Five-year survival in patients with Glioblastoma is overestimated in registry data - A nationwide population-based Swedish survey during 1958 - 1999

Peter Milos (peter.milos@regionostergotland.se)
Linköping University
Edward Visse
Lund University
Abdulrahman Al-Shudifat
The University of Jordan
Peter Siesjö
Lund University

Research Article

Keywords: Glioblastoma, five-year survival, cohort, Sweden, pre temozolomide.

Posted Date: June 4th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-561751/v1

Abstract

Background Some glioblastoma (GBM) patients survive more than five years with hitherto no clearly established epidemiological or molecular causes. Since varying rates of GBM five-year survival have been reported our aim was to assess the true prevalence of five-year survivors in Sweden from 1958 to 1999, before the introduction of concomitant temozolomide treatment.

Methods After screening the Swedish Cancer Registry and the Cause of Death Register 736 out of 12765 patients with high-grade glioma were defined as five-year survivors. The full text pathology report was reviewed in 585 patients. Data on epidemiology and treatment were retrieved from the medical records of 556 patients.

Results 77 five-year survivors with primary GBM were identified which corresponded to 0.60 % of the initial population. During 1990 to 1999 GBM five-year survival was 0. 90%. Younger age, Karnofsky score > 70 and non-eloquent tumour location were found in most but not all five-year survivors.

Conclusion GBM five-year survival was exceedingly rare in Sweden until 2004, comprising less than 1 % of registered HGGs. Relying on registry data without reviewing the pathology report will overestimate the accurate number of five-year survivors. To our knowledge, this is the only nationwide population-based study of five-year survival in GBM patients.

Introduction

Glioblastoma (GBM), the most common malignant brain tumour, carries the worst prognosis of all human tumours, with even shorter survival than in pancreatic cancer and mesothelioma [1]. GBM usually grows aggressively with excessive seeding of tumour cells outside the bulk of the tumour, often infiltrating vital functional brain areas making radical surgical resection impossible [2-4]. The biology of GBM is overly complex with genetic and molecular heterogeneity both between patients but also within the same patient making targeted oncological therapy challenging [5-7]. The current standard treatment for newly diagnosed GBM patients is maximal safe surgery followed by radiotherapy with concomitant temozolomide and then adjuvant temozolomide [8]. The median survival in patients receiving this regimen is about 14 months [9]. However, due to that not all patients receive standard therapy, median survival for all diagnosed GBM patients is considerably less, being reported from 5.8 to 11.2 months [10-13]. Certain clinical and molecular characteristics such as younger age, good performance status and gross total surgical resection have been associated with longer survival together with O6-methylguanine methyltransferase (MGMT) promoter methylation status [14-21]. Recently, studies have indicated a remarkable gain in overall survival in subgroups of GBM patients [22-24], but even in the most favourable conditions the majority succumb to the disease within 2 years [25]. However, a subset of GBM patients seem more amenable to treatment, having longer progression free and overall survival and are called Long Term Survivors (LTS). The definition of LTS varies but is commonly defined as survival >36 months [26]. An even smaller minority survives five years or more after diagnosis. In the original study by Stupp et al five-year survival increased from 2 to 10 % when concomitant temozolomide treatment was introduced and compared with radiotherapy alone [37]. However, numerous reports on five-year survival both before and after the introduction of concomitant therapy differ considerably between 1-10 % depending on population sample, selection method, study design, accuracy of diagnosis and performed interventions [1,10-13,24-36]. Clinical trials and single institutional studies tend to have higher numbers of five-year survivors [21, 25, 37] than population-based studies [10-13]. There is also a concern about the true number of five-year survivors due to misdiagnosis and the varying definition of anaplastic astrocytoma, oligodendroglioma and oligoastrocytoma depending on time and place [28, 38, 39]. Although the reported numbers need to be interpreted cautiously, some GBM patients have undoubtedly benefitted from the last decade's treatment algorithms with a prolonged overall survival, especially concerning two and three-year survival but not necessarily five-year survival [75]. In the post temozolomide era, studies investigating molecular factors in GBM LTS patients has been somewhat conflicting indicating MGMT promoter methylation as a strong predictor for long term survival whereas the role of isocitrate dehydrogenase (IDH) mutations are less clear [15,40-42]. Previous case reports have implied an association between postoperative infections and LTS [43] but recent retrospective reports have not been able to confirm this [44, 45].

Autoimmunity has been reported to prolong survival in glioma [46] but this has not been verified in other series [47]. Nevertheless, GBM patients with extended survival may display important prognostic factors for longer survival, hopefully enabling new targets for treatments in the future.

Historically there has been a gradual implementation of new surgical techniques and oncological treatments for GBM since 1960 but the impact of these methods has not been estimated in population-based studies. It is important to assess these changes to define the survival status before the introduction of temozolomide in the concomitant and adjuvant settings. The aim of this study was therefore to identify GBM five-year survivors in Sweden during 1958 – 1999, before the introduction of temozolomide into clinical practice around 2004, gathering epidemiologic data and searching for clinical features predisposing for five-year survival.

Materials And Methods

After ethical approval, a request was made to the Swedish National Board of Health and Welfare to extract data of HGG patients from the Swedish Cancer Registry and the Swedish Cause of Death Register from 1958 to 1999 with the topography codes 193.0, 191-9 and C71.0-9 (according to ICD 7, ICD 9 and ICD 10) and morphology codes 476 (before ICD-O); 93803, 94403, 94013, 94413, 94423 (from ICD-O after 1990). Social security numbers of HGG patients (= all ages) with at least five-year survival were then gathered and extracted.

