to the 2016 World Health Organization (WHO) classification of tumors of the CNS.[12] All patients provided consent before enrollment in the follow-up, and the study was approved by the ethics committee of Huashan Hospital.

Analysis of the isocitrate dehydrogenase 1 (IDH1) mutation and MGMT promoter methylation

Isocitrate dehydrogenase 1 (IDH1) mutations were detected by immunohistochemistry as described previously.[13] O6-methylguanine-DNA methyltransferase (MGMT) promotor methylation analysis was performed by immunohistochemistry from 2010 to 2015 and methylation-specific polymerase chain reaction (PCR) from 2016 to 2017.[14,15]

Database interrogations

The publicly-available clinical data of patients with glioma was acquired from the REpository for Molecular BRAin Neoplasia DaTa (REMBRANDT) database[11] using the data set available on 25 May 2018 (GSE108476); the French database using the data set available on 26 April 2010 (GSE16011);[16] and The Cancer Genome Atlas (TCGA, https://cancergenome.nih.gov) using the data set available on 15 December 2012.[17] The molecular pathology data of the patients in TCGA were acquired from cBioPortal (https://www.cbioportal.org/). As shown in Figure 1, 2663 consecutive glioma patients who were in the glioma registry of Huashan Hospital from 29 March 2010 through 7 June 2017 were screened for inclusion. Among them, 967 patients newly diagnosed with glioblastoma were included in our study. Public clinical data were retrievable for 515 patients from TCGA database, 275 patients from the REMBRANDT database and 159 patients from the French database, while 67, 81, 27 cases were excluded from the analysis respectively. Only patients diagnosed with glioblastoma (WHO grade IV) after 18 years of age and have received craniotomy but not biopsy were included in the analysis. EOR was defined according to surgeon's operation note. We then compared the prognosis and survival changes of

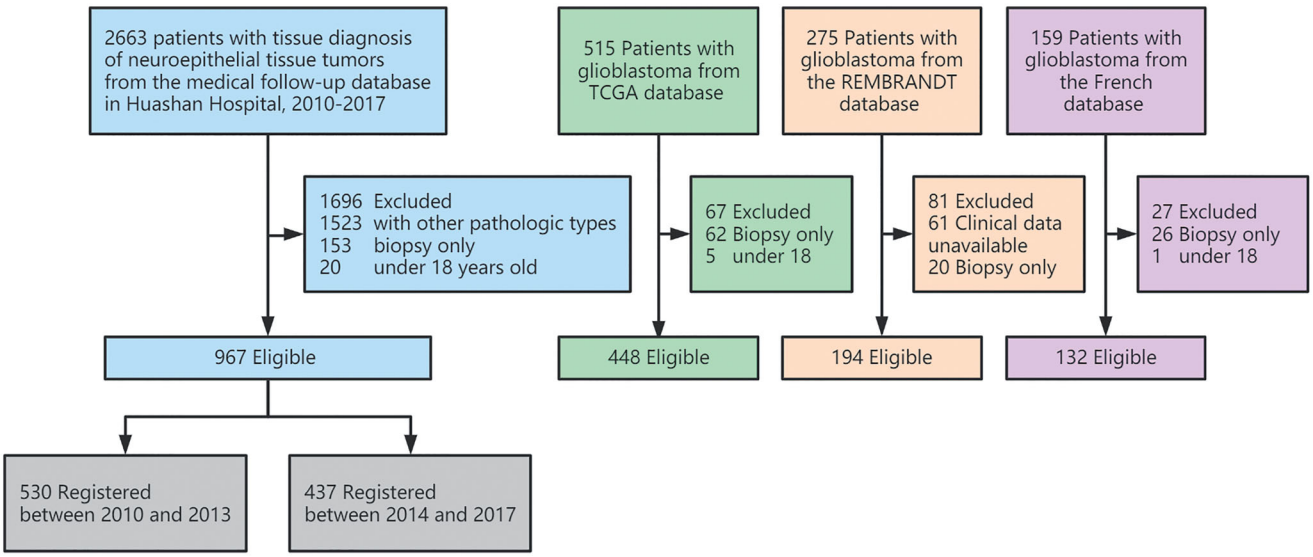

Figure 1. Flow diagram depicting the overall research process. A total of 2663 glioma patients were recorded in the glioma registry of Huashan Hospital from 2010 to 2017. A total of 967 cases were finally included in our study. In total, 132 glioblastoma patients were acquired from the French database; 194 patients were acquired from the REMBRANDT database; and 448 patients were acquired from TCGA.

glioblastoma patients of Huashan Hospital with those from different other databases.

