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ORIGINAL ARTICLE

Initial cognitive impairment predicts shorter survival of patients with glioblastoma

Helena Bruhn[1,2] | Ida Blystad[3,4] | Peter Milos[2,5] | Annika Malmström[2,6] | Charlotte Dahle[2] | Magnus Vrethem[2] | Roger Henriksson[7] | Jonas Lind[1,2]

[1]Department of Neurology, Region Jönköping County, Jönköping, Sweden

[2]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

[3]Department of Radiology in Linköping and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

[4]Centre for Medical Image Science and Visualization (CMIV), Linköping University, Linköping, Sweden

[5]Department of Neurosurgery, Linköping University Hospital, Linköping, Sweden

[6]Department of Advanced Home Care, Linköping University, Linköping, Sweden

[7]Department of Radiation Sciences, Umeå University Hospital, Umeå, Sweden

Correspondence
Helena Bruhn, Department of Neurology, Jönköping, Region Jönköping County and Department of Biomedical and Clinical Sciences Linköping University, Linköping, Sweden.
Email: Helena.bruhn@rjl.se

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Abstract

Objectives: Seizures as presenting symptom of glioblastoma (GBM) are known to predict prolonged survival, whereas the clinical impact of other initial symptoms is less known. Our main objective was to evaluate the influence of different presenting symptoms on survival in a clinical setting. We also assessed lead times, tumour size and localization.

Methods: Medical records of 189 GBM patients were reviewed regarding the first medical appointment, presenting symptom/s, date of diagnostic radiology and survival. Tumour size, localization and treatment data were retrieved. Overall survival was calculated using Kaplan-Meier and Mann-Whitney U test. Cox regression was used for risk estimation.

Results: Cognitive impairment as the initial symptom was often misinterpreted in primary health care leading to a delayed diagnosis. Initial global symptoms (66% of all patients) were associated with reduced survival compared to no global symptoms (median 8.4 months vs. 12.6 months). Those with the most common cognitive dysfunctions: change of behaviour, memory impairment and/or disorientation had a reduced median survival to 6.4 months. In contrast, seizures (32%) were associated with longer survival (median 11.2 months vs. 8.3 months). Global symptoms were associated with larger tumours than seizures, but tumour size had no linear association with survival. The setting of the first medical appointment was evenly distributed between primary health care and emergency units.

Conclusion: Patients with GBM presenting with cognitive symptoms are challenging to identify, have larger tumours and reduced survival. In contrast, epileptic seizures as the first symptom are associated with longer survival and smaller tumours.

KEYWORDS
cognitive functions, epilepsy, glioblastoma, neuro-oncology, radiation, seizures, survival, temozolomide

1 | INTRODUCTION

Approximately 1200 cases with primary brain tumours are diagnosed yearly in Sweden.[1] Glioblastoma (GBM) is the most frequent tumour diagnosis with an incidence of 4/100.000 and the most devastating tumour with a median overall survival (OS) of less than 15 months.[2-4]

The OS of malignant gliomas is affected by several factors, where age, performance status, multiple lesions and resection type are independent prognostic factors.[5-8] The tumour size and localization at surgery have not been shown to influence the OS[9] and relapses usually derive from the residual tumour at the resection border. Subventricular tumours, however, tend to have a worse prognosis since they are larger and have a larger proportion of un-methylated tumours than other localizations.[10]

The different symptoms during the disease course of high-grade glioma are well described and include seizures, cognitive deficits, drowsiness, dysphagia, headache, confusion, aphasia, motor deficits, fatigue and dyspnoea.[11] Epileptic seizures will often lead to more rapid investigations and diagnosis. Patients presenting with seizures have a more prolonged survival,[12] and usually have smaller tumours with less oedema at diagnosis than patients presenting with other symptoms.[13]

Initial cognitive dysfunction is more common in older patients with glioma, whereas seizures are more frequent in younger patients. Headache rarely appears as an isolated symptom and there are conflicting data on how frequent headache is as presenting manifestation.[14,15] The correlation between initial symptoms and their effect on lead times and OS is mainly unknown. We hypothesised other presenting symptoms than seizures could also influence time to diagnosis and survival. The objective of this study was to evaluate the influence of different presenting symptoms, on healthcare level, lead times, treatment and OS in a clinical setting. We also investigated the impact of tumour size, localization and type of treatment on survival.