The Swedish Cancer Registry was founded in 1958 and comprises all cancer diagnosis in Sweden. The registry has been reviewed previously with an overall completeness of approximately 98 % [48] and 96 % [49]. However, in the later survey there was a tendency of underreporting tumours of the nervous system, especially in elderly patients over 70 years. In a recent study reviewing malignant brain tumours in the registry between 1990 – 2014, the completeness was approximately 90 % in the younger population (< 70 years) but considerably less in elderly patients (> 70 years), ranging between 65-75 % [50].

Patients

12765 patients with a diagnosis of HGG were identified. 736 of these were defined as five-year survivors. The aim was to review the full pathology report, neurosurgical and oncological charts in these patients from the six neurooncological regions in Sweden (South, Southeast, Stockholm, West, Middle and North). 585 full pathology reports and 556 medical charts were found. 151 pathology reports and 180 charts were irretrievable (fig 1). The lost charts were mainly from the earlier decades (1958-1969; 1970-1979 – 145 patients, 80%). However, all full pathology reports from patients in the last decade (1990-1999) were retrieved. Data regarding previous disease, presenting symptoms, functional status, previous history of trauma, infection and tumor, radiological exams, neurosurgical operations, re-operations, diagnosis, oncological treatment, and overall survival was extracted from 556 patients with complete medical charts.

Surgical resection was scored as gross total resection (GTR), partial resection or biopsy. Since postoperative MRI was not performed routinely in Sweden until the beginning of the 21st century, resection grade was estimated after reviewing the neurosurgical operative report, i.e. the surgeon´s report. Epidemiological data was collected into a database (File Maker Pro and Excel) for graphics and further statistical analysis.

Statistical methods

Statistical analyses were performed with the free statistical software R-project

(R core team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, https://www.R-project.org/)

Standard descriptive statistics, tables and diagrams were used to display trends and epidemiological data. Differences in overall survival between different age groups and time periods were compared with the Kaplan-Meier log rank test.

Ethical approval

Ethical approval was obtained from the Regional Ethical Review board in Lund, Sweden (Dnr 617/2004). All research was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from alive adult patients and legal guardians from patients < 18 years.

Results

Survival in patients with high-grade glioma was related to time period and age

In the population of 12765 HGG patients, demographics showed a peak in incidence in the sixth and seventh decade (fig 2). There was a highly significant difference ($p < 0.001$) in median survival between the three first time cohorts (*1958-1969* [2.3 months; 80 days]*; 1970-1979* [4.8 months; 145 days]*; 1980-1989* [7.1 months; 213 days]) and a significant difference ($p = 0.017$) between the two last cohorts (*1980-1989* [7.1 months; 213 days]*; 1990-1999* [8.4 months; 252 days]) (fig 3a). When adjusted for the complete number of GBM five-year survivors in the 1990 – 1999 time cohort the median survival was reduced to 7.8 months; 233 days (fig. 3b). There was a tendency to an augmented number of HGG five-year survivors in the latter cohorts (table 1). After stratifying the population into different age cohorts (*0-9; 10-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80 – w* years) there was a stepwise significant difference between all age groups over 39 years (median survival 5.6 months ;168 days for the whole population and for the different age groups: 16.2/485; 20.5/615; 23.2/696; 17.2/517; 10.2/305; 6.9/206; 4.4/132; 2.4/73; 1.1/32 months/days respectively, $p < 0.001$) and only a partially significant difference in age groups < 39 years, with the highest median survival in the 20-29 cohort (fig. 4).

Five-year HGG survivors

736 (5, 8%) patients with registered HGG had a recorded five-year survival or more. The full pathology reports were reviewed in 585 cases and interpreted according to the 1993 WHO classification of Tumors of the Central Nervous System [48]. The most common diagnosis was Anaplastic Astrocytoma (197 patients), followed by Astrocytoma grade II (86 patients), GBM (77 patients), Oligoastrocytoma grade III (34 patients), Pilocytic Astrocytoma grade I (27 patients), Oligodendroglioma grade II (26 patients) and Anaplastic oligodendroglioma grade III (24 patients). In eighteen cases no specific diagnosis was found. Three cases were intramedullary gliomas and nineteen were meningiomas that previously had been registered as HGG (table 2).

Glioblastoma patients

87 patients with a histopathological diagnosis of GBM (mitosis, hypercellularity, vascular proliferation and necrosis) were initially categorized as primary GBM. Patients with a previous diagnosis of diffuse low-grade glioma (DLGG), e.g. secondary GBMs and those with oligodendroglioma features were excluded. However, the primary GBM diagnosis was changed after additional surgery in 10 patients.

Thus, 77 patients were confirmed as primary GBM five-year survivors, constituting 0, 60 % of the total population of 12765 patients and 10, 5 % of 736 registered five-year survival HGG patients. 39 patients (51%) were male, 38 patients (49%) were female. The age at diagnosis ranged from 8-69 years with a median age of 41 years. Twenty-one patients were diagnosed in the age group 40-49 years, followed by 15 patients in 30-39 group, 14 patients in the 50-59 group, 12 patients in the 20-29 group, 8 patients in the 60-69 group, 6 patients in the 10-19 group, and 1 patient in the 0-9 age group (fig 5a). 55 patients (71%) were younger than 50 years and 22 patients (29 %) were older than 50 years when diagnosed.