Statistical analyses

Statistical analyses were conducted with IBM SPSS software version 20 (SPSS, Chicago, IL) and Prism software version 7.0 (GraphPad Software, La Jolla, CA). OS was calculated from the date (recorded in days) of first surgery until death or last follow-up. A survival analysis was calculated using the Kaplan–Meier method to evaluate the OS of patients in different subgroups. The Cox proportional hazards model was used for multivariate analysis. The variables included age, sex, EOR and postoperative radiotherapy and chemotherapy, IDH1/2 status, MGMT promoter status, and preoperative Karnofsky Performance Score (KPS) value. Chi-square test was applied to assess the difference of clinical characteristics between different data sources.

Results

Patient characteristics

The demographics of the patients are presented in Table 1. A total of 967 glioblastoma patients confirmed newly diagnosed glioblastoma between 2010 and 2017 in our study. The follow-up data of 954 patients were complete. These patients came from all parts of China, with the majority from seven provinces (i.e. Jiangsu, Zhejiang, Anhui, Shandong, Henan, Jiangxi, and Fujian) close to Shanghai (Figure 2(A)). A total of 611 (63.2%) of these patients were men and 356 (36.8%) were women; median age at diagnosis was 55 (interquartile range [IQR], 46.0–57.0) years (Table 1). Of the 732 patients with IDH measured, 668 (91.3%) had IDH wild-type tumors; of the 734 with tumor MGMT methylation measured, 286 (39.0%) had MGMT methylated tumors. Patients' status was documented using KPS during admission. A total of 606 (62.7%) patients received total resection according to the record of neurosurgeons' operation note and 717 (74.1%) patients received underwent both radiotherapy and chemotherapy following surgery. Determination for surgery and adjuvant treatments was rendered by the local tumor board.

Table 1. Clinical information of glioblastoma registry in Huashan Hospital.[Q]

Variable		*N* (%)
Age at diagnosis, years	Mean (SD)	52.60 (14.12)
	Median(IQR)	55.0 (46.0–57.0)
Gender	Male	611 (63.2)
	Female	356 (36.8)
IDH1 status	Mutation	64 (6.6)
	Wild type	668 (69.1)
	Missing	235 (24.3)
MGMT Promoter status	Methylated	286 (29.6)
	Unmethylated	448 (46.3)
	Missing	233 (24.1)
KPS value	<80	118 (12.2)
	≥80	847 (87.6)
Surgical treatment	Total resection	606 (62.7)
	Subtotal resection	136 (14.1)
	Partial resection	10 (1.0)
	Missing	215 (22.2)
Adjuvant treatment	R + C	717 (74.1)
	R	64 (6.6)
	C	37 (3.8)
	Neither	149 (15.4)
Tumor location by hemisphere	Right	446 (46.1)
	Left	500 (51.7)
	Bilateral	21 (2.2)
Tumor location by lobe	Frontal	442 (45.7)
	Occipital	39 (4.0)
	Parietal	96 (9.9)
	Temporal	327 (33.8)
	Cerebellum	6 (0.6)
	Brainstem, insular, basal ganglia, or thalamus	57 (5.9)
	Total	967

R: radiotherapy; C: chemotherapy; R + C: radio-chemotherapy; Neither: no chemotherapy or radiotherapy.