2 | MATERIALS AND METHODS

All patients with a histopathological verified GBM in the County of Jönköping between January 2001 and August 2016 were identified using data from the Southeast Regional Cancer Centre. The latter inclusion date was chosen due to the implementation of the 'Standardised care course' for brain tumours in September 2016. Patients who progressed from low-grade gliomas and patients without a biopsy-verified diagnosis were omitted.

Medical records were reviewed (by H.B., senior consultant in neurology) regarding age and gender, the date and level of care of the first medical appointment for symptoms later shown to be caused by a brain tumour (primary health care, emergency unit or other specialised care), presenting symptom/s [(defined as *global symptoms* (cognitive aberrations, headache, dizziness and fatigue), *loss of neurologic function* (paresis, sensory deficit, aberrations in speech, vision and coordination) and *epileptic seizures* (focal or secondary generalised)] and the date of the diagnostic radiology. The cognitive symptoms were identified using specific search terms/sentences in the case files, similar to the method 'content analysis' in qualitative studies.[16] For example, disorientation/confusion: unable to name the date, personal data or location, chaotic behaviour as mentioned by the relatives or noted by the doctor; behavioural change: change of behaviour or 'change of personality', as reported by the relatives as such or as acting strange or differently; apraxia as mentioned by the doctor or described in the case history; depression as reported or described as a low mood, dysthymia and sadness; concentration as reported or as an inability to focus. In very few cases, patients had a cognitive evaluation performed preoperatively by an occupational therapist. As all medical records were scrutinised by H.B. This ensured the same evaluation for all reports. The primary healthcare records were reviewed concerning any previous consultations for similar symptoms within six months before the diagnosis. A neuroradiologist (I.B.) reviewed the images of the diagnostic radiology. Tumour localization was evaluated and was defined as frontal, temporal, parietal, occipital, midline or infratentorial, as well as being left- or right-sided. Multifocality was noted. Tumour size was measured in the axial slice with the largest diameter and a second perpendicular measurement according to RANO criteria.[17] Volumetrics and oedema measurement were not performed as they were not, and are not, routinely used in clinical practise, and since not all patients had an Magnetic Resonanse Image (MRI).

Overall survival was measured from the date of diagnostic radiology. Living patients were censored on 29 November 2018, when the data collection was completed. Since the study comprises patients diagnosed over a long period of time (2001–2016), they were sub-grouped for survival analysis. Cohort *A* was diagnosed 2001–2005 and cohort *B* 2006–2016 when concomitant radiotherapy with temozolomide (CRT) was implemented in the region. The median and mean time between the first consultation and the consultation when a suspicion regarding an intracerebral process was raised, radiology and surgery were calculated and compared between different presenting symptoms. These times are referred to as *lead times*.

The extent of resection (gross total resection, partial resection or biopsy) was noted, using the neurosurgeons' evaluation in the earlier years of the study, since postoperative MRI was not routinely performed until more recently. We did not adjust for the administration of aminolevulinic acid (5-ALA) in surgery, as it was not routinely performed until around 2009. Data on oncologic treatment were retrieved from the oncology case files. MGMT (O6-methylguanine-DNA methyl transferase) status and IDH mutation status were not available for all patients, as these were not routinely investigated during most of the time period studied and hence were not reported for all patients. MGMT status is reported only for those patients where it was performed as part of clinical practise or as part of a previous study.[4]

2.1 | Statistics

Descriptive statistics were provided for patient demographics and treatment factors. The estimates of OS were calculated using the

Kaplan-Meier method and risk estimation using the Cox proportional hazard model. The effects of clinical variables on survival were studied using Mann-Whitney U test, and comparisons were made between having and not having the specified symptom. To examine the associations between different onset symptoms, treatment, age, sex and survival, data were first analysed with univariate regression (not reported) to evaluate which variables to be included in a Cox regression model.