Time periods and geographical location

Most GBM five-year survivors, 48 patients (62%), were diagnosed and treated in in the latter decades (1980-1989; 1990-1999) whereas 29 patients (38%) were treated in the earlier decades (1958-1969; 1970-1979) (table 1).

Symptoms and signs

Medical charts from four patients where the full pathology report had verified GBM diagnosis could not be retrieved. These patients were however included in the survey as five-year survivors. Charts from 73 GBM patients were reviewed. The most common presenting symptom was headache in 46 patients (63 %) followed by focal neurological signs in 38 patients (52 %), nausea and vomit in 28 patients (38 %), seizure in 26 patients (36 %) and vertigo in 18 patients (25 %). 6 patients (8%) had a history of autoimmunity (allergy, asthma, and other autoimmune diseases). No patients had multiple sclerosis. 6 patients (8%) have had previous head trauma. 3 patients (4 %) had a heredity of brain tumours and 6 patients (8 %) of other tumours. 5 patients (7%) have had previous non-CNS tumours, and none have had other brain tumours beside glioma.

Six patients (8%) had been treated for a general bacterial infection prior to surgery. 6 patients (8 %) developed a local, superficial wound infection postoperatively treated with oral antibiotics and 6 patients (8 %) had a deep postoperative infection treated with surgery, intravenous and later oral antibiotics. Three patients with local wound infection eventually developed and were treated for a deep wound infection. Thus, 9 patients (12 %) were treated for a deep postoperative wound infection. The median overall survival in patients with a postoperative infection was 2663 days (7,3 years) which was less than the overall survival in the non-infected population (median survival ≈ 9 years) (table 3).

51 patients (70%) had a preoperative Karnofsky functional status score > 70 and 22 patients (30 %) had < 70 (table 3).

Tumour location

GBM was located in the frontal lobe in 40 patients (55 %), temporal lobe in 14 patients (19%), parietal lobe in 8 patients (11 %), occipital lobe in 6 patients (8 %), ventricle in 2 patients (2,8 %), cerebellum and brain stem in 1 patient (1 %). In one patient (1 %) the tumour was multi lobular. 44 patients (60 %) had tumours in the right hemisphere whereas 29 patients (39 %) had tumours in the left. Forty-three tumours (59 %) were located superficially (< 1 cm below cortex), 30 tumors (41%) were deeply located (> 1 cm below cortex) (table 3).

Treatment

36 patients (49%) were operated with Gross Total Resection (GTR) according to the surgeon's report. 32 patients (44%) had partial resection and 5 patients (7 %) underwent a biopsy. 24 patients (33 %) had repeated surgery whereas 49 patients (67%) did not have any secondary surgery. Among patients with repeated surgery, 19 patients had one, 4 patients had two and one patient had three additional surgeries. Almost all, 69 patients (95%) received postoperative oncological treatment with full radiotherapy (56-60 Gy) whereas 4 patients (5 %) did not. 38 patients (52%) did also receive chemotherapy (table 3).

Sample evaluation

The full neuropathology reports were reviewed by the authors as described above. Thirty-three patient samples had been reexamined during the clinical course due to an unexpectedly long survival, warranting a new examination. In additionally twenty-four patients, the diagnosis of GBM was confirmed through iterated surgeries. In sixteen patients, no new evaluation had been made. Hence, in 57 out of 73 cases the GBM diagnosis had been reexamined and verified. Additional microscopic sample examinations were not performed by the authors.

Overall Survival

Overall survival in GBM five-year survivors ranged between 5-55 years with a median survival of 3251 days or approximately 9 years (8 years, 11 months) (fig 5b). Ten patients were still alive in January 2020. Nineteen patients (24%) survived five but

less than six years after diagnosis, representing the largest cluster in the cohort. Thirty-five patients (0.27%) survived more than ten years.

Discussion

Most of the registered HGG five-year survivors had an actual diagnosis of anaplastic astrocytoma, astrocytoma grade 2 and other non GBM diagnoses. Of the 585 HGG patients with a verified diagnosis, only 77 had a diagnosis of primary GBM which constituted 0.60 % of the total population, illustrating the potential flaws when extracting data from registries without verifying the diagnosis [28, 39]. Considering the 151 reports that could not be retrieved the true number of five-year survivors may be slightly higher but supposedly less than 1% as the 1990-1999 cohort had a five-year survival of 0,9 % (table 1). This number is below the previously reported figures from before year 2000 of 1-2 % [28, 29]. Recent population-based studies estimated GBM five-year survival between 2.0-2.4 % [10, 13]. However, in the American study encompassing over 100000 GBM cases only patient data from accredited cancer centers were included thus possibly overestimating the actual five-year survival [10]. Furthermore, no review of pathology was made adding additional uncertainty of the actual numbers of five-year survivors. Given that completeness of registry data is less in older patients for brain tumors our estimate might still be too high [50]. Notably, thirty-five patients (0.27%) lived more than ten years after diagnosis which is in proximity to data from a systematic review on ten-year survivors of 0.71 % [52].

Headache was the most common presenting symptom in 73 GBM five-year survivors, followed by focal neurological signs, nausea and seizure, correlating with data from other GBM studies [4, 53, 54].

Some studies have reported longer survival in diffuse glioma patients with a history of allergy and autoimmune disease whereas this relationship was unclear in GBM patients [55]. Only six (8%) patients in our study had a history of allergy, asthma or autoimmune disease, which does not support the theory that previous allergy or autoimmune disease have a protective or treatment promoting effect once GBM has been established. However, our findings do not contradict the notion of an inverse association between glioma and allergic conditions, protecting the host from developing glioma [56-61].