We then compared the clinical characteristics between patients from Huashan Hospital and other datasets (Supplementary Tables S1–S3). For metrics only available for a subset of studies, they were not present in the table. The IDH mutation rate of patients from Huashan Hospital and TCGA showed no difference (8.74% *vs.* 8.47%; p=.384), but patients from the French database showed higher IDH mutation rate comparing with those from Huashan Hospital (25.45% *vs.* 8.74%; p<.001). Huashan Hospital applied postoperative synchronous chemo-radiotherapy to 74.14% of the patients, followed by the rate of 66.74% from TCGA, while only 6.82% of the patients from the French database received chemo-radiotherapy.

Survival comparison of glioblastoma patients from Huashan hospital and the three other databases

The median OS of glioblastoma patients from Huashan Hospital and TCGA were 16.3 and 13.8 months, respectively, while the median OS of glioblastoma patients from the French database and the REMBRANDT database were 9.1 and 19.3 months, respectively (Figure 2(B)). The results from multivariate analyses showed that the gender (male/female, HR = 0.846; 95% CI, 0.758–0.946; p=.003), age (<55 years/≥55 years, HR = 1.452; 95% CI, 1.297–1.625; p<.001), IDH1 mutation status (Mut/WT, HR = 1.938; 95% CI, 1.527–2.459; p<.001), adjuvant treatments (Chemoradiotherapy/Radiotherapy/Chemotherapy/Neither, HR = 1.970/1.589/2.708; 95% CI, 1.574–2.466/1.265–1.996/2.334–3.141; p<.001/<.001/<.001) of glioblastoma patients were all independent prognostic factors among all databases (Table 2). Preoperative KPS score (<80/≥80, HR = 0.915; 95% CI, 0.736–1.138; p=.424), on the contrast, brought no significant effect on patients' survival. In addition, Kaplan–Meier estimates revealed that patients experienced prolonged OS after undergoing total resection (Figure 3).

The survival of patients with glioblastoma from Huashan Hospital was significantly better than that of patients from TCGA (TCGA/Huashan Hospital, HR = 1.233; 95% CI, 1.072–1.418; p=.003) (Table 2). In contrast, glioblastoma patients from Huashan Hospital showed relatively worse prognoses when compared to those from the REMBRANDT database (REMBRANDT/Huashan Hospital, HR = 0.716; 95% CI, 0.573–0.893; p=.003). Interestingly, while the univariate analysis showed a better prognosis for glioblastoma patients from Huashan Hospital than for patients from the French database (French/Huashan Hospital, HR = 1.655; 95% CI, 1.367–2.003; p<.001), this difference was not statistically significant according to the multivariate analysis (French/Huashan Hospital, HR = 1.108; 95% CI, 0.830–1.478; p=.487) (Table 2). As an explanation for this differentiation, we found that the ratio of glioblastoma patients who underwent radio-chemotherapy in Huashan Hospital was 10.87-fold higher than the French database (p<.001) (Supplementary Table S3). Most patients from the French database received only radiotherapy after surgery (Supplementary Table S3), which may bring bias to the