Those variables that had a p-value ≤.05 in the first analysis were then included in the final model. The results (p-value) were adjusted for multiple comparisons with Hochberg's method.[18]

Median test with Yates continuity correction was used to compare different onset symptoms in relation to time to radiology and diagnosis. Spearman correlation test was used to correlate onset symptom, tumour size and survival.

Differences were considered significant if the p-value was <.05.

All analyses were performed in SPSS version 24 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics and survival

189 patients were diagnosed with GBM in the County of Jönköping. The County had a mean of 330.000 inhabitants during the time. All patients could be evaluated since all were diagnosed and treated by public health care, and all patients were reported to the Southeast Regional Cancer Centre.

The median age was 64 years (10–90th percentile: 49–76). There were 69 females and 120 males. A summary of patient characteristics is shown in Table 1.

The median survival after radiological diagnosis was 9.2 months (10–90th percentile: 3–18.6) in cohort *A* and 9.7 (10–90th percentile. 2.7–30.7) months in cohort *B*. There were 18 two-year survivors (9.5%) and four five-year survivors (2%) in the entire cohort (*A* + *B*).

Patients with gross total resection (GTR) survived significantly (p <.001) longer (median 12.6 months, 10–90th percentile: 5.0–31.6 months) than those undergoing partial resection (PR) (median 10.9 months, 10–90th percentile: 4.0–37.9 months) or biopsy (median 4.7 months, 10–90th percentile: 1.9–17.3 months). CRT significantly prolonged survival (median 15.2 months, 10–90th percentile: 7.2–63.2 months) compared to radiotherapy alone (median 12.1 months, 10–90th percentile: 5.11–28.6 months) (p <.001). The oncological tumour treatment of seven patients was unknown since they were included in pharmacological studies.

3.2 | MGMT-analysis

Analysis of MGMT was performed on 28 patients, all but one were part of Cohort B. The data on twelve of these patients were >2-year survivors and were analysed as part of research and reported previously.[4] The rest of the analyses were made 2013–2016 as part of the clinical routine.

Amongst the 28 analysed samples, 14 were methylated and 14 were un-methylated. The mean survival was 39.5 and 24.9 months, respectively (p =.047). There was no difference in methylation status amongst patients reporting different onset symptoms; however, the groups were too small for statistical analysis.

3.3 | Presenting symptoms and survival

The majority of patients (n = 124, 66%) presented with global symptoms, which significantly correlated to reduced survival compared to those without global symptoms (see Figure 1 and Table 2). This difference remained after Cox logistic regression including age, sex, tumour diameter, tumour localization, surgical treatment and oncologic treatment. (Hazard ratio (H.R.) 1.8, 95% CI 1.3–2.5). The most common global symptom was cognitive dysfunction; these patients had significantly reduced survival compared to those without cognitive deficits. Amongst the different cognitive aberrations, change of behaviour, memory impairment and disorientation were more frequent than apraxia, depression and concentration difficulties. Patients with these most frequent symptoms also had significantly reduced survival compared to patients without these symptoms. The cognitive symptoms were evenly distributed between the different tumour locations, except for infratentorial tumours where cognitive symptoms were rare. The frequency of cognitive symptoms was the same in midline tumours, as in the other locations. Headache, fatigue and dizziness did not influence survival.

In contrast, presenting with a loss of neurologic function (n = 110, 58%) did not significantly influence survival compared to patients with no loss of function. The most common neurological deficit was paresis.

Sixty patients (32%) presented with epileptic seizures. They had a significantly longer survival compared to patients with other initial symptoms (Table 2 and Figure 2). The difference remained after logistic regression including age, sex, tumour diameter, tumour localization, surgical treatment and oncologic treatment. Presenting with focal epileptic seizures was associated with significantly prolonged survival whereas secondary generalised seizures were not. Eleven of the 18 2-year survivors and three out of four 5-year survivors presented with epileptic seizures.