Five patients (7%) had been treated for prior tumours, but none had a history of other brain tumours which is congruent with previous findings by Zacharia et al stating that approximately 8 % of GBM patients had a prior cancer diagnosis and were more likely to harbor an EGFR or MGMT mutation [62]. The overall survival in this group did not seem to be augmented which corresponds to our results where only a minority of the five-year GBM survivors have had previous tumour disease.

Nine patients had a postoperative wound infection with a median OS of 7.3 years. The effect of postoperative infection on survival has been extensively investigated, not finding any clear evidence of a significant impact on five-year survival, corresponding with our results. [44, 45,63].

Most GBM patients had tumours located superficially in the frontal lobe and in the right hemisphere, had a preoperative Karnofsky functional score > 70 and were younger than 50 years when diagnosed, corroborating that younger patients with a high functional status and non-eloquent located, superficial tumours not in obvious contact with the subventricular zone tend to have better prognosis and a longer overall survival [64-68].

About half of the 73 patients (49%) were operated with GTR, the rest with either partial resection (44%) or biopsy (7%). Twenty-four (33 %) had repeated surgery. This data from the pre-MRI period needs to be interpreted cautiously, being based on surgeon´s report, with a reported low accuracy of approximately 30% [69]. As the extent of resection (EOR) plays a role in GBM survival [14, 22-24, 70-73] the percentage of GTR among GBM five-year survivors in our study seems surprisingly low. Almost all patients (95%) were treated with radiotherapy whereas a small majority (52%) received chemotherapy, mainly BCNU during the latter decades. The current standard therapy with concomitant radiochemotherapy followed by adjuvant temozolomide have had a significant impact on overall survival in clinical trials [9,25,37] and also in population-based reports, especially regarding two- and three-year survival [1, 10-13, 29, 74,75]. However, some of these reports are based on

data from the SEER database, a registry that comprises approximately 35 % of the US population with an uneven geographical distribution (https://seer.cancer.gov/data/). Full concomitant radiochemotherapy is mainly given to younger patients deemed clinically fit and only a minority of elderly patients above 65 years receives this regimen. The overall impact of temozolomide on GBM five-year survival is less clear. In a recent meta-analysis five-year survival was not overly affected before and after 2005 when temozolomide treatment was initiated in clinical practice [75]. Similarly, a newly published population based French study reported a five-year survival of 2, 4 % [13]. Other studies report a wide variety of GBM five-year survival, ranging from 1-10 % [1, 10-12, 27-36]. This variation may be caused by selection bias of treated patients and controls but possibly also due to publication bias, e.g. reporting of lower survival might be less frequent.

There has been an increasing focus on molecular markers in GBM LTS, especially MGMT promoter methylation and IDH mutations. MGMT promotor methylation status is well described as a predictive marker of response to temozolomide in GBM. Several studies have shown a high percentage rate of MGMT promoter methylation in GBM LTS, particularly in patients surviving > 3 years [26, 76-79] but not necessarily in five-year survivors [21]. Mutation in IDH occurs frequently in low grade and anaplastic astrocytoma and is associated with better prognosis. However, this association seems to be weaker and sometimes lacking in GBM LTS (40-42, 78, 79]. Some, especially younger GBM patients with IDH wt together with ATRX mutations, have been reported to have longer overall survival [80] but this has not been corroborated by others [81]. In summary, no single factor has so far been able to explain five-year survival in GBM patients either before or after the introduction of concomitant temozolomide.

Limitations

This study has several limitations. It is retrospective, comprising more than 40 years of the Swedish Cancer Registry. Different brain tumor classifications, errors in registration and lack of completeness are common pitfalls when extracting data from a registry with an obvious risk of gathering and interpreting incorrect data. It is not known how many of the 12765 HGG patients that were true primary GBM and survived less than five years since it would be unfeasible to review the pathology reports for all patients. However, it is probable that non-GBM diagnosis was much less frequent in patients with a survival less than five years. Furthermore, the diagnosis was based on previous pathology assessment and then interpreted according to the 1993 WHO classification. Errors when interpreting the pathology specimen leading to wrong diagnosis has been reported [35, 36]. However, fifty-seven of the GBM five-year survivors (75 %) had been reevaluated and hence reviewed by another neuropathologist verifying the diagnosis. Irretrievable charts from approximately 25 % of the initial study population of 736 patients and the lack of postoperative radiology for definitive estimation of tumour residual are also important limitations.

Conclusions

The actual GBM five-year survival in Sweden was 0, 60% during 1958-1999 and 0.9 % during 1990-1999, prior to implementation of concomitant temozolomide treatment. These numbers are well below reported five-year survival in clinical trials and most population-based studies. Younger age, good preoperative functional status, tumor location and superficially located tumors appears to be the most important clinical prognostic factors for GBM long-term survival but do not explain all five-year survivors. To our knowledge, this is the only nationwide population-based study of five-year survival in GBM patients.

Declarations

Acknowledgements: None

Author contributions:

PM: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, writing – original draft and writing – review and editing

EV: data curation, formal analysis, investigation, software, methodology, validation, and writing – review and editing

AAS: data curation, validation, writing – review and editing

PS: Conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, software, supervision, validation, writing – original draft, and writing – review and editing.