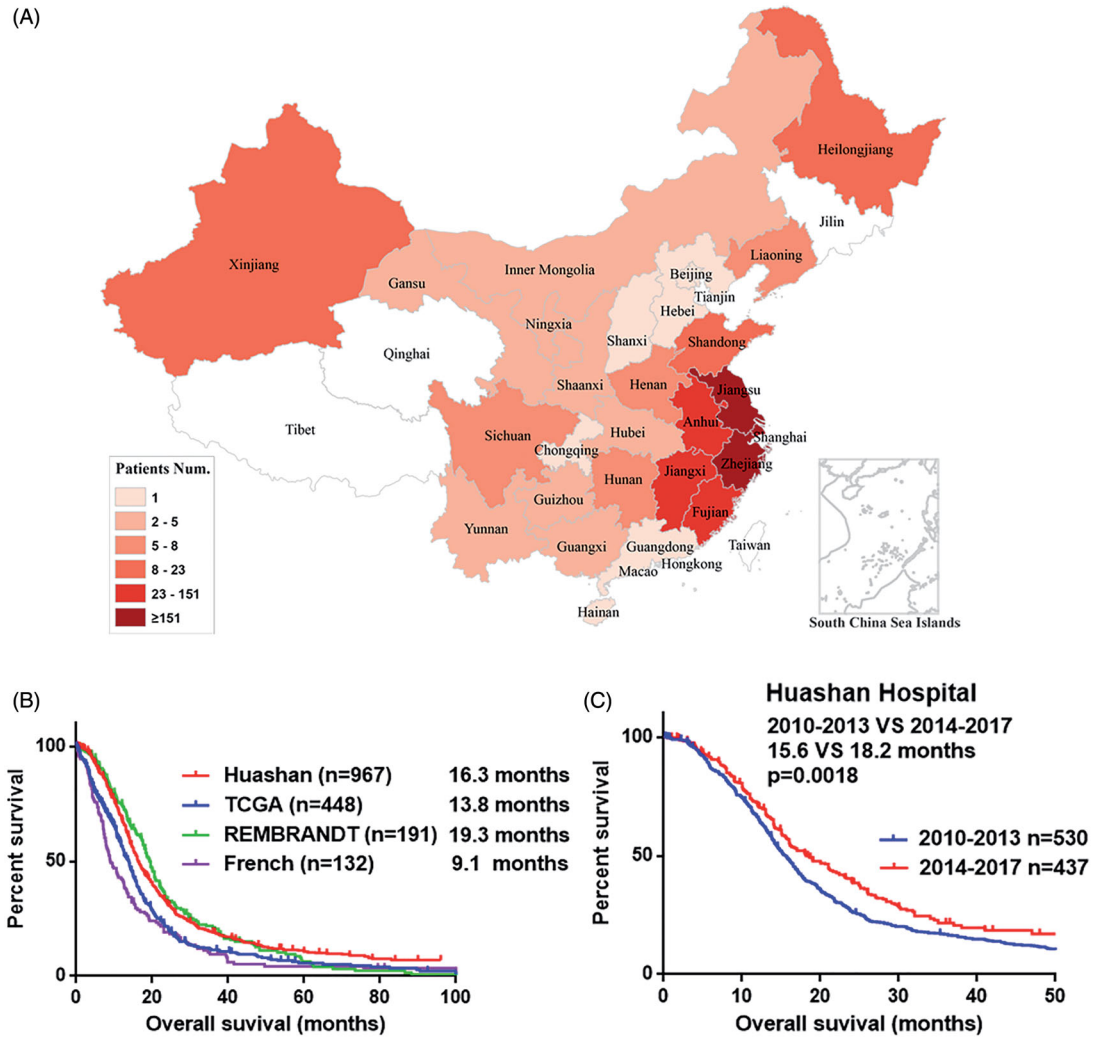

Figure 2. Distribution of the 967 glioblastoma patients from Huashan Hospital and prognosis comparison of glioblastoma patients from different databases. (A) Distribution map of glioblastoma patients from Huashan Hospital. (B) Kaplan–Meier estimates of the OS of glioblastoma patients from Huashan Hospital, TCGA, and the REMBRANDT and French databases. (C) Kaplan–Meier estimates of the OS of glioblastoma patients from Huashan Hospital between 2010–2013 and 2014–2017.

multivariate analysis. Besides, univariate and multivariate COX regression model using data from each individual database was provided (Supplementary Tables S4–S6).

Survival changes for glioblastoma patients from Huashan Hospital between the most recent 4 years (2014–2017) and an earlier 4-year (2010–2013) period

To further analyze changes in survival over the course of the study, the data for the 967 glioblastoma patients from Huashan Hospital were divided into two groups based on the date of their operation. The first group consisted of patients who underwent surgeries between 2010 and 2013 ($n = 530$), and the second group consisted of patients who underwent surgeries between 2014 and 2017 ($n = 437$). The OS for the first and second groups were 18.2 to 15.6 months, respectively (Figure 2(C)). Eight factors were incorporated in the analysis. Among them, the IDH1 mutation ratio in the first group was slightly higher than in the second group, and the mutation detection rate increased significantly (97.2% *vs.* 57.9%; $p<.001$). We also found that more glioblastoma patients underwent postoperative chemoradiotherapy in the most recent 4-year period compared to those from the earlier 4-year period (79.2% *vs.* 70.0%; $p=.005$) (Table 3).