3.4 | The initial level of care

Ninety-three patients (49%) had their first tumour-related medical contact in an emergency unit (EU) and 91 (48%) in primary health care (PHC). The remaining five first consultations were in other specialised care. Sixteen of the 91 PHC patients (18%) had multiple contacts without being referred to radiology or further

TABLE 1 Summary of glioblastoma patient characteristics $n = 189$

Characteristics	Patients *n* (%)	Median overall survival (months)	Percentiles 10–90 (months)	Mean overall survival (months)
Gender				
Male	120 (63%)	9.7	3.0–20.6	11.6
Female	69 (37%)	8.3	2.2–43.6	16.9
Age (years)				
32–50	27 (14%)	11.3	4.0–27.8	14.2
51–65	80 (42%)	12.3	3.6–35.1	17.8
66–83	82 (43%)	6.5	2.2–19.5	8.9
Extent of surgery				
Biopsy only	57 (30%)	5.2	1.9–17.3	6.7
Partial resection	39 (21%)	10.9	4.0–37.9	9.7
Gross total resection	88 (46%)	12.6	5.0–31.6	18.2
Unknown	5 (3%)	10.9	nc	9.7
Therapy				
CRT	51 (27%)	15.2	7.2–63.2	24.8
Radiotherapy only	89 (47%)	12.1	5.2–28.6	16.8
Chemotherapy only	9 (5%)	5.8	nc	9.2
No treatment	33 (17%)	3.1	1.4–6.4	3.5
Study protocol	7 (4%)	nc	-	-
Tumour Localization[a]				
Frontal	68 (36%)	9.3	3.4–30.2	14.5
Temporal	86 (46%)	9.6	2.3–29.9	14.2
Occipital	21(11%)	6.9	1.3–16.8	9.4
Parietal	49 (26%)	6.5	2.1–20.2	10.5
Infratentorial	3 (2%)	4.2	nc	6.4
Midline	25 (13%)	5.2	1.9–16.2	6,3
Left	71 (38%)	11.0	2.9–32.2	16.4
Right	81 (43%)	9.2	3.1–25.8	13.2
Multifocal	21 (11%)	7.4	1.1–19.7	8.4
Missing[b]	9 (5%)	-	-	-

Notes: Note that this includes data before and after the implementation of the concomitant radiotherapy with temozolomide (CRT). Therapy includes all oncologic treatment.

Abbreviation: nc, not calculated due to few cases.

[a]Tumours can be localised in more than one lobe.

[b]The radiology of 9 patients diagnosed in 2001 could not be found.

investigation. They later sought care at the EU either due to progressing symptoms or by their relatives' action. The most common initial symptoms amongst these patients were global symptoms combined with neurological deficits, cognitive symptoms alone or in combination with epileptic seizures. Most patients with delayed diagnosis were interpreted as having a psychiatric disorder, such as depression or burnout. The lead time from the first healthcare contact to radiology was significantly longer for the group with multiple consultations compared to those who were immediately suspected of having a possible intracerebral lesion (median 29 days, vs. median 1 day, $p < .001$). The numbers were too small for statistical evaluation of differences in survival. Amongst patients seeking initial care at the EU, four patients with focal seizures (speech arrest or Jacksonian epileptic seizure) were misdiagnosed as having transient ischaemic attacks (TIA). They were investigated with computed tomography (CT) of the brain without contrast enhancement hence missing the tumour diagnosis until additional symptoms or secondary generalised tonic-clonic seizures appeared. The small numbers in these subgroups do not allow statistical evaluation. There was no significant difference between gender and age regarding the location of the first consultation or between presenting symptoms. The level of care (primary care, EU or other specialised unit) of the first appointment did not influence survival time.

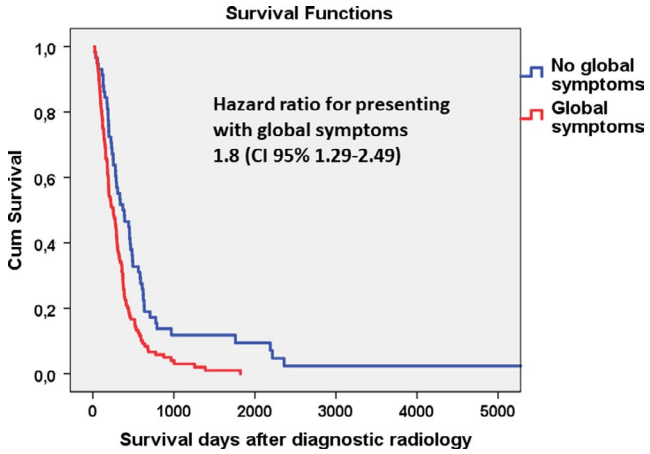

FIGURE 1 Hazard ratio for presenting with global symptoms versus not having global symptoms at onset presented in Kaplan Meier Curves. Median survival for global symptoms 8.4 months versus 12.6 months (p =.001)