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Tables

Table 1. Distribution of total HGG cases, HGG 5-year survivors and verified 5-year GBM survivors

Time Cohorts	Total HGG	HGG 5YS, No (%)	GBM 5YS, No (%)
1958 - 1969	3291	188 (5.7)	10 (0.4)
1970 - 1979	3119	149 (4.7)	19 (0.6)
1980 - 1989	3193	187 (5.8)	21 (0.7)
1990 - 1999	3162	212 (6.7)	27 (0.9)
1958 - 1999	**12 765**	**736 (5.8)**	**77 (0.6)**

HGG = High-Grade Glioma

GBM = Glioblastoma

5YS = Five-year survivors

Table 2. The histopathological diagnosis in 585 five-year survivors with HGG according to the ICD 7, ICD 9, ICD 0 and ICD 10 classifications.

Diagnosis		No	%
Anaplastic Astrocytoma gr III		197	33.7
Astrocytoma gr II		86	14.7
Glioblastoma		77	13.2
Oligoastrocytoma gr III		34	5.8
Pilocytic astrocytoma gr I	27		4.6
Oligodendroglioma gr II	26		4.4
Anaplastic oligodendroglioma gr III	24		4.1
Spongioblastoma (cerebellum)	21		3.6
Oligoastrocytoma gr II	19		3.2
Meningioma	19		3.2
No detectable PAD	18		3.1
Malignant glioma NOS	13		2.2
Ganglioglioma gr I	5		0.9
Ependymoma gr III	4		0.7
Ependymoma gr II	4		0.7
Intramedullary glioma tumor	3		0.5
Ganglioglioma gr III	2		0.3
DNET	2		0.3
Ganglioglioma gr II	1		0.2
Hemangioblastoma gr 1	1		0.2
Ependymoma grade I	1		0.2

HGG = High Grade Glioma

Table 3. Characteristics of GBM five-year survivors from retrieved medical charts, N = 73.

Symtoms and features		Preop Karnofsky		Tumor Location		Surgery		Side		Depth		Onc.Treat.	
Headache	46 (63%)	50	7 (10%)	Frontal	40 (55%)	GTR	36 (49%)	Right	44 (60%)	SF	43 (59%)	RT	69 (95%)
Neurological signs	38 (52%)	60	15 (20%)	Temporal	14 (19%)	Partial	32 (44%)	Left	29 (40%)	D	30 (41%)	CT	38 (52%)
Nausea	28 (38%)	70	27 (37%)	Parietal	8 (11%)	Biopsy	5 (7%)						
Vertigo	18 (25%)	80	10 (14%)	Occipital	6 (8%)	Reop.	24 (32%)						
Vomiting	16 (22%)	90	12 (16%)	Ventricle	2 (3%)								
Infection, deep	9 (12%)	100	2 (3%)	Cerebellum	1 (1%)								
Infection, superficial	6 (8%)			Brain stem	1 (1%)								
Infection, gen preop	6 (8%)			Multilobular	1 (1%)								
Heredity nonCNS tumor	6 (8%)												
Previous TBI	6 (8%)												
Previous tumor nonCNS	5 (7%)												
Heredity tumor CNS	3 (4%)												
Allergy	2 (3%)												
Autoimmunity	2 (3%)												
Asthma	2 (3%)												
Previous RT CNS	2 (3%)												
Previuos CNS tumor	0 (0%)												
Multiple Sclerosis	0 (0%)												

GTR= Gros Total Resection; SF = superficial; D = Deep; RT = radiotherapy; CT = chemotherapy; Onc.Treat; = oncological treatment; GBM = Glioblastoma