Subsequent univariate and multivariate analyses revealed that gender, age, IDH1 mutation status, and postoperative adjuvant therapy were all prognostic factors for glioblastoma patients, which was consistent with the results from the other three databases (Table 4). Importantly, the univariate (2010–2013/2014–2017, HR = 1.268; 95% CI, 1.091–1.474; $p=.002$) and multivariate analyses (2010–2013/2014–2017, HR = 1.252; 95% CI, 1.053–1.488; $p=.011$) both showed that the prognosis of glioblastoma patients in the most recent 4-year period (2010–2013) was significantly better than in the earlier 4-year period (2014–2017, 15.6 months *vs.* 18.2 months) (Figure 2(C)).

Discussion

In 2010, the neurosurgery department of Huashan Hospital started a sub-specialization in different craniocerebral diseases to improve patient survival, especially glioma patient survival. After 9 years, we wanted to know the prognosis difference between glioblastoma patients from Huashan Hospital and those whose data were stored in other databases. Moreover, we were curious about the survival changes of glioblastoma patients from Huashan Hospital. Therefore, we summarized the survival results of glioblastoma patients from Huashan Hospital and compared

Table 2. The effect of demographic, clinical factors, and data source on the OS of glioblastoma between Huashan Hospital, TCGA, the REMBRANDT, and French database.

		Univariate analysis			Multivariate analysis		
Parameters		HR	95% CI	*p* Value	HR	95% CI	*p* Value
Clinical parameters							
Gender	Male	1 (Ref)	–	–	–	–	–
	Female	0.879	0.787–0.981	.021	0.846	0.758–0.946	.003
Age	<55	1 (Ref)					
	≥55	1.616	1.451–1.800	<.001	1.452	1.297–1.625	<.001
Perioperative status							
IDH1 status	Mutation	1 (Ref)	–	–	–	–	–
	Wild type	1.955	1.553–2.461	<.001	1.938	1.527–2.459	<.001
	Missing	–	–	–	–	–	–
Perioperative status							
Preoperative KPS value	<80	1 (Ref)	–	–	–	–	–
	≥80	0.876	0.716–1.072	.198	0.915	0.736–1.138	.424
	Missing	–	–	–	–	–	–
Therapeutic parameters							
Adjuvant Treatment	R + C	1 (Ref)	–	–	–	–	–
	R	1.969	1.670–2.322	<.001	1.970	1.574–2.466	<.001
	C	1.516	1.228–1.872	<.001	1.589	1.265–1.996	<.001
	Neither	2.875	2.491–3.319	<.001	2.708	2.334–3.141	<.001
	Missing	–	–	–	–	–	–
Date source							
	Huashan	1 (Ref)	–	–	–	–	–
	TCGA	1.402	1.234–1.595	<.001	1.233	1.072–1.418	.003
	REMBRANDT	0.985	0.831–1.167	.860	0.716	0.573–0.893	.003
	French	1.655	1.367–2.003	<.001	1.108	0.830–1.478	.487

R: radiotherapy; C: chemotherapy; R + C: radio-chemotherapy; Neither: no chemotherapy or radiotherapy