3.5 | Lead times

The median time from when a brain tumour was suspected to radiological diagnosis was 1 day (10–90th percentile: 0–44). The lead time to radiology did not differ between different symptoms. The median time from radiological diagnosis to surgery was 18 days (10–90th percentile: 4–47 days). It was longer for patients with biopsy (20 days; 10–90th percentile: 10–45 days) and PR (20 days; 10–90th percentile: 5–77 days) compared to patients with GTR (16 days; 10–90th percentile: 2–41 days), p =.003.

3.6 | Radiology and tumour location in relation to survival and treatment

CT was the only radiology performed in 71 patients, and 109 patients had an MRI as well. The diagnostic radiology was missing in the files for nine patients. Those with midline tumours had shorter survival (median 5.2 months) than patients with tumours in other locations (p <.001), see Table 1.

Unexpectedly, multifocality did not influence survival. Parietal location was unfavourable (median survival 6.5 months, p =.037).

The median tumour size was 46 mm (10–90th percentile: 23–65 mm). The midline tumours were significantly larger than tumours on other locations: median 54 mm (10–90th percentile: 25–91mm, p =.006). There was no linear association between maximal tumour diameter at diagnosis and OS ($\rho_{Spearman} = -0.28$, p =.67) for the entire cohort, nor for the subgroup with global symptoms ($\rho_{Spearman} = -0.07$, p =.53) or for the subgroup with epilepsy ($\rho_{Spearman} = -0.181$, p =.29).

Patients with global symptoms generally had larger tumours (median 51 mm 10–90th percentile 29–67) than patients with initial epilepsy (median 35 mm 10–90th percentile 16–58) (p <.001). There was no difference in tumour size between patients with or without loss of neurologic function.

Increasing tumour size correlated with decreasing frequency of treatment with CRT (p =.024).

The significant difference in survival between having and not having cognitive symptoms remained after binary logistic regression analysis including CRT (p =.005).

4 | DISCUSSION

This study examines new aspects of survival in relation to presenting symptoms in patients with GBM, in a clinical setting. Our findings suggest that cognitive dysfunctions as initial symptoms indicate a poorer prognosis (predictive factor). This has previously only been shown postoperatively[19,20] and at tumour progression.[21,22]

Change of behaviour, memory impairment and disorientation/confusion were the presenting symptoms with the shortest survival. These symptoms are less acute and were found to be more challenging to evaluate correctly. The poor survival could not be explained by the tumour size, even though patients with global cognitive dysfunction had larger tumours. This could be due to the oedema component and/or different tumour biology, and further studies are needed. It has been reported that patients with epileptic seizures or headaches preoperatively have more prolonged survival than patients with focal neurological deficits or cognitive changes have.[23] We could confirm these findings regarding cognitive dysfunction and seizures, but not for headache or focal deficits, possibly due to the relatively small number of patients in our cohort.

It has previously been reported that patients with global symptoms such as confusion and/or memory loss and even limb weakness often have a delayed diagnosis as the patients and relatives often misinterpret their symptoms as part of a normal ageing process.[24] Spouses to brain tumour patients often report months of global deterioration preceding the symptoms that finally lead to the consultation.[25] In our study, many patients with cognitive dysfunction as the initial complaint were misinterpreted in PHC as having psychiatric disorders. In a significant proportion of the cases, PHC never suspected a brain tumour and patients were not examined with neuroradiology until their symptoms progressed, and the patient consulted the emergency care. Focal seizures also seem to be challenging to identify. A few patients evaluated in the EU were misdiagnosed as having TIA, which prolonged the time to correct diagnosis.