Figures

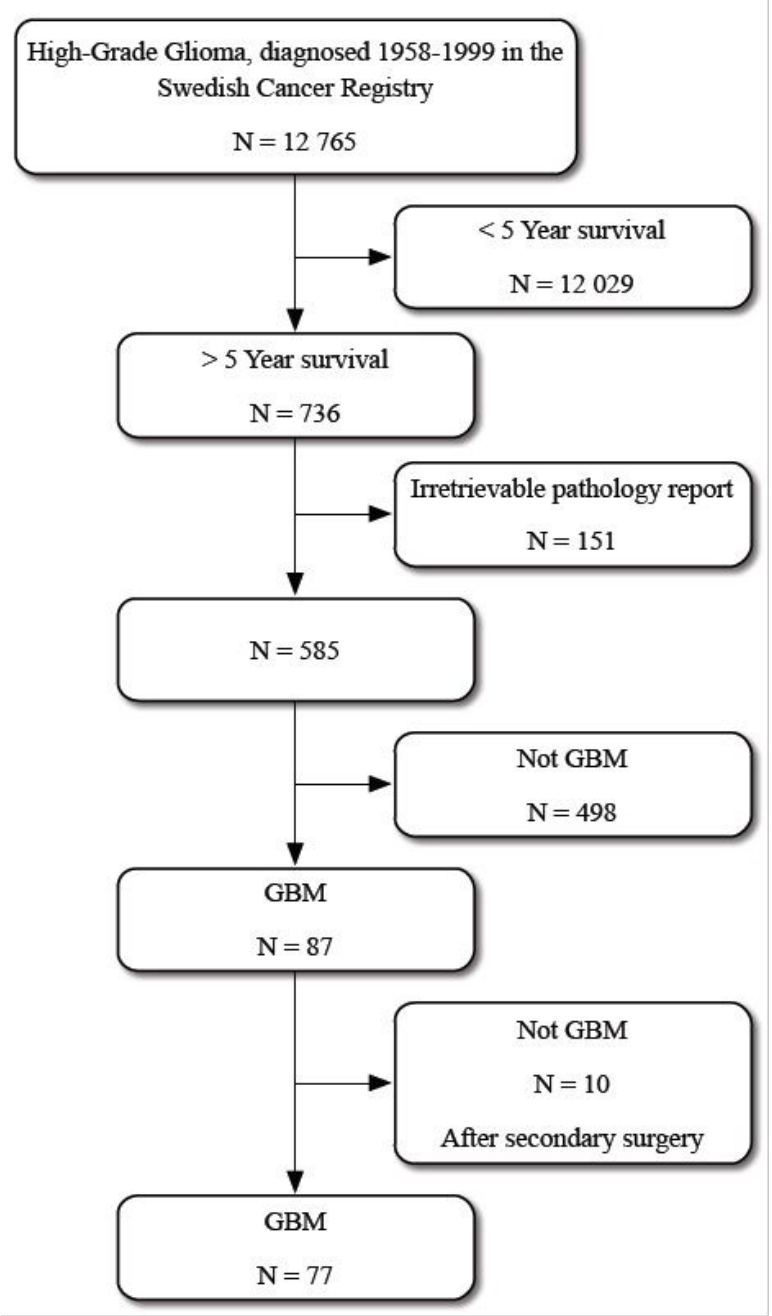

Figure 1

Flow chart of high-grade glioma and glioblastoma five-year survivors from the Swedish Cancer Registry and the Swedish Cause of Death Register between 1958-1999.

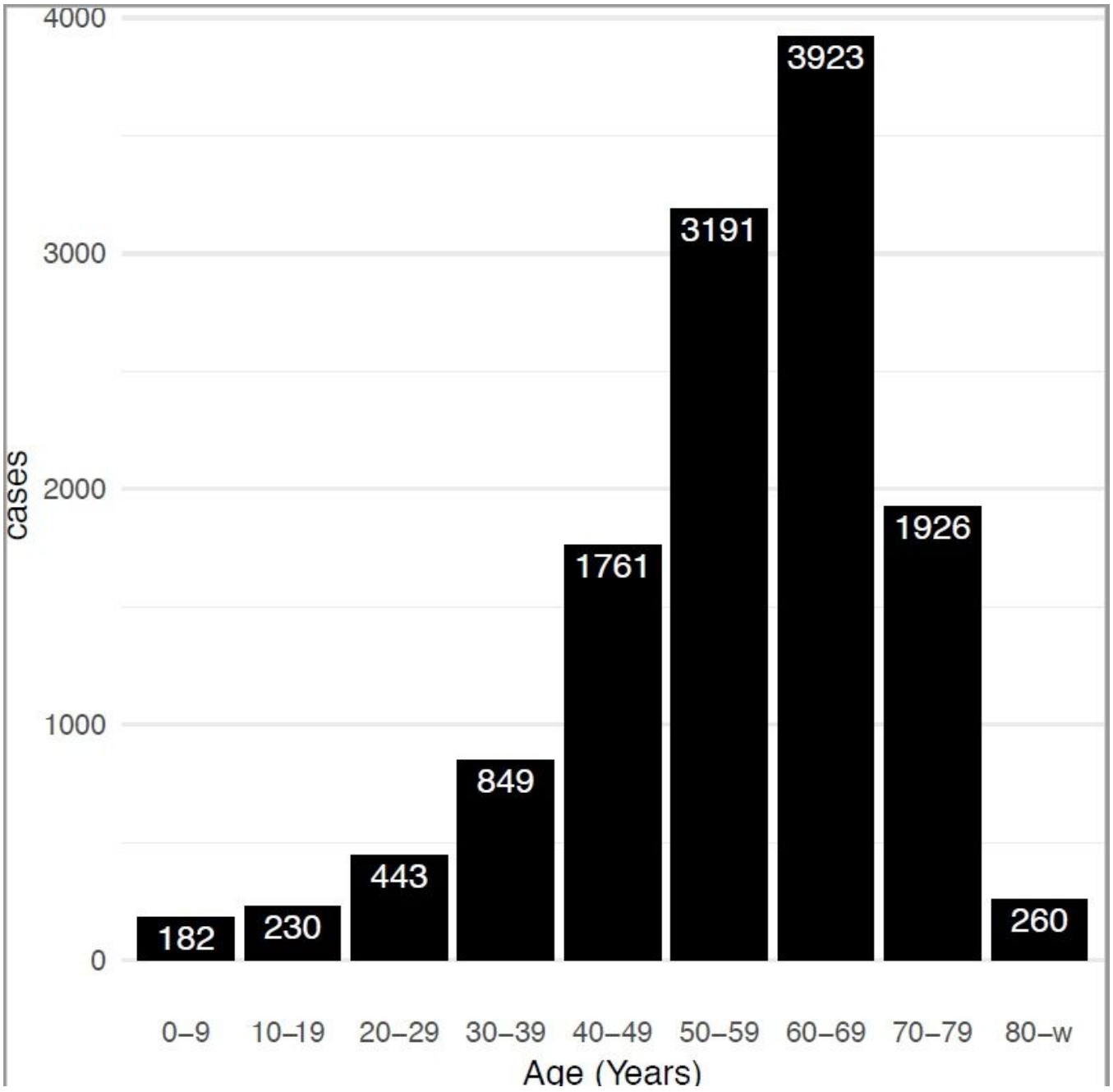

Figure 2

Age distribution of patients with number of patients added to each bar.