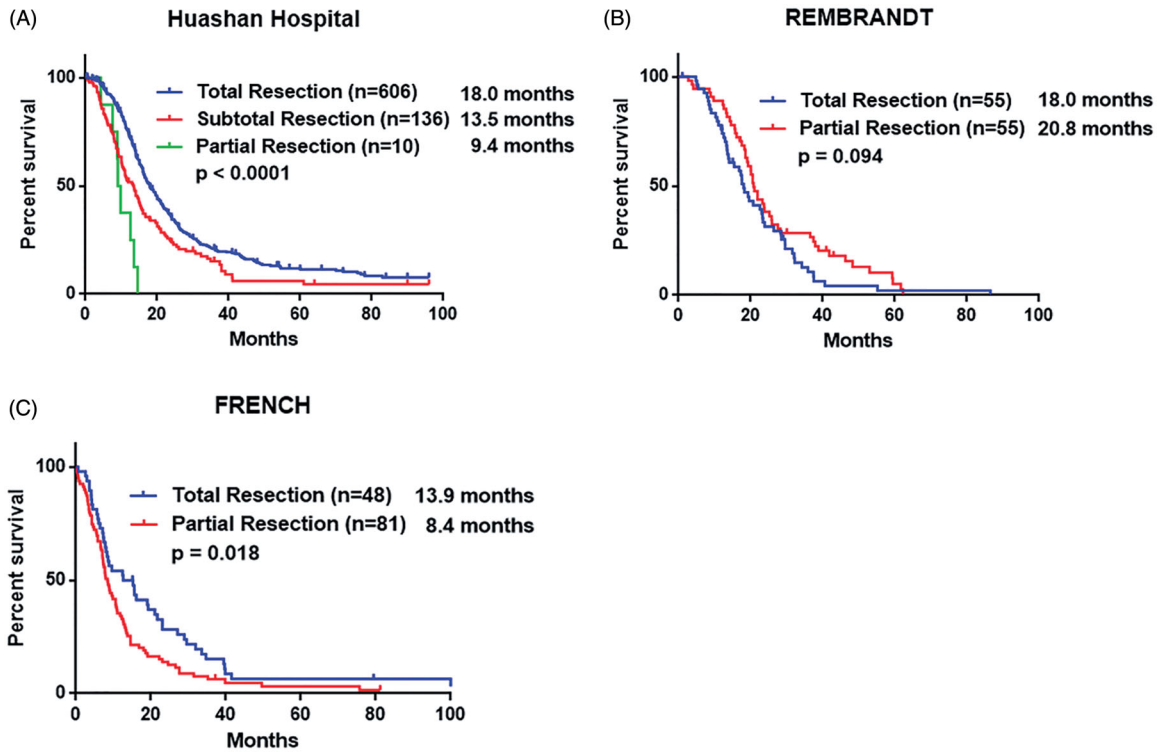

Figure 3. Distribution of the 967 glioblastoma patients from Huashan Hospital and prognosis comparison of glioblastoma patients among the different databases. (A) Kaplan–Meier estimates of the OS of glioblastoma patients from Huashan Hospial who underwent total resection, subtotal resection, and partial resection of tumorous lesions. (B and C) The relevant analysis of the OS of glioblastoma patients from the REMBRANDT and French databases.

them to those of patients from the three other databases. In addition, the survival changes of glioblastoma patients from Huashan Hospital were analyzed.

Kaplan–Meier estimates of the median OS of glioblastoma patients from Huashan Hospital, TCGA, and the REMBRANDT and French databases were 16.3, 13.8, 19.3, and 9.1 months, respectively (Figure 2). According to the survival curve, the prognosis of glioblastoma patients from Huashan Hospital was relatively good compared with that of patients from TCGA and the French databases. It is worth mentioning that the databases we interrogated are from different eras, which could lead to the diversity of comprehensive diagnosis and treatment strategy and explain the improved survival. For example, patients from the REMBRANDT database, which was available in 2018, were more

likely to benefit from developed neurosurgical technologies and targeted therapy, comparing to those from the French database available in 2010.