Amongst the 2- and 5-year survivors, the majority had epileptic seizures at onset. Patients with seizures as presenting symptom are known to survive longer[26-28] and to have smaller tumours,[13] which is also in agreement with our findings. If additional preoperative symptoms develop, typically due to tumour growth and/or surgical delay, the initial seizures prognostic benefit is lost.[29]

We could not find any correlation between survival and tumour size, possibly indicating that other tumour factors, such as surrounding oedema or specific molecular biological and genetic factors may have significant impact on survival.

Headache was one of the presenting symptoms in 30% of the patients similar to what other groups have found.[15,24] In our study,

TABLE 2 Presenting symptoms

Presenting symptom	Patients *n* (%)	Symptom present		Symptom absent		Statistical significance for symptom present versus absent	Hazard ratio (95% CI)
		Median survival (months)	Percentiles 10–90	Median survival (months)	Percentiles 10–90		
Global symptoms	126 (66)	8.4	2.5–20.5	12.6	4.2–48.1	p =.001	1.8 (1.3–2.5)
Cognitive dysfunction	76 (40)	6.4	2.1–18.4	11.3	3.9–30.4	p =.002	1.8 (1.3–2–5)
• Behavioural change	32 (17)	6.5	2.0–12.9	9.7	2.7–26.8	p =.015	1.7 (1.1–2.6)
• Memory i pairment	27 (14)	6.2	1.1–18.9	9.8	2.9–26.3	p =.010	1.9 (1.3–2.8)
• Disorientation/confusion	25 (13)	5.2	2.0–15.2	10.0	2.85–26.1	p =.001	2.1 (1.3–3.2)
• Apraxia	9 (5)	4.0	2.9–18.6	9.6	2.6–25.9	ns	-
• Depression	8 (4)	6.5	2.1–13.7	9.4	2.8–25.9	ns	-
• Concentration	3 (2)	17.4	1.7–12.3	9.3	2.7–25.8	ns	-
Headache	63 (33)	8.6	2.9–19.1	9.8	2.4–29.6	ns	-
Dizziness	34 (18)	7.2	2.7–20.3	9.8	2.6–27.1	-	-
Fatigue	34 (18)	11.4	2.8–28.2	9.3	2.5–24.5	ns	-
Loss of function	110 (58)	9.6	2.7–22.0	8.8	2.3–27.1	ns	-
Paresis	62 (33)	8.8	2.5–20.3	9.8	2.9–29.5	ns	-
Speech aberrations	42 (22)	9.8	2.7–28.4	9.3	2.6–25.8	ns	-
Vision	20 (11)	10.2	2.5–58.7	9.4	2.8–25.8	ns	-
Sensory	12 (6)	9.8	2.5–42.1	9.4	2.6–23.1	ns	-
Coordination	5 (3)	10.2	3.0–16.2	9.3	2.6–25.9	ns	-
Epileptic seizures	60 (32)	11.2	4.0–36.0	8.3	4.5–20.7	p =.002	0.6 (0.4–0.9)
Focal	35 (18)	12.3	4.0–32.1	8.4	2.5–22.7	p =.012	0.7 (0.5–1.0)
Generalised tonic–clonic seizures	25 (13)	9.8	3.7–44.5	9.4	2.7–22.7	ns	-

Note: Survival from radiological diagnosis tested using Mann-Whitney U test. Note that 'symptom absent' means that the patient does not have that specific symptom, but other presenting symptoms. Patients can have more than one symptom.

Abbreviation: ns, not significant.

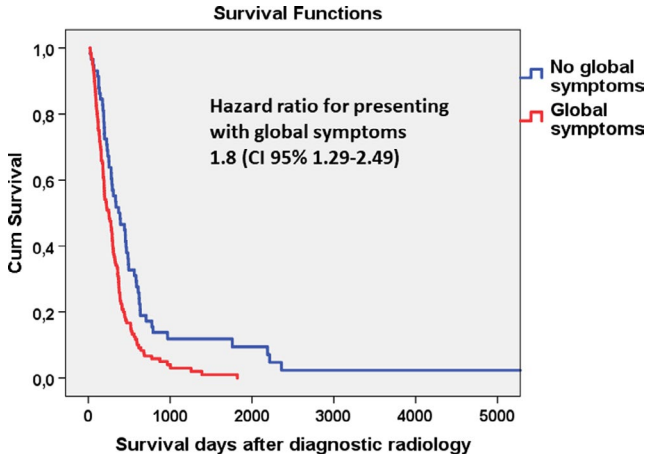

FIGURE 2 Hazard ratio for presenting with seizures (onset epilepsy) versus other presenting symptoms without seizures (no onset epilepsy) presented in Kaplan Meier Curves. Median survival for 'onset epilepsy' was 11.2 months versus 8.3 for 'no onset epilepsy' (p =.002)