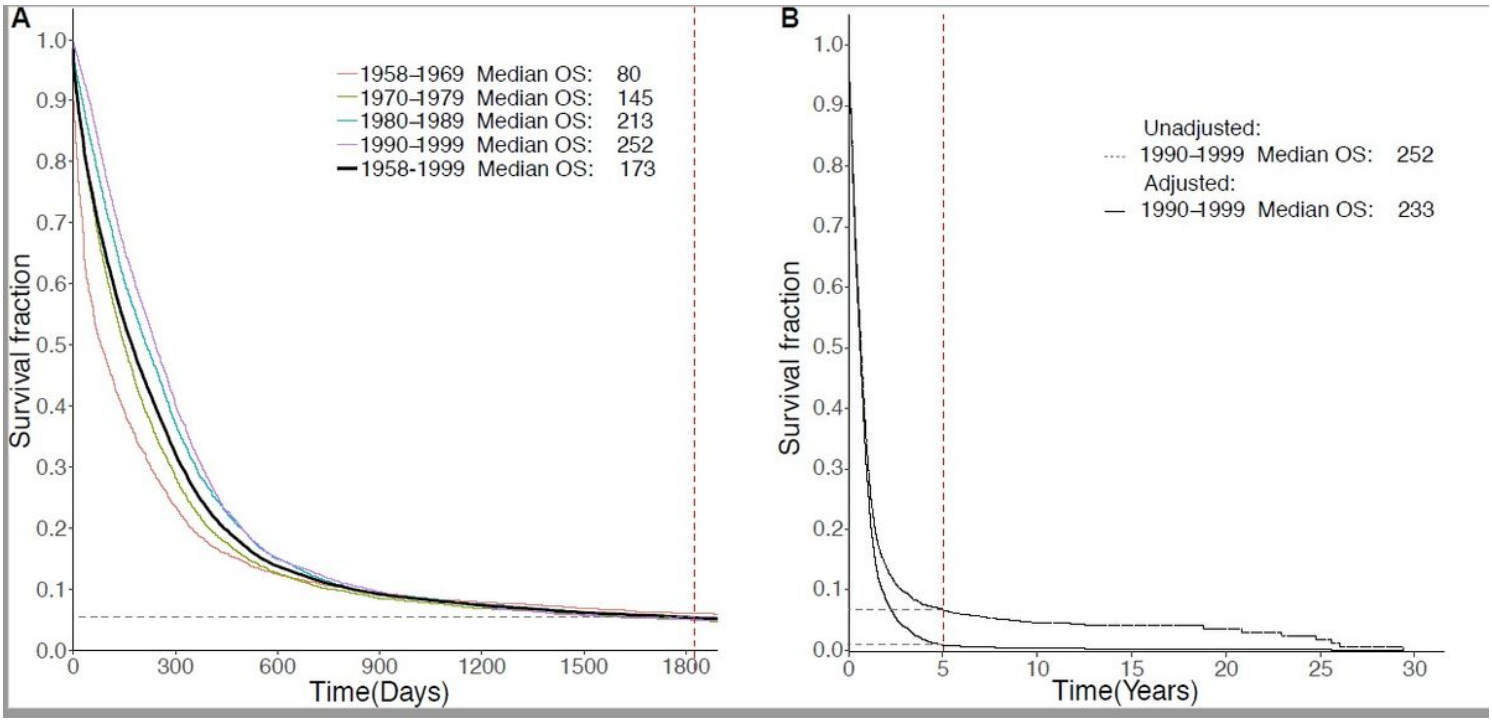

Figure 3

a. Patient survival. Patients divided in four time-period cohorts. Median survival is noted. b. Patient survival. Adjusted 90-99 time cohort when all pathology reports were retrieved. Median survival is noted.