Cox univariate and multivariate analyses revealed that gender, age, IDH mutation status, and postoperative adjuvant therapy were all independent prognostic factors for glioblastoma patients, which was consistent with previous reports.[4,8,16] In a word, young, female glioblastoma patients (less than 55 years) with the IDH1 mutation who underwent postoperative synchronous chemoradiotherapy treatments had better prognoses (Tables 2 and 4). Meanwhile, MGMT methylation was proved to be a supportive factor for prognosis of patients from Huashan Hospital, corresponding to its role as the main prognostic factor for response to Alkylating agent chemotherapy (Table 4). Furthermore, as shown in Figure 3, the role of surgery in patients' prognoses was highlighted in our research. There was a significant positive correlation between patients' OS and the EOR according to the data from Huashan Hospital and the French database. It was shown that maximal safe resection should be ensured as a part of the standard treatment policy, corroborating the general view on glioblastoma treatments. On the contrast, patients from the REMBRANDT database did not show a significantly different EOR. We attribute this finding to differences in the classification criteria of surgical outcomes among different data sources. Further investigation into such phenomena is required.

Only 9 of 132 patients from the French database glioblastoma underwent postoperative synchronous chemoradiotherapy (Supplementary Table S3). Although patients from the French possessed a relatively higher IDH1 mutation ratio than those treated at Huashan Hospital, we assume that the difference in postoperative adjuvant therapy was the main cause of poorer prognoses. Besides, due to lack of data on MGMT status, we are unable to assess its influence on the OS of patients from the French database.

The median OS of Huashan Hospital patients increased from 15.6 (2010–2013) to 18.2 months (2014–2017) after 8 years (Figure 2). The IDH1 missing rate significantly decreased and the ratio of glioblastoma patients who underwent postoperative synchronous chemoradiotherapy markedly increased. Since publication of the WHO guidelines on glioma in 2016,[12] molecular pathology has become one of the most important parts of the diagnosis and treatment of glioma. Therefore, an increase in the rate of IDH1 mutation detection and patients undergoing

Table 3. Main characteristics of the study subjects in huashan hospital between 2010–2013 and 2014–2017.

Clinical parameters		Sum	2010–2013	2014–2017	*p* Value
Gender	Male	611	339	272	.581
	Female	356	191	165	–
Age	<55	450	247	203	.963
	≥55	517	283	234	–
Molecular pathology					
IDH1 status	Mutation	64	30	34	<.001
	Wide type	668	277	391	–
	Missing	235	223	12	–
MGMT promoter status	Methylated	286	163	123	<.001
	Unmethylated	448	282	166	–
	Missing	233	85	148	–
Perioperative status					
Preoperative KPS value	<80	118	64	54	.892
	≥80	847	465	382	–
Therapeutic parameters					
Surgical treatment	Total	606	300	306	<.001
	Subtotal	136	60	76	–
	Partial	10	10	0	–
	Missing	215	160	55	–
Adjuvant treatment	R + C	717	371	346	.005
	R	64	45	19	–
	C	37	25	12	–
	Neither	149	89	60	–

R: radiotherapy; C: chemotherapy; R + C: radio-chemotherapy; Neither: no chemotherapy or radiotherapy.

Table 4. The effect of demographic, clinical factors, and data source on the OS of glioblastoma in Huashan Hospital between 2010–2013 and 2014–2017.

		Univariate analysis			Multivariate analysis		
Parameters		HR	95% CI	*p* Value	HR	95% CI	*p* Value
Clinical parameters							
Gender	Male	1 (Ref)	–	–	–	–	–
	Female	0.817	0.704–0.948	.008	0.780	0.670–0.907	.001
Age	<55	1 (Ref)					
	≥55	1.368	1.184–1.580	<.001	1.213	1.045–1.407	.011
Perioperative status							
IDH1 status	Mutation	1 (Ref)	–	–	–	–	–
	Wild type	1.808	1.309–2498	<.001	1.840	1.321–2.562	<.001
	Missing	–	–	–	–	–	–
MGMT promoter status	Methylated	1 (Ref)	–	–	–	–	–
	Unmethylated	1.146	0.970–1.354	.109	1.198	1.002–1.433	.047
	Missing	–	–	–	–	–	–
Perioperative status				–	–	–	–
Preoperative KPS value	< 80	1 (Ref)	–	–	–	–	–
	≥ 80	0.874	0.700–1.092	.238	0.930	0.734–1.180	.930
Therapeutic parameters							
Surgical treatment	Total	1 (Ref)	–	–	–	–	–
	Subtotal	1.522	1.237–1.871	<.001	1.644	1.332–2.029	<.001
	Partial	4.292	2.208–8.341	<.001	3.004	1.515–5.956	.002
	Missing	–	–	–	–	–	–
Adjuvant treatment	R + C	1 (Ref)	–	–	–	–	–
	R	2.594	1.985–3.389	<.001	2.392	1.817–3.149	<.001
	C	2.070	1.462–2.929	<.001	1.985	1.383–2.848	<.001
	Neither	3.298	2.705–4.020	<.001	3.603	2.927–4.437	<.001
Date of operation							
	2014–2017	1 (Ref)	–	–	–	–	–
	2010–2013	1.268	1.091–1.474	.002	1.252	1.053–1.488	.011