all but two patients with headaches also had additional symptoms, which is essential when evaluating patients with sole headaches. In our study, speech aberrations were more common (22%) than previously reported (6%). The lead times, however, did not differ as they did in the previous study[24] probably due to the limited size of our cohort. The doctors' delay in this study was due to problems identifying the patients need for radiology of the brain. Therefore, we believe that this problem will remain even after the implementation of 'Standardised care course'. The lead times from suspicion of an intracerebral process to radiology and treatment will hopefully improve.

The anatomical tumour localization is not always associated with the presenting symptom [14], apart from the lateralization of pyramidal withdrawal symptoms, such as paresis. Survival has been shown to be longer for patients with frontal, parietal or posterior fossa tumours, whilst no difference was detected concerning brain lateralization.[24] In the evaluation of this cohort, parietal and midline tumours had shorter survival than other tumour localizations. Surprisingly, tumour size and multifocality did not influence survival, which could be due to our cohort's limited size. Other factors could also be important, such as variation in biological properties between different tumour locations,[30] which warrants further studies.

Our study shows that the benefits of GTR, followed by CRT with temozolomide seen in clinical trials and recent population studies[4,23,31] are also applicable in an unselected population. It should be emphasised that the survival difference between cohort A and B cannot only be explained by the implementation of CRT with temozolomide since other treatment regimens have been introduced in the later years, such as postoperative MRI and the use of 5-ALA.

The strength of our study is the complete coverage of all GBM cases in one healthcare region during a 16-year period, and the extensive information available from the medical charts for all patients during the whole disease course. Thus, the risk of selection bias is low, and we consider confounding factors to be of low risk. The relationship between survival and initial symptoms has not previously been well documented, except for epileptic seizures. Data on which healthcare level GBM patients seek before diagnosis have rarely been reported previously.

On the contrary, there are limitations to our study, mainly due to the limited number of patients, especially in some subgroups. It is also a retrospective study. Doctors of different specialties and with varying competence made the symptom evaluations of the patients. The initial symptoms reported in the medical charts are a combination of the patient self-reported symptoms, the symptoms the relatives report and the physicians' report of the first consultation and physical examination. The study of the medical charts could also be biassed by the investigator of the medical records being aware that the patient later was diagnosed with GBM. Unfortunately, the neurosurgeons' preoperative assessment of performance status is not included in this study, since it was rarely reported in the medical charts. No cognitive testing was made before surgery, except for a few patients, since that was not included in clinical practise at that time. The resection grade was mainly evaluated by the neurosurgeon in the earlier part of the study since postoperative MRI was not routinely performed until towards the end of this study. Therefore, we have no volumetric data on the residual tumour. The patients were diagnosed according to the 1993 or 2007 World Health Organization Classification of Tumours of the Central Nervous System[32] and not according to the current 2016 edition.[33] Molecular data concerning O6-methylguanine-DNA methyl transferase (MGMT) or IDH mutations were not routinely investigated during the study period and hence were missing for most patients in our analysis.

In conclusion, this clinical study of unselected GBM patients, from a defined region of Sweden, indicates that cognitive symptoms at onset often are misinterpreted, and the diagnosis is thereby delayed since relevant investigations are not performed until patients deteriorate. These patients have shorter survival compared to GBM patients with other types of onset symptoms.

ETHICAL APPROVAL

The study was approved by The Regional Ethics Committee in Linköping D-nr 215/315-31.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (HB). The data are not publicly available due to restrictions, for example they are containing information that could compromise the privacy of research participants.

ORCID

Helena Bruhn https://orcid.org/0000-0001-6998-1300

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