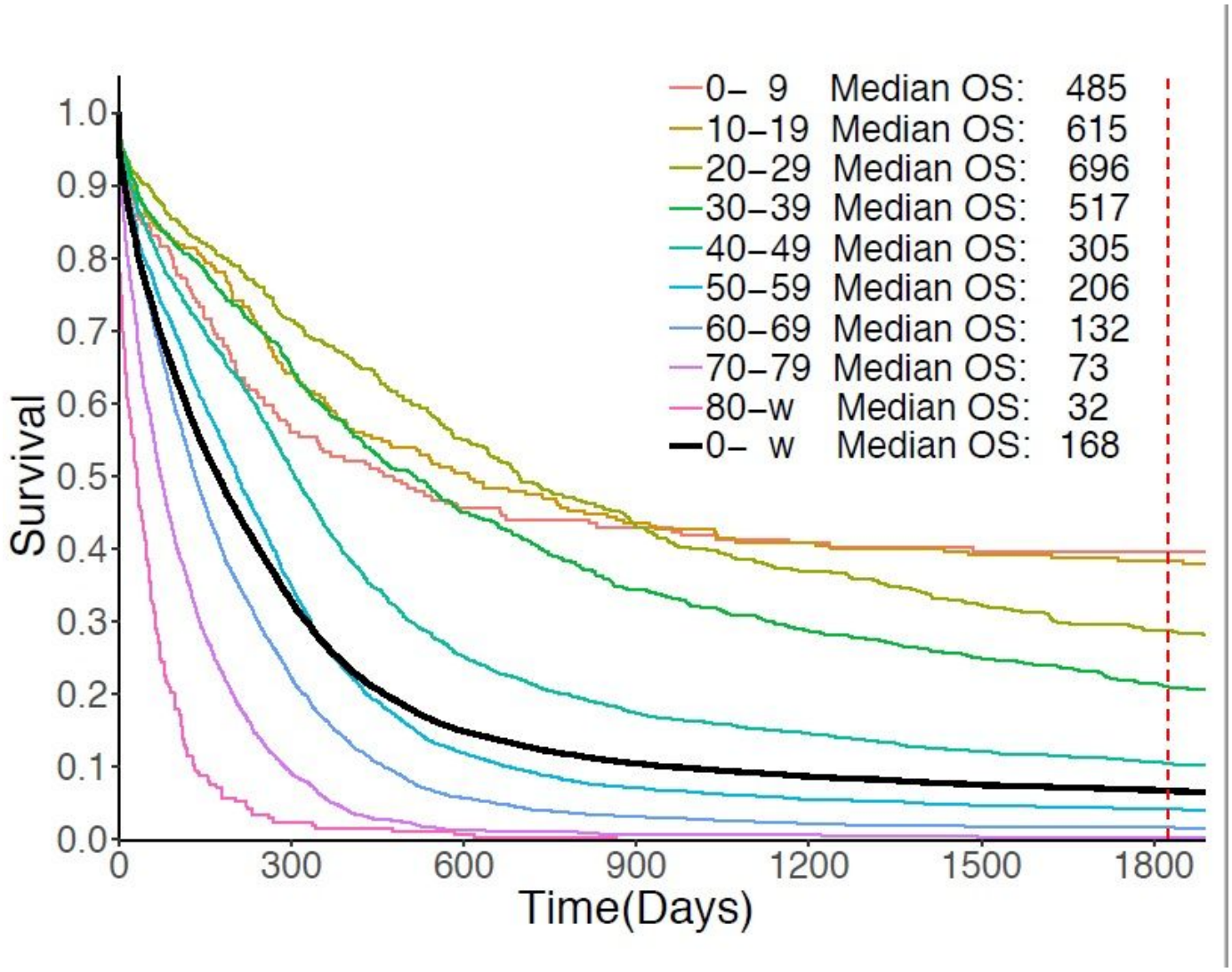

Figure 4

Patient survival. Patients divided into age-groups. Median survival is noted.

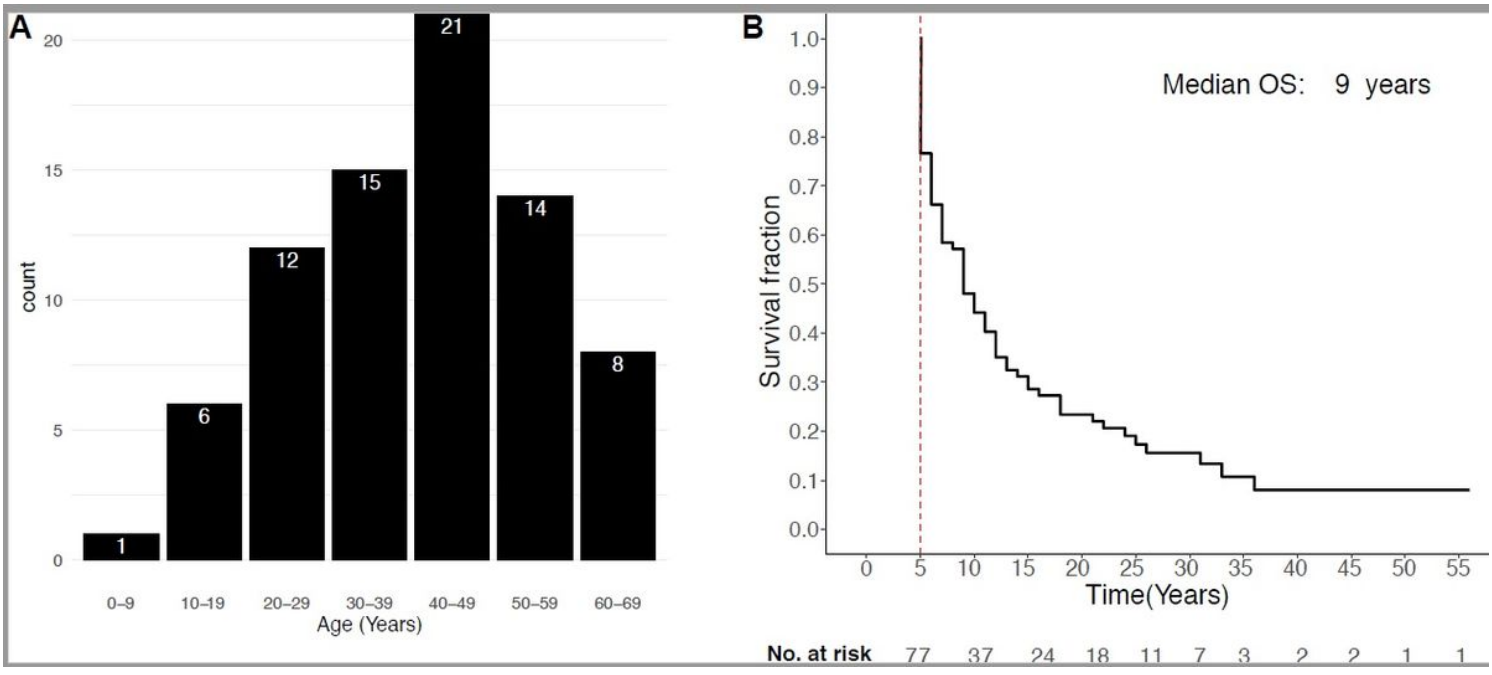

Figure 5

Age distribution of glioblastoma five-year survivors when diagnosed. Number of patients added to each bar. b. Overall survival of glioblastoma five-year survivors with median OS noted.