R: radiotherapy; C: chemotherapy; R + C: radio-chemotherapy; Neither: no chemotherapy or radiotherapy.

postoperative synchronous chemoradiotherapy both demonstrate improvements in the diagnosis and treatment levels of glioma in Huashan Hospital.

A common view on glioblastoma is that the prognosis of this fatal disease strictly depends on surgical resection. Consistent with previous reports,[18] the EOR was an independent prognostic factor according to our results. Around 2013–2014, Department of Neurosurgery in Huashan Hospital attached unprecedented importance to neurosurgical multimodal technologies, such as neuronavigation, awake craniotomy, intraoperative MRI, and intraoperative neurophysiological monitoring, to preserve the functional integrity of critical brain structures during glioma surgery. It was shown in Tables 3 and 4 that significant improvements were found in the prognosis of patients diagnosed with glioblastoma in 2014–2017 comparing to those in 2010–2013, even if the influence of all aforementioned clinical factors had been excluded. We reasoned that a more adequate excision of each lesion was achieved using neurosurgical multimodal technologies in the latter period, which resulted in the safer removal of tumors and the adoption of a new standard of neurosurgical treatment regarding the EOR of glioblastomas. The application of techniques including intra-operative mapping, iMRI have already been identified as one of the predictive and prognostic factors for better outcomes in glioblastoma patients.[19–21] Collectively, these results emphasize the importance of maximal safe possible resections on the survival of glioblastoma patients, especially with precise imaging and fiber tracking.

There were several limitations in the study. Our investigation was limited by biases inherent to all retrospective analyses, including selection bias and confounding bias. No metric was available to measure the duration between suspected diagnosis and surgery, potentially affecting OS calculation. The MGMT promoter methylation status was detected by immunohistochemistry from 2010 to 2015 in Huashan Hospital, and the detection of the IDH1 R132H mutation relied upon immunohistochemistry but not sequencing. These factors may lead to misreporting of IDH mutation and MGMT promoter methylation, resulting in measurement bias across the study population and the interpretability of study findings. The supplementary work on molecular pathology of these patients is still being performed. Besides, due to lack of data on confounding factors, such as MGMT status (for three public databases), other mutations (TERT, EGFR, etc.), and previous radiation and chemotherapy exposure, we are unable to determine how these variables further define the subpopulations in our study. The lack of details about adjuvant treatment, intact imaging data, and non-volumetric nature of the imaging analysis resulted in the inaccurate hierarchical model and heterogeneity across different data sources. The baseline differences in clinical metrics and classification criteria may confound comparison of the four groups.

Conclusion

In a large retrospective study, we investigated prognostic factors and baseline data in glioblastoma. We confirmed that treatment centered around maximal safe surgical resection brought survival benefits to glioblastoma patients. Indicators for well prognosis included: Female, age under 55, IDH1 mutation, MGMT methylation, postoperative synchronous chemo-radiotherapy treatments, and total tumor resection. In addition, an improvement in prognosis was observed among glioblastoma patients from Huashan Hospital over the course of our study. We attributed it to the adoption of a new standard of neurosurgical treatment on the basis of neurosurgical multimodal technologies Even though the prognosis of glioblastoma patients remains poor, gradual progress is being made.

Disclosure statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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